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[Authors]. [Abstract Title]. Program No. XXX.XX. 2016 Neuroscience Meeting Planner. San Diego, CA: Society for Neuroscience, 2016. Online.

Poster

775. Dendritic Arborization

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 775.01/A1

Topic: A.05. Axon and Dendrite Development

Support: NJCBIR# CBIR15FEL009

NJCBIR# CBIR14IRG019

NJCBIR# CBIR12MIG011

Title: A role for PSD-95 and its binding partners in models of Traumatic Brain Injury.

Authors: *M. V. PATEL[1], D. F. MEANEY[2], B. L. FIRESTEIN[1];
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Abstract: Traumatic brain injury (TBI) damages neuronal networks, resulting in disrupted brain function and cognitive deficits. Normal dendrite morphology and synapse formation are required for proper neuronal signaling and survival. The study of new molecular targets to repair deficits in dendritic arbors and spines post-trauma will yield promising future directions for drug development for the treatment of patients who have suffered a TBI. Postsynaptic density-95 (PSD-95) is of particular interest as it is required for proper neuronal development. Specifically, PSD-95 inhibits dendrite branching by regulating microtubule dynamics and sequestering end-binding protein 3 (EB3), and potentially Adenomatous polyposis coli (APC), from the +TIPs of microtubules. Overexpression of PSD-95 causes decreased dendrite branching and increased number of mature spines, while knockdown has the opposite effect. Previous studies of TBI have shown a delayed reduction in PSD-95 levels post-trauma, suggesting a role for inhibition of PSD-95 after TBI. Based on these facts, we propose that altering PSD-95 protein levels post-injury will rescue dendritic arborization and synaptogenesis after injury. In line with a role for PSD-95 post-injury, we find increased interaction of PSD-95 with its binding partners, APC and EB3, in an in vitro TBI model of mechanical stretch injury, while total protein levels of PSD-95 and EB3 are decreased. In parallel, we use controlled cortical impact (CCI) in mice as an in vivo model of TBI, which shows decreased dendrite number in the early phase (0-3 days) and decreased synapse number in the late phase (3-7 days) post-injury. We find that there is no change in the interaction of PSD-95 and its binding partners 24 h after injury, while total EB3 protein decreases significantly at 24 h post-injury. As EB3 is involved in the promotion of dendrite branching, decreased levels of EB3 at 24 h post-injury suggests a role for EB3 in decreasing the dendritic network during the early injury phase after TBI. We began our studies with a time point of 24 h post-injury and are now examining brains at earlier and later time

points to determine changes in interaction of PSD-95 and its binding partners and total levels of these proteins. To aid in recovery, we will downregulate PSD-95 in the early phase post-injury to rescue dendritogenesis followed by upregulation of PSD-95 during the late phase post-injury to rescue spine number. We predict that PSD-95 will rescue normal function by promoting neuronal survival, dendrite branching, and spine formation after TBI.

Disclosures: **M.V. Patel:** None. **D.F. Meaney:** None. **B.L. Firestein:** None.

Poster

775. Dendritic Arborization

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 775.02/A2

Topic: A.05. Axon and Dendrite Development

Support: National Alliance for Research on Schizophrenia and Depression 2012 Marion G. Nicholson Distinguished Investigator Award from the Brain and Behavior Research Foundation

National Science Foundation Grant IBN-1353724

Title: The role of CPE and its interactor, $p150^{Glued}$, in regulation of neuronal cytoskeleton and migration

Authors: *C. LIANG[1,2], D. CARREL[1], H. KIM[1], B. L. FIRESTEIN[1];
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Abstract: Carboxypeptidase E (CPE) is a member of carboxypeptidase family that processes neuropeptides and peptide hormones and regulates processes in the endocrine and nervous systems. CPE knockout mice have neurobehavioral deficits, including deficits in learning and memory. It was previously reported that $p150^{Glued}$ and CPE exist in a complex in cultured cells; our current study confirms this interaction in mouse brain and identifies the region in $p150^{Glued}$ that is responsible for CPE binding. In addition, our studies in cell lines suggest that CPE overexpression redistributes endogenous $p150^{Glued}$ from the centrosome, disrupts microtubule organization, and mediates the post-translational modification (PTM) of microtubules. As $p150^{Glued}$ is the largest subunit of the Dynactin complex, which is indispensible for the functional motor activity of dynein, we hypothesized that CPE exerts its effect on the cytoskeleton by altering PTMs of microtubules, resulting in alterations in localization of motor protein complexes and/or other microtubule-binding proteins. Thus, we extended our studies to assess the role of CPE in dendrite branching in primary cultured neurons, and in cortical neuron

migration via *in utero* electroporation since dendritogenesis and neuronal migration rely heavily on motor protein complexes and the stability of cytoskeleton. Preliminary data show that knockdown of CPE protein results in disrupted migration and altered cellular morphology in neurons in the cortical plate and decreased dendrite branching in cultured hippocampal neurons. Together, our studies provide new evidence for the role of CPE and its interactor, $p150^{Glued}$, in regulating multiple processes involved in neuronal development.

Disclosures: C. Liang: None. **D. Carrel:** None. **H. Kim:** None. **B.L. Firestein:** None.

Poster

775. Dendritic Arborization

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 775.03/A3

Topic: A.05. Axon and Dendrite Development

Support: NIH R21 MH101655

NSF DBI 14-50962 EAGER

NSF STC CBET 0939511

Title: Mir125b mediated filopodial dynamics in developing dendrites

Authors: *R. IYER[1], T. KIM[2], M. E. KANDEL[2], G. POPESCU[3,2], M. U. GILLETTE[1,3,4]; [1]Cell and Developmental Biol., Univ. of Illinois At Urbana-Champaign, Urbana, IL; [2]Electrical & Computer Engin., [3]Beckman Inst., [4]Neurosci. Program, Univ. of Illinois at Urbana Champaign, Urbana, IL

Abstract: Neurons have complex dendritic arbors, which contribute to the intricate circuitry found in the nervous system. The interplay between the intrinsic cellular machinery of neurons and external stimuli is critical for the establishment of this arbor, allowing dendrites to find their intended axonal partners. This process, however, is not well understood. Recent studies have pointed to microRNAs (miRNA), small noncoding RNAs about 22 nucleotides long, as potential sites for integration of external stimuli to changes in local protein expression. This can lead to rapid and local changes in filopodial and dendritic structures, a key requirement to navigate the spatio-temporally variant signals dendrites receive. Here we investigate the brain-abundant miRNA, miR125b, to elucidate its role in the dynamics of filopodia and the corresponding changes in filopodial and dendritic structure during development. miR125b has been shown to be maximally expressed at the developmental period corresponding to filopodial outgrowth in dendrites. We inhibit its activity in cultured neurons as dendritic filopodia explore their

microenvironment. Using a combination of confocal microscopy and high resolution image analysis we study the effect of miR125b inhibition on filopodial structure and density, dendritic outgrowth, as well as the expression and localization of a confirmed target of miR125-b: the GluN2A subunit of the NMDA receptor. Using microfluidic devices, we deliver a cell permeant inhibitor of miR125b to isolated dendrites, and study local changes in filopodial structure and GluN2A incorporation. To understand the effect of miR125b in the dynamics of filopodia, we use an innovative imaging technique, Spatial Light Interference Microscopy (SLIM), an interferometry-based, label-free, live imaging system that has topographic accuracy comparable to atomic force microscopy (Wang et al, Opt Express, 2011). Using SLIM, we characterize the rate of filopodial extension and retraction, and stability in response to miR125b inhibition. These high-resolution analyses reveal fresh insights into the process by which neurons integrate multiple external signals to establish the correct connections. Such insights are critical to understanding the implicated role of miR125b in various neurological disorders, *e.g*., Fragile X Syndrome and Alzheimer's Disease.

Disclosures: R. Iyer: None. **T. Kim:** None. **M.E. Kandel:** None. **G. Popescu:** None. **M.U. Gillette:** None.

Poster

775. Dendritic Arborization

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 775.04/A4

Topic: A.05. Axon and Dendrite Development

Support: Funded by Vicerrectoria de Investigaciones Pontificia Universidad Javeriana Grant 00004975

Funded by Vicerrectoria de Investigaciones Pontificia Universidad Javeriana Grant 00005879

Title: Effect of the flavonoids quercetin and rutin in the dendritic branching of rat cortical neurons *In vitro*

Authors: *J. J. SUTACHAN-RUBIO[1], A. F. DIAZ ELJAIEK[2], H. G. GÓMEZ JIMÉNEZ[2], M. MUÑOZ[2], M. P. LOZANO[2], S. L. ALBARRACIN CORDERO[2];
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Abstract: Recent studies have shown that activity-dependent pathways play an important role in the formation, growth and branching of dendrites. Additionally, it has been found that a

reduction in the complexity of the dendritic tree is a common feature share by neurodegenerative diseases, and different psychiatry and addiction disorders. For this reason, molecules that can impact in the signaling pathways that regulate the maintenance and complexity of dendrites may have therapeutic potential in the treatment of these diseases. Flavonoids are secondary metabolites from plants that have been shown to activate several signaling pathways that regulate the development and function of the nervous system. Although the prospective of flavonoids, there are not studies evaluating the potential of these molecules in regulating dendritogenesis. In the present work, we evaluated if the flavonoid quercetin and its glycosylated form rutin could regulate the dendritic branching of rat cortical neurons in vitro. The obtained results showed that rutin but no quercetin at low concentrations (0.1μM) increases the complexity of the dendritic tree. At higher concentrations (10 μM) neither rutin nor quercetin affects the complexity of the dendritic branching, however rutin stimulates dendritic growth. Additionally, the rutin-dependent effect on dendritic complexity was inhibited by the use of the LY294002 y PD98059 inhibitors, suggesting that rutin achieves its stimulatory effect by regulating the PI_3 and MAP kinase pathways. The obtained results suggest that glycosylated flavonoids have the potential to regulate not only the dendritic length but also the branching throughout the activation of several signaling pathways.

Disclosures: **J.J. Sutachan-Rubio:** None. **A.F. Diaz Eljaiek:** None. **H.G. Gómez Jiménez:** None. **M. Muñoz:** None. **M.P. Lozano:** None. **S.L. Albarracin Cordero:** None.

Poster

775. Dendritic Arborization

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 775.05/A5

Topic: A.05. Axon and Dendrite Development

Title: Wnt5a is essential for dendrite maintenance and cognitive functions in adult brain

Authors: ***C.-M. CHEN**[1], L. OREFICE[2], S.-L. CHIU[3], T. LEGATES[1], S. HATTAR[1], R. HUGANIR[3], H. ZHAO[1], B. XU[2], R. KURUVILLA[1];
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Abstract: The stability of neuronal connectivity is critical for brain functions, and morphological perturbations are a hallmark of neurodegenerative disorders. However, how neuronal morphology is maintained in the adult brain is not well understood. Here, we identify Wnt5a, a secreted morphogen, as an essential factor in maintaining dendritic architecture in the

adult hippocampus and for related cognitive functions in mice. Hippocampal neurons express Wnt5a, and the expression begins postnatally. Wnt5a deletion in hippocampal neurons does not compromise hippocampal development, but causes pronounced regression of dendrite arbors and spine densities in CA1 pyramidal neurons in adult life. Wnt5a loss results in attenuated CaMKII and Rac1 signaling and reduced expression of the GluN1 glutamate receptor subunit in the mature hippocampus, as well as defects in synaptic plasticity and spatial learning and memory, all of which precede the structural abnormalities. These findings identify a maintenance factor and provide insight into neuroprotective mechanisms in the adult brain.

Disclosures: C. Chen: None. **L. Orefice:** None. **S. Chiu:** None. **T. LeGates:** None. **S. Hattar:** None. **R. Huganir:** None. **H. Zhao:** None. **B. Xu:** None. **R. Kuruvilla:** None.

Poster

775. Dendritic Arborization

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 775.06/A6

Topic: A.05. Axon and Dendrite Development

Support: Edward Sai Kim Hotung Paediatric Education and Research Fund

Seed Funding from the University of Hong Kong

Postgraduate Studentship from the University of Hong Kong

Edward & Yolanda Wong Scholarship

Title: LRRC7 regulates neurite morphogenesis through mGluR5

Authors: *C. CHONG[1], C. NG[1], H. MAK[1], Q. LI[2], G. MCALONAN[3], S. CHAN[1]; [1]Paediatrics and Adolescent Med., [2]Psychiatry, The Univ. of Hong Kong, Hong Kong, Hong Kong; [3]Forensic & Neurodevelopmental Sci., King's Col. London, London, United Kingdom

Abstract: *LRRC7 (Leucine-rich repeat containing 7)* encodes for Densin-180, a scaffold protein in the postsynaptic density. *LRRC7* has been reported as a risk allele for childhood emotional dysregulation and autism spectrum disorder. Knockout mice were reported to have defects related to metal illnesses and abnormal dendritic spine development. To further define the role of LRRC7 in behavioural control, we made use of our transgenic mice line carrying a hypomorphic allele of *Lrrc7*. Mutant mice exhibited features of childhood emotional dysregulation, including excessive following and fighting at juvenile stage. Behavioural tests in young adults confirmed increased anxiety, abnormal social behavior and defective spatial working memory in mutants.

To reveal the molecular defects, we examined the dendritic complexity of hippocampal neurons in adult brain and in primary neurons from embryos. Mutant mice showed reduced dendritic complexity in both cases. Using primary neurons, we demonstrated that there was a reduced surface localization of mGlu5 receptor. Furthermore, augmentation of mGlu5 with CDPPB rescued the defects of neurite growth. To test for therapeutic potential of augmenting mGlu5 signaling in developmental emotional dysregulation, we tried acute injection of CDPPB and found that the treatment could alleviate the anxiety-like behavior and excessive social interaction of mutant mice. Our data suggested that *Lrrc7* mutant mice provide a valuable model for developmental emotional dysregulation and identify a novel role of LRRC7 as a scaffold for the regulation of mGlu5 trafficking and activity. Our data also highlight a novel role of mGlu5 signaling in early neuron morphogenesis.

Disclosures: C. Chong: None. **C. Ng:** None. **H. Mak:** None. **Q. Li:** None. **G. McAlonan:** None. **S. Chan:** None.

Poster

775. Dendritic Arborization

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 775.07/A7

Topic: A.05. Axon and Dendrite Development

Support: NSF Grant IOS-1353724

1K12 GM093854

Title: Using small peptides to study protein interactions and dendrite branching

Authors: *H. MENON[1], J. ROSHAL[1], H. M. CHAPMAN[2], T. L. WANG[2], M. R. SPALLER[2], B. L. FIRESTEIN[1];
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Abstract: Appropriate dendritic patterning is essential for proper development of neuronal circuitry. Interestingly, a number of neuropsychiatric diseases, such as autism, schizophrenia and Alzheimer's disease, display abnormal dendritic branching. We previously reported that the protein cypin (cytosolic PSD-95 interactor) plays a key role in dendritic arborization. The interaction between cypin and PSD-95, via cypin binding to the first two PDZ domains of PSD-95, is essential for the promotion of stable dendrites. Cypin is a positive regulator of dendrite branching while PSD-95 inhibits dendrite branching. To test the importance of binding partners

to the PDZ domains of PSD-95 in the regulation of dendritogenesis, we characterized a set of small peptides that specifically bind to the PDZ domains of PSD-95. Our co-immunoprecipitation studies showed competition between cypin and a subset of the compounds for binding to PSD-95. Interestingly, a slightly different subset of compounds altered dendritic branching in cultured rat hippocampal neurons. This suggests that the observed branching phenotype is due to interaction of PSD-95 with a protein/s different than cypin. We are currently testing candidate proteins that interact with PSD-95 to determine whether they play a role role in dendritogenesis. Our studies will allow us to understand how the dendritic tree is shaped and elucidate potential therapies for disorders that show aberrant dendrite patterning and numbers.

Disclosures: H. Menon: None. **J. Roshal:** None. **H.M. Chapman:** None. **T.L. Wang:** None. **M.R. Spaller:** None. **B.L. Firestein:** None.

Poster

775. Dendritic Arborization

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 775.08/A8

Topic: A.05. Axon and Dendrite Development

Support: K01MH101639

R01NS065856

Title: Elucidating the mechanism by which the GTPase Rem2 negatively regulates dendritic complexity

Authors: *K. M. KENNY, L. ROYER, A. R. MOORE, S. PARADIS;
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Abstract: Neurons in the mammalian CNS have a distinctive dendritic arbor, which is typically extensively branched, and this arbor influences the specific function of the neuron in part by ensuring that the proper synaptic connections are made within neural circuits. In addition, the nervous system has the amazing capacity to transform sensory experience from the environment into changes in neuronal activity that, in turn, cause long-lasting alterations in synaptic connections and dendritic arborization, Surprisingly little is known about the molecular mechanisms by which changes in neuronal activity are translated into changes in neuronal architecture.
We have identified Rem2, a member of the Rad/Rem/Rem2/Gem/Kir (RGK) family of small Ras-like GTPases, as an activity dependent negative regulator of dendritic complexity. Neurons

in which the Rem2 gene has been knocked down exhibit a dramatically increased dendritic arbor. Additionally, when Rem2 is overexpressed in neurons, they are unable to increase their dendritic arbor in response to increased neuronal activity. Taken together, these data indicate that Rem2 functions to restrict the dendritic arbor in response to experience.
We have placed Rem2 in a signal cascade downstream of Ca(2+)/Calmodulin-dependent kinase II (CaMKII) and upstream of CaMKIV to regulate dendritic complexity. We found that Rem2 is a direct substrate for CaMKII phosphorylation at serine 241 and 308; phosphorylation at these sites regulates Rem2 nuclear abundance. When we constitutively localize Rem2 to the nucleus, we observe significant decrease in dendritic complexity compared to control neurons, indicating that the function of nuclear Rem2 is to restrict dendritic arborization. Thus, we hypothesize that nuclear Rem2 regulates gene expression, possibly by mediating the activity of CaMKIV and its downstream target, the CREB transcription factor. As a first step towards investigating this hypothesis, we took an unbiased approach using mRNA sequencing to identify Rem2 dependent changes in gene expression. We are currently working to validate the hits from the mRNA sequencing to determine whether they could be novel regulators of dendritic complexity.

Disclosures: **K.M. Kenny:** None. **L. Royer:** None. **A.R. Moore:** None. **S. Paradis:** None.

Poster

775. Dendritic Arborization

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 775.09/A9

Topic: A.05. Axon and Dendrite Development

Support: Hussman Foundation HIAS15003

Title: Autism-associated mutation of syntaxin binding protein 5 disrupts dendrite arborization

Authors: *W. SHEN, Y.-C. LIN;
Hussman Inst. For Autism, Baltimore, MD

Abstract: Autism is a neurological condition that characterizes marked qualitative differences in communication and social interaction. As many as 1/3 of individuals with autism spectrum condition also have epilepsy. Consistent with the extremely heterogeneous presentation of autism, genetic studies have implicated numerous genes that may contribute to the autism phenotype. Deletion and mutations of syntaxin binding protein 5 (STXBP5, also known as tomosyn) are identified in association with autism and epilepsy. STXBP5/tomosyn is a syntaxin binding protein that contains a WD40 domain at the N-terminus and a SNARE motif at the C-terminus. STXBP5/tomosyn has a presynaptic role that negatively regulates neurotransmitter

release by forming syntaxin-SNAP25-tomosyn complex. STXBP5/tomosyn has also been shown to regulate neurite outgrowth in immature neurons. WD40 as scaffolding domains, have a variety of functions such as signal transduction and vesicle trafficking. Interestingly, two autism-associated variants of *STXBP5* exhibit missense mutations at the WD40 domain. Here, we hypothesize that the autism-associated STXBP5/tomosyn mutants affect dendrite arborization by regulating vesicle trafficking. To test this hypothesis, we first determined the subcellular localization of wildtype (WT) and mutant STXBP5/tomosyn in cultured hippocampal neurons. We transfected cultured neurons with GFP-tagged WT-tomosyn as well as two autism-associated tomosyn mutants. We found that WT- and mutant tomosyn all localize to axons, dendrites and dendritic spines. Overexpression of WT-tomosyn increased dendritic arbor complexity by increasing total dendrite length and branch tip number, compared to control neurons. The autism-associated tomosyn mutant failed to induce the dendrite complexity when compared to the WT-tomosyn. In conclusion, STXBP5/tomosyn plays a role in regulating dendrite arborization. Mutations of *STXBP5* found in individuals with autism may alter dendrite arborization and potentially disrupt normal developmental processes in the brain.

Disclosures: **W. Shen:** None. **Y. Lin:** None.

Poster

775. Dendritic Arborization

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 775.10/A10

Topic: A.05. Axon and Dendrite Development

Support: CIHR Grant MOP142215

The Scottish Rite Charitable Foundation of Canada

NSERC Discovery Grant

University of Victoria Division of Medical Sciences

Michael Smith Foundation for Health Research Scholar Award

British Columbia Schizophrenia Society Foundation Scholar Award

NSERC studentship support

Title: Pannexin 1 regulation of neurite development: molecular mechanisms

Authors: *L. SWAYNE, A. K. J. BOYCE, L. E. WICKI-STORDEUR, J. C. SANCHEZ-ARIAS;
Med. Sci., Univ. of Victoria, Victoria, BC, Canada

Abstract: Peak expression of the Pannexin 1 (Panx1) ion and metabolite channel in neurons coincides with critical periods in dendritic spine development. Foundational in vitro studies in our lab have established that Panx1 regulates neurite outgrowth. To begin to unravel the specific molecular mechanisms involved, we examined Panx1 protein interactions that we discovered using an unbiased proteomic approach. We focused primarily on Collapsin Response Mediator Protein 2 (Crmp2), a cytoskeleton-regulating protein. We confirmed an association between Panx1 and Crmp2 in vitro and in vivo and mapped the interaction site to the distal C-terminus of Panx1. To probe the role of this interaction in neurite outgrowth, we next used a cell-permeable peptide of the interaction site (CT3) in our experimental models (in vitro: neurite outgrowth in cultured neural cells assayed by Incucyte live cell kinetic imaging, in vivo: dendritic spines of layer 5 cortical neurons by Diolistic labeling in early postnatal mouse brain). Treatment with CT3 enhanced neurite outgrowth both in vitro and in vivo. We further probed the precise mechanisms with supportive imaging and biochemical studies focusing on cytoskeletal dynamics. In summary, here we present several novel findings that expand our understanding of the molecular players underlying the cellular role of Panx1 in neurite development in the brain.

Disclosures: L. Swayne: None. **A.K.J. Boyce:** None. **L.E. Wicki-Stordeur:** None. **J.C. Sanchez-Arias:** None.

Poster

775. Dendritic Arborization

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 775.11/A11

Topic: A.05. Axon and Dendrite Development

Support: NIH Grant RO1EY018605

NIH Grant T32NS051112

NIH Grant F32EY021942

Title: Dscam promotes self-avoidance in neurodevelopment by masking diverse cell adhesion molecules

Authors: *A. M. GARRETT[1], A. L. D. TADENEV[1], A. KHALIL[2], P. G. FUERST[3], R. W. BURGESS[1];

[1]The Jackson Lab., Bar Harbor, ME; [2]CompuMAINE Lab., Univ. of Maine, Orono, ME; [3]Dept. of Biol. Sci., Univ. of Idaho, Moscow, ID

Abstract: During development, neurons balance attractive and repulsive signals to properly position cell bodies and neurites, and to form synapses with appropriate partners. The Dscams (from Down syndrome cell adhesion molecule) are Ig-superfamily members important for self-avoidance. *Drosophila Dscam1* promotes self-avoidance by generating up to 19,008 strongly homophilic isoforms, providing a code by which neurites can recognize and actively repel those from the same cell while still interacting with neighboring cells. Mammalian Dscams - *Dscam* and *Dscaml1* - serve a similar function without extensive isoform diversity. In the retina, mutant neurons of a given subtype form tight dendritic fascicles and lose their non-random mosaic spacing as their cell bodies pull into clumps. These clumps are homotypic, indicating that a shared cell-type identity promotes this interaction. Reasoning that this self-avoidance was likely to involve intracellular signaling common to both DSCAM and DSCAML1, we chose to focus on the C-terminal PDZ-interacting domain: The sequences encoding the final ten amino acids of both DSCAM and DSCAML1 were replaced by epitope tag sequences to eliminate the canonical PDZ-interacting domains. These mutations completely recapitulated the null phenotypes in some cell types, but left others relatively unaffected, leading us to hypothesize that Dscams mask cell-type-specific repertoires of CAMs in different cell types to prevent excessive adhesion, and that the PDZ-interacting domain is required to mask only some of these classes of CAMs. To test this, we focused on retinal ganglion cells labeled in *Cdh3-GFP* transgenic mice, a population that depends on DSCAM for self-avoidance and expresses a known repertoire of CAMs including *Cdh3* and *Cdh6*. We reasoned that if excessive adhesion provided by these Cadherins was normally masked by DSCAM, but was mediating unbalanced adhesion in our *Dscam* mutants, then Cadherin/ *Dscam* double-mutants would partially rescue the fasciculation phenotype. We quantified fasciculation via a novel image analysis approach in these double-mutants, and found that indeed there is reduced fasciculation compared to *Dscam* null mice. We found a similar reduction in fasciculation of melanopsin-positive ipRGCs in mice mutant for both *Dscam* and the *Pcdhg* cluster, indicating that DSCAM can mask diverse adhesion systems. We are currently testing other candidate adhesion systems in other cell types to ask if making double mutants with Dscam and PDZ-interacting CAMs can rescue fasciculation in cell types that require the PDZ interaction.

Disclosures: **A.M. Garrett:** None. **A.L.D. Tadenev:** None. **A. Khalil:** None. **P.G. Fuerst:** None. **R.W. Burgess:** None.

Poster

775. Dendritic Arborization

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 775.12/A12

Topic: A.05. Axon and Dendrite Development

Support: NSERC Discovery Grant

CIHR Grant MOP142215

The Scottish Rite Charitable Foundation of Canada

University of Victoria Division of Medical Sciences

Michael Smith Foundation for Health Research Scholar Award

British Columbia Schizophrenia Society Foundation Scholar Award

University of Victoria Fellowship Graduate Award

Title: A pannexin 1 blocker modulates the development of dendritic spines in the postnatal cerebral cortex

Authors: *J. C. SÁNCHEZ-ARIAS[1], L. E. WICKI-STORDEUR[1], L. A. SWAYNE[1,2];
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Abstract: Probenecid is an approved drug used for the treatment of gout, and has also recently become recognized as a blocker of Pannexin 1 (Panx1) ion and metabolite permeable channels. We recently demonstrated that Panx1 is essential for neural precursor cell (NPC) maintenance (Wicki-Stordeur, Sanchez-Arias et al., J Neurosci, 2016) and also that Panx1 negatively regulates neurite outgrowth in NPCs (Wicki-Stordeur and Swayne, Cell Commun Signal, 2013). NPCs and Neuro2a cells treated with Probenecid exhibited a dramatic increase in neurite extension. Panx1 has been localized to cell bodies as well as the post-synaptic membrane. In the cortex, Panx1 is relatively highly expressed in the early postnatal period and then drops off rapidly (highest at postnatal day 0 (P0) and dropping off after P10). This expression profile is closely associated with critical periods in the formation of dendritic spines and synapses. Taken together, these data led us to hypothesize that Panx1 plays a role in the development of dendritic spines, a process that occurs during the early postnatal period. To begin to investigate the role of Panx1 in the development of dendritic spines in vivo, we treated young male and female wildtype mice (C57BL/6J) with either Probenecid or Normal Saline (control) for discrete periods of time, with one group (n=20) receiving chronic treatment (every third day from P7 to P13); and a second

group (n=20) receiving exclusively an acute treatment at P13. Animals were sacrificed 24 hours after the last injection (P14), and we performed diolistic labelling (DiI) of the apical dendrites of Layer 5 Primary Somatosensory Cortex pyramidal neurons. Chronic Probenecid treatment resulted in a significant increase in length and number of spines (spine density) in both male and female treatment groups when compared to the control treatment groups. On the other hand, acute probenecid treatment resulted only in a significant total increase in spine density in the treatment groups (with no differences in length). Our results suggest Panx1 could play an important role in the development of dendritic spines in the cerebral cortex. These findings taken together with our recent work further establish Panx1 as an important modulator of developmental plasticity.

Disclosures: J.C. Sánchez-Arias: None. **L.E. Wicki-Stordeur:** None. **L.A. Swayne:** None.

Poster

775. Dendritic Arborization

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 775.13/A13

Topic: A.05. Axon and Dendrite Development

Support: Drexel University, Department of Neurobiology and Anatomy Startup Funds

Title: Regulation of neuronal morphogenesis by 14-3-3epsilon (Ywhae) via the microtubule binding protein, doublecortin

Authors: *B. T. CORNELL, W. TOMOKA, V. ZHUKAREV, K. TOYO-OKA;
Neurosci., Drexel Univ. Col. of Med., Philadelphia, PA

Abstract: 17p13.3 Microduplication Syndrome is a newly identified genetic disorder and is characterized by various sized gene duplications in the 17p13.3 chromosome locus resulting in autism spectrum disorder (ASD), epilepsy and mental retardation. Importantly, a minimum duplication region strongly associated with the ASD phenotype has been classified and this 72kb region exclusively contains the gene encoding the protein 14-3-3ε, strongly implicating the overexpression of 14-3-3ε in ASD. In this work, through the use of *in vivo* and *in vitro* techniques, we have found that 14-3-3ε binds the microtubule binding protein Doublecortin in a phosphorylation specific manner and prevents its degradation resulting in an increase in Doublecortin protein levels. We also found that 14-3-3ε overexpression severely disrupts neurite formation by preventing the invasion of microtubules into primitive neurites, and this is rescued by the knockdown of Doublecortin in 14-3-3ε overexpressing neurons. Furthermore, using 14-3-3ε flox mice we found that the spatiotemporal deficiency of 14-3-3ε results in an increase in

neurite formation. Our findings provide the first evidence of cellular pathology in 17p13.3 Microduplication Syndrome.

Disclosures: B.T. Cornell: None. **W. Tomoka:** None. **V. Zhukarev:** None. **K. Toyo-oka:** None.

Poster

775. Dendritic Arborization

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 775.14/B1

Topic: A.05. Axon and Dendrite Development

Support: NSF IGERT 0965918

NSF STC EBICS CBET 0939511

NSF CBET 1040462

NSF EAGER DBI 1450962

NIH R21 MH101655

Title: Femtogram-level analysis of mass-change dynamics in filopodia on the tips and shafts of developing dendrites in response to semaphorin3A

Authors: *A. JAIN[1], T. KIM[2], G. POPESCU[2], M. U. GILLETTE[1];
[1]Dept. of Cell and Develop. Biol., [2]Electrical & Computer Engin., Univ. of Illinois at Urbana-Champaign, Urbana, IL

Abstract: The intricate wiring of the nervous system relies on filopodial navigation to form complex interconnections between neurons through their axons, dendrites, and the cell soma itself. Until recently, cellular investigations into filopodial dynamics had focused primarily on axonal growth cone filopodia. Spurred by technological advances, scientists have now begun to explore the structural and functional landscape of dendritic filopodia. Here we investigate the role of Sema3A in guiding dendritic morphogenesis, spinogenesis, and synaptogenesis. We show that it acts not only at the level of the dendrites, promoting neurite survival and growth, but also at the level of the filopodia. Since there has been some evidence indicating a difference in filopodia borne along dendrite tips *vs.* those borne along dendrite shafts, we treat the two populations as distinct and tease apart their different responses. Structural analyses of numbers, lengths, and locations are complemented by studies of dynamic functional aspects, such as

growth and shrinkage rates detected as mass changes in individual filopodia. This is made possible through Spatial Light Interference Microscopy (SLIM), an innovative quantitative phase imaging method for high-resolution, label-free imaging of live cells through interferometry (Wang *et al.*, *Opt. Express*, 2011). SLIM permits measurement of the dry mass of live neurons at femtogram levels (Mir *et al.*, *Sci. Rep*., 2014). This convergence of filopodial investigations and the technology for engineering micro-environments, when coupled with high resolution imaging and analysis, enabled new insights on local signals, including Sema3A, that initiate and establish neuron-neuron interactions at the filopodial level. A greater comprehension of such processes that shape the development of neuronal networks is helping unravel the mechanistic bases of developmental disorders and diseases.

Disclosures: **A. Jain:** None. **T. Kim:** None. **G. Popescu:** None. **M.U. Gillette:** None.

Poster

775. Dendritic Arborization

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 775.15/B2

Topic: A.05. Axon and Dendrite Development

Support: Hampden-Sydney College Honors Research Fellowship

Randolph-Macon College Craigie Research Grants

Title: Effects of an early postnatal intoxication event on medium spiny neuron morphology throughout mouse development

Authors: *J. INGERSOLL, E. B. D. CLABOUGH;
Biol., Hampden-Sydney Col., Farmville, VA

Abstract: Prenatal alcohol exposure can result in the emergence of a broad spectrum of anatomical or neurological abnormalities termed Fetal Alcohol Spectrum Disorders (FASD). The effects of ethanol exposure during development depend on the timing of exposure, as ethanol interrupts the specific brain development processes that are ongoing at the time of exposure. The severity of dysfunction varies with the dosage level of ethanol and, importantly, whether the dosage is chronic or acute. We investigated the effects of a single postnatal intoxication event on neuronal development in mice. We characterize the immediate effects of the ethanol exposure on the branching of the neurons in the striatum, but also examined the long term effects throughout development. Animals were exposed to brief, high levels of ethanol during the early postnatal period (during the most robust period of synaptogenesis). Mice were administered 2 doses of

ethanol (2.5 g/kg) on postnatal day 5 (P5) two hours apart. Brains were removed and processed for Golgi-Cox staining in order to capture the cellular morphological response to the insult after one day or after five months. These data find immediate alterations in the branching morphology of MSNs as a consequence of neonatal exposure to ethanol. The results enhance not just our understanding about the impact of toxins on neurons, but also highlights the dynamic nature of dendritic branching in the neuron. In addition, basic research on striatal MSNs is of interest to many fields, as the striatum is involved not only with the execution of complex motor skills, but also regulates aspects of long-term learning and addictive behavior.

Disclosures: J. Ingersoll: None. **E.B.D. Clabough:** None.

Poster

775. Dendritic Arborization

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 775.16/B3

Topic: A.05. Axon and Dendrite Development

Title: Comparison of Matrigel® and Poly-D-Lysine as plating matrix for mouse embryonic neuronal cell cultures and their effect on cell growth

Authors: *E. SEKERDAG, Y. CETIN TAS, G. NUR SAHIN, S. KARAHUSEYINOGLU, I. SOLAROGLU, Y. GURSOY-OZDEMIR;
Neurosci., Koç Univ., Istanbul, Turkey

Abstract: Aim: Extracellular matrix is important in the field of 2D and 3D cell culture techniques. Depending on the chosen culture matrix, cells can grow and differentiate in different manners, as fits most properly in the goal of the cell culture experiment. Our aim is to investigate and compare the cell growth manners of primary cortical neuron cells plated in poly-D-lysine (PDL) and matrigel culture matrices in order to obtain the most suitable culture condition for further studies.
Methods: Glass coverslips were coated by incubating the coverslips in 1 mL of 100 µg/mL of PDL solution or Matrigel® (BD) solution (dilution according to the manufacturer's protocol) overnight at 4 °C. PDL coated coverslips were directly used (without drying) for cell plating after washing twice with sterile distilled water. Coverslips incubated in matrigel solution were incubated for 1 hour at 37 °C, and cells were directly plated after removal of the matrigel solution. Primary cortical neuron cells were prepared from E17 mouse pups according to a modified protocol as described elsewhere [1]. At DIV3-14's, cultured neurons plated in both PDL and matrigel groups were fixed in 4% paraformaldehyde or 2.5% glutaraldehyde solution for immunofluorescence and SEM analysis, respectively. Immunofluorescent (IF) stainings,

Western blot and PCR analysis were performed and analyzed for antibodies against GFAP, Neu-N, Caspase-3 and NG2.
Results & Conclusion: According to preliminary data, neuronal cell cultures had a higher dimensional network in matrigel coated matrix compared to PDL coated matrix. Moreover, the axons were more tight, thick and linear compared to neuronal axons on PDL coated matrix. Axonal bundling and maturation which developed between groups of neurons, confirmed by both live-unstained cultures and cytoskeletal and neuron-specific IF stainings documented by 3D images, supported that this structure would posses a more 3D effect in vitro, hence may mimic a more physiological condition compared to conventional neuronal cultures and PDL-coated matrix enhanced neuronal cultures.
1. Lesuisse, C. and L.J. Martin, *Long-term culture of mouse cortical neurons as a model for neuronal development, aging, and death.* Journal of Neurobiology, 2002. **51**(1): p. 9-23.

Disclosures: E. Sekerdag: None. **Y. Cetin Tas:** None. **G. Nur Sahin:** None. **S. Karahuseyinoglu:** None. **I. Solaroglu:** None. **Y. Gursoy-Ozdemir:** None.

Poster

775. Dendritic Arborization

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 775.17/B4

Topic: A.05. Axon and Dendrite Development

Support: National Natural Science Foundation of China (No. 31271176)

Title: Histone deacetylase 1 regulates neuronal structure and function via bdnf signaling in developing xenopus tectum *In vivo*

Authors: *W. SHEN[1], H. RUAN[2], Y. TAO[3], J. GAO[2], X. QI[2], X. GUO[2];
[1]Col. of Life and Envrn. Sci., Hangzhou Normal Univ., Zhejiang, China; [2]Hangzhou Normal Univ., HANGZHOU, China; [3]Nanjing Med. Univ. Affiliated Jiangsu Cancer Hosp., Nanjing, China

Abstract: Histone deacetylases (HDAC) are predominantly localized to the cell nuclei and play pivotal roles in brain formation and neurological diseases as a gene transcription repressor. Several studies have shown that application of broad-spectrum HDAC inhibitors can improve the deficits in learning and memory. Histone deacetylase 1 (HDAC1) is thought to play pivotal roles in neurogenesis and neurodegeneration. However, the role of HDAC1 in neuronal growth and structural plasticity in the developing brain in vivo remains unclear. In the present study, we examined the role of HDAC1 in excitatory and inhibitory synaptic transmission and experience-

dependent structural plasticity by knockdown or overexpression of HDAC1 in Xenopus optic tectal neurons in vivo. We made molecular tools of HDAC1-GFP for overexpression and HDAC1 morpholino (HDAC1-MO) for knockdown. Here, we show that HDAC1 knockdown dramatically decreases AMPAR-mediated synaptic currents and increases GABAAR-mediated currents, whereas HDAC1 overexpression significantly decreases the frequency of GABAAR-mediated synaptic currents. We find that HDAC1 activity is also critical for dendritic arbor growth and visual experience-dependent structural plasticity. We show that overexpression or knockdown of HDAC1 activity decreases dendritic arbor growth and visual experience-dependent structural plasticity. Interestingly, knockdown of HDAC1 but not of HDAC2/HDAC3 decreases the expression of BDNF. Epigenetic modification of histone has been shown to participate in synaptic plasticity and learning memory. We report that HDAC1 knockdown significantly increases the activity of histone acetylation (H4K5), which is partially rescued by acute BDNF treatment in the HDAC1-MO tadpoles. In particular, the deficits in dendritic growth and visually guided avoidance behavior in HDAC1-knockdown tadpoles are also rescued by acute treatment with recombinant BDNF. Our data establish an essential roles for HDAC1 and BDNF signaling in the regulation of dendritic growth, structural plasticity and function in intact animals in vivo.

Disclosures: **W. Shen:** None. **H. Ruan:** None. **Y. Tao:** None. **J. Gao:** None. **X. Qi:** None. **X. Guo:** None.

Poster

775. Dendritic Arborization

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 775.18/B5

Topic: A.05. Axon and Dendrite Development

Support: NSF Grant 1355045

Title: Expression of a null mutation gap junction protein during development results in neuronal arbor loss.

Authors: I. V. KATRITCH, D. DE GUZMAN, *E. R. MACAGNO, M. W. BAKER;
Div. Biol. Sci., Univ. of California San Diego Div. of Biol. Sci., La Jolla, CA

Abstract: The unique morphologies and patterns of connections made by neurons during development arises in part by an extended period of growth in which cell-cell interactions help to sculpt the arbor into its final shape, size, and participation with different synaptic networks. Here we examine the role of the gap junctions (GJs) in forming the neural arbor of a sensory neuron in

the medicinal leech *Hirudo Verbana*. Using a dominant-negative point mutation transgene (Inx1-PL; Yazdani et al., 2013 Dev. Neurobiol.73), we selectively knocked down innexin 1-based GJ formation in single dorsal Touch neurons (T_D) using intracellular nuclear transgene injection in leeches from mid-embryonic development onwards. Cells co-expressing EGFP were imaged 10 to 20 days later, and digitally reconstructed in 3D.
Initial observations of cells 20 days later, at the juvenile stage, knockdown cells, when compared to intracellular dye-injections and neurons expressing the wild-type innexin 1 transgene, developed a much sparser neural arbor, with a ~92% decrease in branch points, ~51% shorter total neurite path length, and a ~90% decrease in varicosities. On the other hand, both Inx1-PL cells and control cells, when imaged after only 10 days, had an extensive arbor, with a ~50% increase in branch points and ~43% increase in total neurite path length as compared to the control cells from the 20 day time point. This pattern of exuberant growth followed by a later retraction of branches without GJ formation suggests that electrical synapses are necessary for arbor stabilization during a critical period in the neurons development (Todd et al., 2010 J. Neurosci. 30).
Ongoing experiments will test whether the arbor is stabilized by electrical activity by overexpressing a voltage-gated potassium channel in the T_D as a means of reducing electrical activity in the cell. Additionally, if GJs and their cellular distribution help sculpt neuronal arbors, we will test if we can alter the T_D's arbor by ectopically expressing different leech innexin genes in the cell and thereby promote the formation of new synaptic connections and observe the effects on the development of the cell's arbor.

Disclosures: I.V. Katritch: None. **D. de Guzman:** None. **E.R. Macagno:** None. **M.W. Baker:** None.

Poster

775. Dendritic Arborization

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 775.19/B6

Topic: A.05. Axon and Dendrite Development

Support: NIH Grant EY011912

NSF predoctoral award to R.A. Santos

Title: Retinotectal circuit arbor remodeling through DSCAM knockdown *In vivo*

Authors: R. A. SANTOS, G. SHORT, *S. COHEN-CORY;
Neurobio. and Behavior, Univ. of California Irvine, Irvine, CA

Abstract: Wiring functional neural circuits during embryonic development requires coordinated organization between developing axon and dendritic arbors. The spatial pattern of dendritic branching is critical to the neuron's input connectivity so that incoming information from afferent axons is efficiently integrated. Although neurons can adopt an array of dendritic patterns to suit their input connectivity, dendrites of an individual neuron commonly self-avoid. Presynaptic axon arbors also exhibit patterned branching and self-avoidance as they innervate their targets. Down Syndrome Cell Adhesion Molecules (DSCAMs) have been shown to play key roles in dendrite and axon self-avoidance in Drosophila and other species. How DSCAM influences axon to dendrite interconnectivity in developing vertebrate neural circuits remains unknown. In this study, we utilized *Xenopus laevis* as a model to examine developmental effects of DSCAM *in vivo* and provide a unique temporal and spatial understanding of how visual circuits are dynamically shaped. In *Xenopus*, DSCAM immunoreactivity was localized to retinal ganglion cells (RGCs), midbrain neurons and tectal neuropil, at the time that retinotectal connections are made. To define cell-autonomous, cellular actions of DSCAM during pre- and postsynaptic neuron differentiation, we used single-cell loss-of-function approaches and analyzed changes in RGC axon targeting and branching and in tectal neuron dendrite elaboration through dynamic two-photon *in vivo* microscopy imaging. Single-cell electroporation of morpholino antisense oligonucleotides (MOs) to DSCAM together with Alexa-fluor 488 dextran in stage 43 *Xenopus* retina showed that RGC axons path find normally to the neuropil, but that their arbors exhibit abnormal branching patterns when compared to axons from control MO transfected RGCs. Conversely, single-cell DSCAM MO knockdown in tectal neurons did not impair dendrite self-avoidance. Rather, tectal neurons exhibited exuberant dendritic arbor growth within 24 hours of single-cell DSCAM MO transfection, an effect that became more robust over a three-day period of imaging. Together, our observations implicate DSCAM in the control of both pre- and postsynaptic neuronal cytoarchitecture and connectivity in the retinotectal circuit, whereby it primarily acts as a neuronal brake to limit and guide postsynaptic neuron dendrite growth. How these cell-autonomous changes in structural connectivity, as mediated by DSCAM, influence normal visual circuit function is an important question that is currently being investigated.

Disclosures: **R.A. Santos:** None. **G. Short:** None. **S. Cohen-Cory:** None.

Poster

775. Dendritic Arborization

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 775.20/B7

Topic: A.05. Axon and Dendrite Development

Support: The National Program on Key Basic Research Project of China(973 Program,2014CB542205)

The National Science Foundation for Distinguished Young Scholars of China (31200826)

Title: Celsr2 regulates neuronal dendritic development and neural function

Authors: *L. CHEN[1], Y. HUANG[3], J. HU[2], J. DUAN[2], Y. QU[2];
[1]Jinan Univ., Guangdong, China; [2]Jinan Univ., Guangzhou, China; [3]Hongkong Univ., HongKong, China

Abstract: The seven-pass cadherin *Celsr2* is one of the core PCP proteins, whose ortholog Flamingo regulates dendrite development in Drosophila. *Celsr2* is expressed both in neural precursors and posmitotic cells, and the expression of *Celsr2* persists in the adult brain. Here, we studied neuronal dendritic development and neural function in *Celsr2* mutant mice. Defective neurite growth is observed in primary neuronal culture, and live cell imaging shows *Celsr2* affects neurite appearance. Increased spine formation is found in *Celsr2* mutant mice by in vivo two-photon imaging. Celsr2 mutant mice display cognitive deficits in several behavior tests.

Disclosures: L. Chen: None. **Y. Huang:** None. **J. Hu:** None. **J. Duan:** None. **Y. Qu:** None.

Poster

775. Dendritic Arborization

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 775.21/B8

Topic: A.05. Axon and Dendrite Development

Support: NIH R21 NS088943

Title: Adult hippocampal neurogenesis and its regulation by components of FGF signaling

Authors: *M. GRONSKA[1], M. SCHACHNER[2], J. HEBERT[1];
[1]Albert Einstein Col. of Med., Bronx, NY; [2]Rutgers Univ., Piscataway, NJ

Abstract: Adult neurogenesis is a process of high interest due to the ability of newborn cells to integrate into the existing adult hippocampal circuits. Identification of the molecular pathways that determine different steps in the generation and maturation of newborn neurons would facilitate using adult neural stem cells (ANSC) to treat multiple brain disorders. We previously showed that loss of Fibroblast Growth Factor Receptors (FGFRs) 1-3 in ANSCs decreases cell

proliferation and dendritic elaboration. However, the identities of downstream components of the FGFRs in adult neurogenesis are unknown. In addition, FGFRs' interaction with non-canonical upstream ligands such as L1CAM, a cell adhesion molecule, previously shown in cell culture to interact with FGFRs to promote neurite extension is unknown. We are determining how cell proliferation and dendritic elaboration in the adult dentate gyrus (DG) are affected in FGFR conditional mutant mice that lack binding sites for the downstream mediators phospholipase-C gamma (PLCγ) or Fgf receptor substrate (FRS), and in L1CAM conditional mutant mice. In addition, we will test the consequences of the mutations on learning and memory in hippocampus-related tasks. Our data suggest that FRS- and PLCγ-mediated FGFR signaling is required for cell proliferation and dendrite elaboration. We are also testing whether L1CAM acts in a cell-type autonomous or non-autonomous manner to promote dendritogenesis in the DG. Determining which intra- and extracellular pathways deferentially affect hippocampal learning and memory will not only provide a better understanding of adult neurogenesis but will also provide targets for reversing deficiencies in this process, which leads to age-related memory decline.

Disclosures: **M. Gronska:** None. **M. Schachner:** None. **J. Hebert:** None.

Poster

775. Dendritic Arborization

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 775.22/B9

Topic: A.05. Axon and Dendrite Development

Support: UK BBSRC BB/G530233/1

German BBF 01GQ1406

Title: Properties of optimally tapered dendrites

Authors: ***A. D. BIRD**[1,2], H. CUNTZ[1,2];
[1]FIAS, Frankfurt, Germany; [2]Ernst Strungmann Inst. for Neurosci., Frankfurt, Germany

Abstract: Somatic integration of synaptic inputs relies on the propagation of currents arising from sources across the dendritic tree. Whilst active processes strongly contribute to current flow in most neurons, understanding the passive backbone to transmission allows a better intuitive grasp of dendritic function; the results of Rall in highlighting the properties of cylindrical dendrites are of foundational importance in compartmental modelling and computational neuroscience. Dendrites are, however, not generally cylindrical; they tend to taper in a way that

contributes to the normalisation of input currents towards the soma and which has a number of other potentially important computational effects.
We have recently derived an asymptotic approximation to the voltage in dendrites with an arbitrary taper profile using the insight that voltage attenuation is substantially faster than radius change in realistic morphologies. This result allows faster computation and greater insight than standard approaches using large numbers of cylinders or frusta to numerically compute voltage profiles. In addition, it provides easy generalisations of the standard results of cable theory involving transients and branches. In particular, our result allows the optimal dendritic taper profile for the propagation of synaptic currents towards the soma to be determined analytically. The optimal form has been shown to match results from non-parametric numerical optimization which predicted a quadratic form for the diameter taper.
We have further shown analytically the effects of optimal taper on a number of other important dendritic phenomena, including a more general robustness in response to morphological changes and increased sensitivity to distributed inhibitory input.

Disclosures: **A.D. Bird:** None. **H. Cuntz:** None.

Poster

775. Dendritic Arborization

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 775.23/B10

Topic: A.05. Axon and Dendrite Development

Title: Dendrite remodeling in the developing olfactory circuits

Authors: ***K. TOGASHI**, S. TAKEUCHI, H. KOIZUMI, K. EMOTO;
Dept. of Biol. Sciences, Grad. Sch. of Sci., The Univ. of Tokyo, Tokyo, Japan

Abstract: In the central nervous system, neuronal circuits are dynamically remodeled during the perinatal ages to establish functional circuits. In the mammalian olfactory bulb, mitral cells initially extend redundant dendrites radially from each cell body. After birth, excessive dendrites are eliminated and individual mitral cells form multiple "tufted-dendrites" called as primary dendrites radially, and extend several lateral dendrites tangentially. According to the maturation, each mitral cell eliminates the primary dendrites except only one. However, how mitral cells determine the primary and the lateral dendrites and whether all mitral cells develop uniformly remain elusive. To tackle these issues, we have established a technique to label developing mouse mitral cells at single cell resolution using adeno-associated virus (AAV). Quantitative analyses revealed that nearly 50 % of the mitral cells at embryonic day 18.5 (E18.5) already had primary dendrites and more than 80 % of the mitral cells at postnatal day 0 (P0) had primary

dendrites, indicating that tuft formation is independent on the exposure to odorants by respiration after birth. Based on these observations, we will discuss how mitral cells take their functional dendrites in the developing olfactory circuits.

Disclosures: **K. Togashi:** None. **S. Takeuchi:** None. **H. Koizumi:** None. **K. Emoto:** None.

Poster

775. Dendritic Arborization

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 775.24/B11

Topic: A.05. Axon and Dendrite Development

Support: Japanese Ministry of Education, Science, Sports, Culture, and Technology (MEXT)

Japan Society for the Promotion of Science

Japan Science and Technology Agency

Naito foundation

Japan Agency for Medical Research and Development

Title: Dendritic Eph specifies pheromone-sensing circuit by organizing dendrite segregation in *Drosophila*

Authors: *T. CHIHARA[1,2,3], M. ANZO[2], S. SEKINE[2], S. MAKIHARA[2], K. CHAO[2], M. MIURA[2,3];
[1]Dept. of Biol. Science, Grad. Sch. of Sci., Hiroshima Univ., Higashi-Hiroshima, Japan; [2]Dept. of Genetics, Grad. school of Pharmaceut. Sci., The Univ. of Tokyo, Tokyo, Japan; [3]AMED-CREST, Tokyo, Japan

Abstract: The proper function of the neural network results from the precise connections among an enormous numbers of neurons. In order to organize a complex nervous system, the accurate targeting of both axon and dendrite from pre- and post-synaptic neurons is required. Previously, various molecular mechanisms for axon targeting have been revealed, however the dendrite-targeting mechanism and the way dendrites form a boundary to segregate each other are largely unknown due to the dendrites' diversity and complex morphology. As the model system, we utilized Drosophila olfactory projection neurons (PNs), which stereotypically target their dendrites to one of 50 glomeruli in the antennal lobe (AL), the first olfactory center in the brain. The previous study from our laboratory suggested that Eph/Ephrin signaling, well known axon

guidance molecule, is involved in dendrite targeting. Indeed, high Eph expression was observed specifically in the sex-related glomeruli in the developing AL. In addition, from genetic mosaic analysis, we have found that the widely conserved Eph receptor tyrosine kinase family member and its ligand, Ephrin, are essential for PN dendrites to segregate one another in some sex-related glomeruli. Our genetic data suggest that Eph/Ephrin signaling prevents the dendrites that target to one of the sex-related glomeruli (DA1) from getting entangled with dendrites targeting to adjacent glomeruli. In this study, we present that Eph/Ephrin signaling is required not only for axon guidance, but also for dendrite targeting. Furthermore, in PN dendrites, Eph/Ephrin signaling is designed to work for segregation.

Disclosures: **T. Chihara:** None. **M. Anzo:** None. **S. Sekine:** None. **S. Makihara:** None. **K. Chao:** None. **M. Miura:** None.

Poster

775. Dendritic Arborization

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 775.25/B12

Topic: A.05. Axon and Dendrite Development

Title: *In vivo* imaging of golgi complex of neurons in *Drosophila*

Authors: ***W. ZHOU**[1], J. CHANG[2];
[1]Room G303, Wuhan Natl. Lab. for Optoelectronics, Huazhong Univ. of Sci. and Technol. (HUS, Hubei, China; [2]Britton Chance Ctr. for Biomed. Photonics, Wuhan Natl. Lab. for Optoelectronics-Huazhong Univ. of Sci. and Technol., Wuhan, China

Abstract: Vast majority of studies in cell biology are from the cultured cells. Although cultured cells have the same cellular environment, but it cannot provide the physiological or pathological conditions, which are required for cell growth, differentiation and proliferation. As a particular type of cell, neuron is consisted by soma, axons and dendrites, which are responsible for signal input and output. In vivo study put a neuron into an intact neuronal circuit; it is ideal for the study of the structure and function of neurons. Based on the development of fluorescent protein, it allows us to minitor the structure and function of neuron by in vivo labeling methods. As a model organism, Drosophila powerful genetics provides an opportunity for studying of cell biology. Drosophila larvae, which have a transparent epidermis, provide an opportunity to get high-resolution images by confocal microscopy. Here, we use fluorescent protein -labeled Golgi markers observed the structure of dendritic Golgi outposts in da neurons, further revealed the molecular mechanism of this structure; moreover, studied the funtion of dendritic golgi outposts. In cell biological level, this study provides a powerful tool to study biogenesis of Golgi complex;

meanwhile, Golgi outposts, as part of secretory pathway of the cell, gain an insight to understand dendritic formation, developmental regulation and plasticity.

Disclosures: W. Zhou: None. **J. Chang:** None.

Poster

776. Autism: Neuromimmune, Microbiota, and Environmental Factors

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 776.01/B13

Topic: A.07. Developmental Disorders

Support: NIH/OD DP5OD009134

NIH/NICHD U54HD083092

Title: Abnormal anxiety and social approach behavior in a neonatal model of Ureaplasma infection is associated with increased ammonia levels in brain during early life

Authors: *S. SORIANO[1], B. E. O'NEILL[2], A. J. LIANG[1], C. M. MCGRAW[1], L. E. WEISMAN[3], R. S. SAMACO[1];
[1]Baylor Col. of Medicine/Jan and Dan Duncan NRI, Houston, TX; [2]Tulane Sch. Of Med., New Orleans, LA; [3]Neonatology, Baylor Col. of Med., Houston, TX

Abstract: Bacterial infection has been implicated in preterm birth, which is a risk factor for the clinical features present in autism spectrum disorders (ASDs), such as poor sociability, impaired communication and perseverative behavior. A commonly found bacterial species in the placenta of preterm births is the gram negative bacteria *Ureaplasma* (UP). The bacterial load of UP correlates with a higher incidence of chorioamnionitis and preterm labor. This suggests that preterm birth with UP infection may be contributing factors for ASD, and possibly the heterogeneity of ASD phenotypes given the widespread presence of UP in the urogenital tract of humans. Indeed, a significantly higher risk for poor neurological and developmental outcomes in UP-infected versus -uninfected preterm births has been reported, however, a causal relationship demonstrating if and how UP infection may cause potential ASD phenotypes, has not been shown. In addition, a significant finding that may provide insight into the pathogenesis of UP-related neurological defects was demonstrated in an antenatal mouse model of chorioamnionitis in which histochemical markers of GABAergic inhibitory interneurons were reduced in the absence of cell death. These data suggest an alteration in excitation-inhibition (E/I) balance within key neural networks of the brain, a theory that has been proposed to explain the behavioral and cognitive aspects of ASDs. Therefore, we generated an early neonatal mouse

model of UP infection to test whether mice exposed to UP infection at birth display neurobehavioral deficits in adulthood. We found that male mice infected with UP at birth showed altered anxiety and reduced social approach behavior whereas female mice infected at birth displayed normal behavior in all measurements. Interestingly, the brains of male but not female UP-infected neonatal pups showed increased levels of ammonia; however, male mice exposed to UP using the identical infection paradigm did not display abnormal levels of ammonia in brain during adulthood despite the observed behavioral deficits. Taken together, these data suggest that Ureaplasma infection may lead to altered ammonia levels in brain during a critical early developmental window which may result in sexually-dimorphic neurobehavioral outcomes.

Disclosures: S. Soriano: None. **B.E. O'Neill:** None. **A.J. Liang:** None. **C.M. McGraw:** None. **L.E. Weisman:** None. **R.S. Samaco:** None.

Poster

776. Autism: Neuromimmune, Microbiota, and Environmental Factors

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 776.02/B14

Topic: A.07. Developmental Disorders

Support: MIND Institute's Intellectual and Developmental Disabilities Research Center (IDDRC) Pilot Grants HD079125-01 (JLS)

Title: Early life exposure to the organophosphorus pesticide chlorpyrifos produces behavioral phenotypes relevant to neurodevelopmental disorders

Authors: *E. L. BERG[1], J. K. RIVERA[1], M. CAREAGA[1], D. A. BRUUN[2], P. J. LEIN[2], J. L. SILVERMAN[1];
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Abstract: Organophosphorus pesticides (OPs) are among the most widely used pesticides in the world. OPs have been implicated in the etiology of neurodevelopmental disorders including developmental delay and autism spectrum disorder (ASD) (Shelton et al., 2014; Shelton et al., 2012). Exposure to chlorpyrifos (CPF), one of the most widely used OPs, has been linked to mental and motor delays as well as increased rates of attentional issues, specifically attention deficit/hyperactivity disorder (ADHD), in children (Rauh et al., 2006). The present study examined sophisticated social and cognitive behaviors in a novel rat model of CPF exposure. Newborn Sprague-Dawley rats were administered either peanut oil vehicle, 1.0 mg/kg CPF, or

3.0 mg/kg CPF via daily s.c. injections from postnatal day (PND) 1 to PND 4. Isolation-induced ultrasonic vocalizations (USVs) were collected from pups on PND 5, 8, and 11. Sociability and repetitive self-grooming were assessed at the juvenile age using the ASD-relevant behavioral assays of three-chambered social approach and dyadic reciprocal social interaction. Locomotion was evaluated via an open field exploration assay and cognitive testing was carried out using pairwise visual discrimination and reversal learning in an operant touchscreen chamber. Pups exposed to 1.0 mg/kg CPF emitted fewer USVs than did pups treated with vehicle or 3.0 mg/kg CPF, and this effect was markedly higher in females. CPF did not affect the sociability phase of three-chambered approach; however, performance in the social novelty portion suggests that CPF disrupts recognition of previously acquired social cues. Relative to vehicle controls, CPF altered juvenile reciprocal social interactions on several key social parameters in a sexually dimorphic manner. CPF-treated females but not males displayed decreased rough and tumble playing while CPF-treated males exhibited increased chasing and anogenital sniffing, behaviors which were unaffected by CPF exposure in females. Moreover, self-grooming was elevated in both sexes at different doses. Similar exploratory behavior in a novel open arena was observed across treatment groups, eliminating hypo- and/or hyperactivity as confounding behaviors. Performance in the touchscreen learning task did not differ between CPF-treated rats and vehicle controls. Several pieces of evidence point to deficits in sex-dependent and/or species typical sociability in juvenile rodents. Impairments were noted in a range of behavioral assays which, taken together with existing literature, suggests that developmental OP exposures disrupt neurological development and neural correlates that underlie complex behaviors.

Disclosures: **E.L. Berg:** None. **J.K. Rivera:** None. **M. Careaga:** None. **D.A. Bruun:** None. **P.J. Lein:** None. **J.L. Silverman:** None.

Poster

776. Autism: Neuromimmune, Microbiota, and Environmental Factors

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 776.03/B15

Topic: A.07. Developmental Disorders

Title: Sex differences in autism-like repetitive behavior in response to postnatal opiate exposure in mice

Authors: A. REYNOLDS[1], K. KESAVAN[2], *D. M. CORDERO[3], D. SHIN[1], A. MAZARATI[1]; [1]Pediatrics- Neurol., [2]Pediatrics- Neonatology, [3]Pediatrics-Neonatology, UCLA, Los Angeles, CA

Abstract: Background:
Optimal management of pain is of vital importance in the neonatal intensive care unit (NICU), as a growing body of evidence has shown the detrimental impacts of untreated neonatal pain during a critical period in neurologic development. Opiates remain the gold standard for treatment of pain in the NICU; however there are serious concerns with long term neonatal opioid exposure, in particular, to the developing brain. Behavioral effects of opiate exposure in animals include (a) altered sensitivity to pain, (b) affective liability, (c) stereotyped behaviors, and (d) reduced socialization (refs) which are consistent with some of the symptoms of autism. With continued high rates of opiate use in the NICU, as well as maternal opiate use during pregnancy, it is critical that we understand the effects of opiates on development of autism-like behavior. Moreover, it is important to study these effects in male and female models given that both autism and opioid analgesia have known sex-differences.
Objective: This study aims to examine the relationship between neonatal opioid exposure and the development of autism-like behavior in male and female mice.
Methods: We exposed neonatal mice to either 2mg/kg of morphine twice a day or saline solution subcutaneously during postnatal day (P) 7-14. At P60, all pups (N=44: 7 morphine-exposed males, 10 morphine-exposed females, 16 naïve males, and 11 naïve females) were assessed for autism-like repetitive behavior using the marble burying test. A 2x2 ANOVA and post-hoc t-tests were conducted to examine independent and interactive effects of morphine and sex on behavior.
Results: We found a significant sex*postnatal opioid exposure interaction ($p<0.01$), wherein males showed increased repetitive behavior in response to morphine exposure (11 vs. 16 marbles buried in naïve vs. exposed males; $p=0.057$), and females displayed significantly decreased repetitive behavior in response to morphine exposure (15 vs. 9 marbles buried in naïve vs. exposed females; $p<0.05$).
Conclusion: Postnatal opioid exposure induces opposite effects on repetitive behavior in male and female mice. Specifically, opioid exposure increases autism-like repetitive behavior in males and decreases the behavior in females. This may be related to reports of increased repetitive behaviors in males with autism relative to females with autism.

Disclosures: **A. Reynolds:** None. **K. Kesavan:** A. Employment/Salary (full or part-time): University of California, Los Angeles. **D.M. Cordero:** A. Employment/Salary (full or part-time): University of California, Los Angeles. **D. Shin:** A. Employment/Salary (full or part-time): University of California, Los Angeles. **A. Mazarati:** A. Employment/Salary (full or part-time): University of California, Los Angeles.

Poster

776. Autism: Neuromimmune, Microbiota, and Environmental Factors

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 776.04/B16

Topic: A.07. Developmental Disorders

Support: NIEHS Grant R01ES021707

NIEHS Grant R01ES014901

NIEHS Grant T32ES007059

Title: Cumulative impact of large chromosomal duplications and PCB exposure on DNA methylation, chromatin, and expression of synaptic genes in autism spectrum disorder

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Abstract: The etiology of autism spectrum disorders (ASD) is complex, involving interactions between genetic and environmental risk factors. Genetic evidence showed a convergence of multiple genes with functions in chromatin regulation and neuronal synapses, but how multiple genetic and environmental hits may impact the epigenetic regulation of synaptic genes is unknown. To investigate the cumulative impacts of large chromosomal copy number variants (CNV) on the brain methylome, whole genome bisulfite sequencing (WGBS) was performed on 41 post-mortem human cortical samples including chromosome 15q11-13 duplication (Dup15q), Prader-Willi (PWS), Angelman (AS), Down syndrome (DS), idiopathic ASD without detectable CNVs, and neurotypical controls. Significant global DNA hypomethylation was observed compared to controls specifically in brain samples from Dup15q, but not AS, PWS, DS, or idiopathic ASD. Based on a previously observed interaction between Dup15q and PCB 95, a Dup15q neuronal cell culture model (SH15M) and the parental SH-SY5Y (SH) cell line were cultured with or without PCB 95 and analyzed by WGBS. Similar to Dup15q brain, a significant global hypomethylation was observed in SH-15M compared to SH. Genes mapped to PMDs gained in SH-15M compared to SH were significantly enriched for ion channels at the post-synaptic membrane and these genes and functional categories overlapped with those independently altered with PCB 95 exposure, demonstrating a compounding effect of genetic duplication and chemical exposure. Most hypomethylated genes exhibited increased transcript levels in SH-15M, SH+PCB, and SH-15M+PCB compared to SH in short term cultures,

however, most transcript levels were reduced or heterogeneously dysregulated in long-term cultures, similar to the dysregulation in transcript levels in Dup15q brain samples. Mechanistically, overexpression of maternal UBE3A in Dup15q decreased RING1B which reduced ubiquitinated H2A levels, including monoubiquitin of acetylated H2A.Z, resulting in loss of this poised promoter chromatin mark and hypomethylation. These results demonstrate the compounding effects of cumulative genetic and environmental events on the neuronal methylome, leading to a convergence in transcriptional dysregulation of chromatin and synaptic gene pathways relevant to ASDs.

Disclosures: **M.S. Islam:** None. **K. Dunaway:** None. **R. Chu:** None. **S. Lopez:** None. **R. Coulson:** None. **I. Pessah:** None. **P. Lott:** None. **D. Yasui:** None. **C. Mordaunt:** None. **M. Horike:** None. **S. Horike:** None. **I. Korf:** None. **J. LaSalle:** None.

Poster

776. Autism: Neuromimmune, Microbiota, and Environmental Factors

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 776.05/B17

Topic: A.07. Developmental Disorders

Title: Effects of A1 vs A2 beta casein containing diet on glutathione levels: Linking the Gut and the brain via redox -based epigenetic changes

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Abstract: Background Glutathione (GSH) is produced in every cell in the body, where it acts as an antioxidant to neutralize free radicals and prevent oxidative cellular damage. Alterations in GSH levels are reported in neurological, inflammatory diseases as well as immune dysfunction. Several studies in animals and humans involving supplementation with whey protein or whey protein isolates from milk have documented increases in plasma and tissue glutathione concentrations along with reductions in oxidative stress, while the effects of casein on GSH are as yet not clear. One of the major components of the casein family is beta-casein and evolutionarily there are two major type of beta-casein: A1 and A2. The presence of histidine at position 67 allows a protein fragment of seven amino acids, known as beta-casomorphin-7 (BCM-7), to be produced on enzymatic digestion only from A1 but not from A2 beta-casein. BCM7 is an opioid peptide and can act on mu-opioid receptor similar to morphine. We have previously reported that BCM-7 can reduce cysteine uptake in cultured human neuronal and gastrointestinal epithelial cells by activating opioid receptors, inducing oxidative stress by

decreasing the levels of GSH.Objective The current work was undertaken to investigate the effects of A1 vs A2 type of beta-casein containing diet on antioxidant GSH levels and inflammatory status in pre-clinical and clinical trials.Methods A pre-clinical study was performed using mouse and rabbit animal models fed on A1 and A2 beta-casein containing diet. The clinical study was performed in collaboration with researchers in China (NCT02406469https://clinicaltrials.gov/ct2/show/NCT02406469). We collected liver, brain and gut tissues in our preclinical study, whereas serum GSH was measured in our clinical study. In both cases HPLC coupled to an electrochemical gradient detector was used to evaluate GSH levels.Results In our preclinical study we observed significant decrease in GSH levels (indicating oxidative stress) in liver, gut and brain samples from animals (both mice and rabbit, $p<0.05$, N=12) fed on an A1 beta-casein containing diet as compared to animals fed on A2 beta-casein containing diet. Concurrently, we also observed elevated TNFalpha levels and NFkB levels in gut tissues of mice and rabbit on an A1 beta-casein containing diet as compared to animals fed on A2 beta-casein containing diet, indicating elevated inflammatory status ($p<0.05$, N=12). Similarly, in our clinical trial, human participants consuming A1 beta-casein containing milk had decreased GSH serum ($p<0.05$, N=45)

Disclosures: **M.S. Trivedi:** None. **R. Deth:** None. **Y. Zhang:** None.

Poster

776. Autism: Neuromimmune, Microbiota, and Environmental Factors

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 776.06/B18

Topic: A.07. Developmental Disorders

Title: Effects of maternal serotonin transporter genotype and stress on microbiota throughout pregnancy

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Abstract: Maternal stress during pregnancy (prenatal stress) has been shown to have potentially long lasting negative effects on offspring, including an increased risk for neurodevelopmental disorders such as autism spectrum disorder (ASD). A common deletion in the promoter region of the serotonin transporter gene (SLC6A4) has been associated with increased anxiety and increased stress reactivity. Previous work from our lab has established an interaction between this genetic polymorphism in mothers and prenatal stress in the risk for autism diagnosis in the

child. Further, data suggest there is a critical window of time during pregnancy (late second and early third trimester) in which mothers who are exposed to acute stressors and carry the short SLC6A4 allele are more likely to have a child diagnosed with autism. This phenomenon has also been demonstrated in heterozygous SERT knockout (Slc6a4+/-) mice, which display serotonin activity alterations similar to those found in humans carrying the short allele. Pups from Slc6a4+/- dams that have been subjected to stress display decreased social interactions and increased anxiety compared to offspring of wild type. Stress and stress reactivity can also interact to impact the gut microbiome. While wild type mice experience changes in microbiota as a result of an inflammatory stressor, we have found evidence that Slc6a4+/- mice have some protection against these effects. Vaginal and gut microbiota are also altered by pregnancy. In order to explore the interaction between stress, microbiome and pregnancy, the current study compared pregnant wild type and Slc6a4+/- mice divided into either a control condition or stress condition, in which they received two hours of restraint stress daily beginning embryonic day 12. At embryonic day 13.5, 15.5 and 18.5, dams were sacrificed for fetal tissue/placental collection and any fecal matter present was collected. Using next-generation sequencing of the bacterial 16s rRNA marker gene, we explored differences between microbial communities in order to help shed light on the complex interplay between stress, genetics and the microbiome at various stages of pregnancy.

Disclosures: **B.M. Kille:** None. **D.J. Davis:** None. **P.M. Hecht:** None. **A.C. Ericsson:** None. **D.Q. Beversdorf:** None.

Poster

776. Autism: Neuromimmune, Microbiota, and Environmental Factors

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 776.07/B19

Topic: A.07. Developmental Disorders

Support: Swedish Research Council (grant no. K2015-62X-22745-01-4)

Swedish Brain Foundation

Olle Engkvist Byggmästare Foundation

Strategic Research Program in Neuroscience at Karolinska Institutet

Knut and Alice Wallenberg Foundation

Title: The bacterial peptidoglycan sensing molecule Pglyrp2 modulates brain development and behavior

Authors: *R. DIAZ HEIJTZ, H. FORSSBERG, T. ARENTSEN;
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Abstract: Recent studies have revealed that the gut microbiota modulates brain development and behavior, but the underlying mechanisms are still poorly understood. Here, we show that bacterial peptidoglycan (PGN) derived from the commensal gut microbiota can be translocated into the brain and sensed by specific pattern-recognition receptors (PRRs) of the innate immune system. Using expression-profiling techniques, we demonstrate that two families of PRRs that specifically detect PGN (i.e., PGN-recognition proteins and NOD-like receptors) are highly expressed in the developing brain during specific windows of postnatal development, and their expression is sensitive to manipulations of the gut microbiota. To begin addressing the potential influence of PGN-sensing molecules on brain development and behavior, we explored the role of PGN-recognition protein 2 (Pglyrp2) in the process. Using transgenic mice, we first investigated the effect of deleting Pglyrp2 on the expression of brain-derived neurotrophic factor (*Bdnf*) in the developing brain. *Bdnf* mRNA expression levels were significantly reduced in the striatum of three-day-old Pglyrp2 KO male mice compared to wild-type controls. We then subjected juvenile Pglyrp2 KO mice to a battery of tests for exploratory activity, anxiety and social behavior. In the open field, light-dark box and elevated plus maze tests, no significant behavioral changes were observed in Pglyrp2 KO mice. In the three-chamber social approach test, however, juvenile Pglyrp2 KO male mice spent significantly more time in the chamber containing the stimulus mouse than in the chamber containing the novel object, compared to control mice. Moreover, they also spent significantly more time sniffing and interacting with the stimulus mouse than the wild-type males did, indicating high sociability. Although juvenile Pglyrp2 KO female mice spent significantly more time in the chamber containing the stimulus mouse, they spent a similar amount of time as the wild-type females around the stimulus mouse. These results indicate that Pglyrp2 modulates the development of social behavior in mice. Moreover, these findings suggest that the central activation of PRRs by bacterial products could be one of the signaling pathways mediating the communication between the microbiota and the developing brain.

Disclosures: R. Diaz Heijtz: None. **H. Forssberg:** None. **T. Arentsen:** None.

Poster

776. Autism: Neuromimmune, Microbiota, and Environmental Factors

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 776.08/B20

Topic: F.04. Stress and the Brain

Support: US Office for Naval Research (ONR) (N00014-14-1-0787)

Canadian-Israel Health Initiative, jointly funded by the Canadian Institutes of Health Research, the Israel Science Foundation, the International Development Research Centre, Canada and the Azrieli Fundation

Alimentary Health Inc, Cork, Ireland for their generous gift of Lactobacillus rhamnosus JB-1TM.

Title: Early life clinical dose penicillin exposure induces longterm effects on gut microbiota, brain inflammation and behavior which are partially restored by beneficial microbe administration

Authors: S. LECLERCQ[1], F. MIAN[1], A. STANISZ[1], L. BINDELS[2], O. KOREN[3], P. FORSYTHE[1], *J. BIENENSTOCK[1];
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Abstract: Antibiotics (AB) are the most frequently dispensed drugs in pediatric patients and there is currently increasing concern that AB exposure early in life may have long-term consequences for health. Epidemiological studies have revealed that early life AB exposure increases the risk of developing allergies, inflammatory bowel diseases and obesity. The effects of AB on brain and behavior have been demonstrated by others, using very high doses of cocktails of mainly broad-spectrum antibiotics administered to adolescent or adult rodents. In this study, we have investigated the long-term effects on gut, microbiota, brain and behavior of a clinically relevant dose of oral penicillin given early in life, to both male and female Balb/c mice. Pregnant dams received penicillin V in drinking water 1 week before delivery and until weaning. Penicillin is absorbed by the gastro-intestinal tract, crosses the placenta and is found in the breast milk. The pups therefore received penicillin *in utero* and during the first 3 weeks of life while nursing. At weaning, pups were separated from their mothers and received regular drinking water. At 6-weeks old, the offspring were subjected to a battery of behavioral tests and gut (ileum, colon) and brain (hippocampus, frontal cortex) tissues were collected after the last test. We found that early life AB exposure had lasting effects on gut microbiota composition, modified the tight junctions of the blood-brain barrier, induced inflammation in the frontal cortex but not in the gut, and was associated with changes in brain neurochemistry (Corticotropin releasing hormone receptor 2, Brain derived neutrophic factor, Arginine vasopressin receptor 1b). Also, AB-treated mice exhibited decreased anxiety-like behavior, reduced social behavior and preference for social novelty as well as an unexpected aggressive behavior. Supplementation with *Lactobacillus rhamnosus* JB-1^{TM} during AB treatment restored certain biological and behavioral parameters. This study revealed that clinical pediatric low dose penicillin given early in life to mice had longterm effects on behavior, brain inflammation and microbiota, and may raise concerns about the behavioral consequences of AB therapy.

Disclosures: **S. Leclercq:** C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Department of Pathology and Molecular Medicine, McMaster University, Hamilton, Ontario, Canada.. **F. Mian:** None. **A. Stanisz:** None. **L. Bindels:** None. **O. Koren:** None. **P. Forsythe:** C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Firestone Institute for Respiratory Health and Department of Medicine, McMaster University, Hamilton, Ontario, Canada. **J. Bienenstock:** C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Department of Pathology and Molecular Medicine, McMaster University, Hamilton, Ontario, Canada..

Poster

776. Autism: Neuromimmune, Microbiota, and Environmental Factors

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 776.09/B21

Topic: A.07. Developmental Disorders

Support: Hearst Foundation

Hartwell Foundation

NIEHS Grant P01 ES011269-11

NICHD Grant 5U54HD079125-03

Title: Autism-relevant sociability deficits, repetitive behaviors, and neuroanatomical findings in the antigen-driven mouse model of maternal autoantibody related autism

Authors: ***K. L. JONES**[1], J. ELLEGOOD[3], E. EDMISTON[1], M. PRIDE[2], M. YANG[2], J. SILVERMAN[2], J. LERCH[3], J. CRAWLEY[2], J. VAN DE WATER[1];
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Abstract: Maternal autoantibodies reactive to proteins in fetal brain have been described by numerous researchers in a subset of mothers of children with autism spectrum disorder (ASD), but not in mothers of typically developing children. Our lab identified 7 protein antigens for maternal autoantibody related (MAR) ASD and recently mapped the antigenic epitope sequences recognized by these ASD-specific maternal autoantibodies. While previous passive transfer animal models yielded promising results, they did not reflect a constant exposure to the salient autoantibodies throughout gestation, as would be the case in the clinical setting. Therefore, we aimed to generate the first biologically relevant animal model of MAR ASD to directly assess

the pathologic significance of prenatal exposure to epitope-specific autoantibodies in generating ASD-relevant behaviors in offspring. In order to generate epitope-specific autoantibodies that mimic those found in the mothers of children with ASD, female C57BL/6J mice randomly assigned to MAR-ASD treatment received a series of immunizations containing peptide epitope sequences of the four primary target proteins of MAR ASD (lactate dehydrogenase A and B, collapsin response mediator protein 1, and stress-induced phosphoprotein 1). Control females were injected with saline only. Females were then paired with male breeders to produce the experimental offspring of interest. Subsequent male and female offspring were tested in a sequence of autism-relevant behaviors and developmental milestones from an early postnatal period through adulthood. Following behavioral testing, neuroanatomical differences in offspring were assessed via structural MRI at approximately 6 months of age. Our results indicate offspring prenatally exposed to autism-specific antibodies display robust deficits in social interactions and increased repetitive self-grooming behaviors as juveniles and adults during dyadic social interactions. Furthermore, the head sizes of MAR-ASD offspring were significantly larger than controls during early postnatal and adult time points, suggesting an altered neuroanatomical trajectory relative to control offspring. Increases in several cortical regions and white matter tracts were also observed in MAR-ASD adult brains relative to controls, with observed differences primarily driven by MAR-ASD females. By generating the MAR ASD-specific epitope antibodies in female mice prior to breeding, our antigen-driven mouse model demonstrates for the first time that these ASD-specific maternal autoantibodies are directly responsible for alterations in behaviors.

Disclosures: **K.L. Jones:** None. **J. Ellegood:** None. **E. Edmiston:** None. **M. Pride:** None. **M. Yang:** None. **J. Silverman:** None. **J. Lerch:** None. **J. Crawley:** None. **J. Van de Water:** None.

Poster

776. Autism: Neuromimmune, Microbiota, and Environmental Factors

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 776.10/B22

Topic: A.07. Developmental Disorders

Support: Nancy Lurie Marks Clinical and Research Fellowship Program in Autism

Robert and Donna Landreth Fund

Lurie Center for Autism

Title: Interactions between prenatal and early postnatal immune challenges in a mouse model of autism

Authors: E. L. MOKLER[1], A. J. ALEXANDER[1], S. M. LANDINO[1], B. C. FINGER[1], *Y. LI[2,1], V. Y. BOLSHAKOV[1], G. MISSIG[1], C. J. MCDOUGLE[3], W. A. CARLEZON, Jr.[1]; [1]Dept. of Psychiatry, Harvard Med. School, McLean Hosp., Belmont, MA; [2]Mailman Resch Ctr., McLean Hosp., Belmont, MA; [3]Lurie Ctr. for Autism, Massachusetts Gen. Hosp.,, Lexington, MA

Abstract: The role of immunological responses in the etiology of autism spectrum disorder (ASD) has long been hypothesized. A "multiple hit" model whereby multiple exposures to early life immune insults may contribute to the development of ASD. We developed a repeated immune challenge mouse model where pregnant mice were injected with the viral mimic poly(I:C) (20 mg/kg) on gestational day 12.5 of pregnancy. A subset of the offspring was injected with lipopolysaccharide (LPS) (10 mg/kg) on postnatal day 9 to induce a second robust innate immune response. A battery of behavioral assays were performed to characterize the behavioral phenotype of this model in relation to the core symptoms of ASD: deficits in communication and social interaction, and increases in stereotyped behaviors. To assess communication-related behavior, ultrasonic vocalizations (USVs) were recorded from male pups during a maternal separation test on postnatal days 10-16 and from adult males at seven weeks evoked from the presence of urine from a female in estrus. In both LPS treated pups and adults there were altered number of evoked USVs suggesting a dysregulation of communication. To measure social behavior, a one-chamber social interaction test was performed at 8 weeks. In males, postnatal LPS decreased social preference. To evaluate for the presence of stereotypic or repetitive behavior, mice were tested on a Rotarod at 7 weeks and were placed in a Y-Maze at 10 weeks to observe spontaneous alternations. Anxiety-like behaviors were measured from both males and females at 10 weeks in the open field test. There was heightened anxiety-like behavior for both sexes that received postnatal LPS. In sum, postnatal LPS was sufficient to produce a robust ASD-like behavioral phenotype, producing alterations in communication, social preference, stereotypic, and anxiety-like behavior. However, following prenatal poly(I:C) treatment we did not observe a reliable ASD-related behavioral phenotype, and found that the combination of polyI:C plus LPS produced only modest differences from the behavioral phenotype seen with postnatal LPS alone. Our findings provide evidence that perinatal immune insults can produce behavioral changes in mice resembling those found in ASD and lend further support to a potential immunological involvement in ASD.

Disclosures: E.L. Mokler: None. **A.J. Alexander:** None. **S.M. Landino:** None. **B.C. Finger:** None. **Y. Li:** None. **V.Y. Bolshakov:** None. **G. Missig:** None. **C.J. McDougle:** None. **W.A. Carlezon:** None.

Poster

776. Autism: Neuromimmune, Microbiota, and Environmental Factors

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 776.11/B23

Topic: A.07. Developmental Disorders

Support: Robert and Donna Landreth Fund

Nancy Lurie Marks Family Foundation

Title: Sleep and epileptiform activity in a perinatal immune activation mouse model of autism spectrum disorder (ASD)

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Abstract: Increasing evidence suggests a role for inflammatory processes in autism spectrum disorders (ASDs). Some individuals with ASDs show elevated inflammatory markers and neuroimmune responses, as well as epidemiological association with familial autoimmune disorders. These findings raise the possibility that there is a subtype of ASD that is immunological in origin. Previous research in mice has shown that immune insults during critical developmental periods can result in a phenotype that reproduces some of the core features of ASD. We have recently developed a “multiple hit” immune model, whereby mice are exposed to repeated perinatal immune insults. In this model, pregnant mice are injected with the viral mimic poly(I:C) (20 mg/kg) on gestational day 12.5 in accordance to an established model of maternal immune activation. A subset of these offspring receives a second injection of LPS (lipopolysaccharide) (10 mg/kg) to induce a robust innate immune response on postnatal day 9. We have previously found that this model leads to a pronounced ASD-like behavioral phenotype with mice displaying deficits in social and communication behavior, increased repetitive behavior, as well as inducing a state of ongoing immune activation that persists into adulthood. Here, we examine this multiple hit immune activation model on two physiological measures that are commonly dysregulated in individuals with ASD, sleep and electroencephalography (EEG) epileptiform activity. Using a remote telemetry system, a transmitter was implanted at postnatal week 6 and measurements of EEG, electromyography (EMG), activity, and temperature were made for multiple weeks. During this period levels of activity, sleep, and circadian rhythm were analyzed. Prenatal LPS resulted in several alterations, including overall greater level of activity, consistent with the hyperactivity and sleep disturbances frequently observed in ASD. Considering that epilepsy is found in a higher percentage of individuals with ASD than in the general population and there is evidence for increased in epileptiform activity even in the

absence of epilepsy, we examined EEG recordings from perinatal immune activated mice for the presence of epileptiform activity. Analysis revealed that a subset of the mice that received postnatal LPS displayed heightened levels of epileptiform activity, which included the presence of spike-wave discharges during sleep. In sum, perinatal immune activation resulted in alterations in sleep and epileptiform activity resembling aspects of ASD, further supporting a potential immunological involvement in ASD.

Disclosures: G. Missig: None. **A.J. Alexander:** None. **E.L. Mokler:** None. **A.J. Wells:** None. **B.C. Finger:** None. **C.J. McDougle:** None. **W.A. Carlezon:** None.

Poster

776. Autism: Neuromimmune, Microbiota, and Environmental Factors

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 776.12/B24

Topic: A.07. Developmental Disorders

Support: HRSA UA3 MC11054 – Autism Intervention Research Network on Physical Health

Title: Associations between cytokines, endocrine stress response, and gastrointestinal symptoms in autism spectrum disorder

Authors: *B. J. FERGUSON[1,2], S. MARLER[3], L. ALTSTEIN[4], E. LEE[3], M. MAZUREK[5,2], A. MCLAUGHLIN[6], K. HARTNETT[2], E. MACKLIN[7], E. MCDONNELL[4], D. DAVIS[2], A. BELENCHIA[2], C. GILLESPIE[8], C. PETERSON[2], M. BAUMAN[9], K. MARGOLIS[10], J. VEENSTRA-VANDERWEELE[10], D. BEVERSDORF[2];
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Abstract: Many children and adolescents with Autism Spectrum Disorder (ASD) have significant gastrointestinal (GI) symptoms, but the etiology is currently unknown. Some individuals with ASD show altered reactivity to stress, as well as altered immune markers, particularly stress-responsive cytokines including TNF-α and IL-6. To assess potential relationships between GI symptoms and stress response, we examined whether GI symptoms were associated with increases in stress-associated endocrine and cytokine biomarkers in ASD. We hypothesized that positive relationships would exist between GI symptomatology and cortisol, TNF-α, IL-6. Furthermore, we conducted exploratory analyses to examine the effects of

the presence or absence of key co-occurring medical and psychological conditions on these relationships in ASD. A sample of 120 individuals aged 6-18 with ASD participated in the study. Participants provided pre- and post-stress salivary cortisol samples to measure the endocrine stress response, and a pre-stress blood sample to measure levels of interleukin 6 (IL-6) and tumor necrosis factor alpha (TNF-α). To assess the response to stress, cold pressor and vibrotactile stimulation were applied to the hands in independent trials. Upper and lower GI tract symptomatology were assessed using the QPGS Rome III. Exploratory analyses were conducted between measures of intelligence, key co-occurring conditions in ASD, and IL-6, TNF-α, and pre- and post-stress cortisol to examine potential relationships. Lower GI tract symptoms were significantly associated with post-stress cortisol concentration. This relationship between cortisol response to stress and GI functioning was greater for children who had a history of regression or loss of skills that were previously acquired. Exploratory analyses also revealed significant correlations between cortisol change score, IQ, and inappropriate speech. In contrast, lower GI tract symptoms were not associated with levels of TNF-α or IL-6. Significant correlations were found, however, between TNF-α and IL-6 and irritability, socialization, and IQ. These findings suggest that individuals with ASD and lower GI tract symptoms may have an increased response to stress, but this effect is not associated with concomitant changes in stress-associated cytokines. This relationship with stress may be relevant for future individualization of treatment of lower GI tract symptoms in ASD. The relationship between endocrine stress reactivity and lower GI tract symptoms in children with loss of skills, as well as the relationships between cortisol, IL-6, and intelligence in ASD, warrant further investigation.

Disclosures: **B.J. Ferguson:** None. **S. Marler:** None. **L. Altstein:** None. **E. Lee:** None. **M. Mazurek:** None. **A. McLaughlin:** None. **K. Hartnett:** None. **E. Macklin:** None. **E. McDonnell:** None. **D. Davis:** None. **A. Belenchia:** None. **C. Gillespie:** None. **C. Peterson:** None. **M. Bauman:** None. **K. Margolis:** None. **J. Veenstra-VanderWeele:** B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution; Seaside Therapeutics, Forest, SynapDx, Novartis, Roche. F. Consulting Fees (e.g., advisory boards); Roche, Novartis, SynapDx. **D. Beversdorf:** Other; Research in Autism Spectrum Disorders - Associate Editor.

Poster

776. Autism: Neuromimmune, Microbiota, and Environmental Factors

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 776.13/B25

Topic: A.07. Developmental Disorders

Support: Science without borders/CAPES

Integration of Medicine and Science/School of Medicine Pilot Grant (UL1TR001120)

Title: Gene X environment interactions in the development of an autistic-phenotype in mice.

Authors: *D. S. COELHO[1], K. JIMENEZ[1], L. REDUS[1], L. MYATT[1], J. C. O'CONNOR[1,2]; [1]Pharmacol., Univ. of Texas Hlth. Sci. Ctr. At San A, San Antonio, TX; [2]Audie L. Murphy VA Hosp., San Antonio, TX

Abstract: The etiology of autism spectrum disorder (ASD) is not well understood. Prenatal exposure to certain environmental factors or genetic mutations increase the risk for developing ASD. However, whether exposure to environmental risk factors by genetically susceptible individuals increases the severity of the disorder remains unknown. Therefore, we tested the hypothesis that mice with a targeted deletion of the contactin associated protein-like 2 (CNTNAP2) gene would exhibit a more severe ASD-like behavioral phenotype following maternal immune activation during gestation. CNTNAP2 mutation has been associated with the development of autism in humans and a mild ASD-like phenotype, characterized by deficits in communication, sociability and stereotypic behavior, in mice. Additionally, maternal immune challenge with the viral mimetic polyinosinic:polycytidylic acid (poly I:C) during gestation results in a neurodevelopmental and behavioral phenotype resembling ASD (i.e. impaired communication, disrupted social behavior and repetitive, stereotypic behaviors). Pregnant dams were administered poly I:C (20mg/kg) or saline intraperitoneally on gestational day 12.5. At various ages, the behavior of offspring was measured in the following tests; ultrasonic vocalization, juvenile play behavior, grooming, marble burying, Y-maze, 3-chamber social interaction and pre-pulse inhibition. Consistent with previous reports, CNTNAP2 gene deletion independently caused an increase in ASD-like behaviors, but in contrast with much of the literature, maternal immune challenge with poly I:C failed to induced a robust ASD-like phenotype in WT mice. In CNTNAP2 deficient mice, maternal immune challenge with poly I:C did precipitate several ASD-like behaviors in affected offspring, including increased marbles buried and decreased social interaction in the juvenile play test. Additionally, social interaction was significantly more impaired in male mice versus female mice born from poly I:C challenged dams. Consistent with previous reports, our data indicate that deletion of the CNTNAP2 gene in mice results in an ASD-like phenotype, and males appear more vulnerable to some, but not all, of the behavioral consequences of maternal immune challenge with poly I:C. In our hands, poly I:C had little behavioral impact on WT mice as they developed, and the severity of the CNTNAP2 phenotype was more profound than previous reports. The latter could have obscured our ability to measure gene x environment interactions in the development of an autistic-like phenotype in mice.

Disclosures: D.S. Coelho: None. **K. Jimenez:** None. **L. Redus:** None. **L. Myatt:** None. **J.C. O'Connor:** None.

Poster

776. Autism: Neuromimmune, Microbiota, and Environmental Factors

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 776.14/B26

Topic: A.07. Developmental Disorders

Support: DoD Grant #AR120066

Autism Science Foundation Pre-Doctoral Fellowship

Title: Maternal inflammation impacts fetal neurodevelopment via placental serotonergic dysfunction

Authors: *N. GOEDEN[1], J. VELASQUEZ[1], K. A. ARNOLD[1], Y. CHAN[1], B. T. LUND[1], G. M. ANDERSON[2], A. BONNIN[1];
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Abstract: Maternal inflammation during pregnancy affects placental function and is associated with increased risk of neurodevelopmental disorders in the offspring. The molecular mechanisms linking placental dysfunction to abnormal fetal neurodevelopment remain unclear. During typical development, serotonin (5-HT) synthesized in the placenta from maternal L-tryptophan (TRP) reaches the fetal brain. There, 5-HT modulates critical neurodevelopmental processes. We investigated the effects of maternal inflammation in mice triggered in mid-pregnancy by the immunostimulant polyriboinosinic-polyribocytidylic acid [poly(I:C)] on TRP metabolism in the placenta, and its impact on fetal neurodevelopment, postnatal formation of the serotonergic system, and several adult behaviors typically associated with serotonergic dysfunction. We show that a moderate maternal immune challenge rapidly upregulates placental TRP conversion to 5-HT through successively transient increases in substrate availability and TRP hydroxylase (TPH) enzymatic activity, leading to accumulation of exogenous 5-HT and blunting of endogenous 5-HT axonal outgrowth specifically within the fetal forebrain. The pharmacological inhibition of TPH activity blocked these effects. Postnatally, these effects lead to the disruption of several adult behaviors that are commonly associated with neurodevelopmental disorders like autism and schizophrenia. These results establish altered placental TRP conversion to 5-HT as a new mechanism by which maternal inflammation disrupts 5-HT-dependent neurogenic processes during fetal neurodevelopment. The findings presented here lay the framework for more detailed studies of infectious agents on placentally-derived modulators of neurodevelopment, particularly in view of recent infectious disease outbreaks (such as H1N1 influenza or Zika virus), suggesting that pregnant women and their fetuses are high-risk groups for severe and long-lasting complications

Disclosures: **N. Goeden:** None. **J. Velasquez:** None. **K.A. Arnold:** None. **Y. Chan:** None. **B.T. Lund:** None. **G.M. Anderson:** None. **A. Bonnin:** None.

Poster

776. Autism: Neuromimmune, Microbiota, and Environmental Factors

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 776.15/C1

Topic: A.07. Developmental Disorders

Support: SIMONS 1175502-100-UAFUT

Title: Synergy between partial loss of GABRB3 and gestational immune events in a mouse model of autism

Authors: ***H.-R. LEE**, T. WEERAKKODY, G. C. NASTARIN, Y.-W. WU, J. HUGUENARD, J. B. DING, T. D. PALMER;
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Abstract: Autism spectrum disorders (ASDs) involve persistent deficits in social communication and social interaction, along with characteristic repetitive patterns of behavior. The symptoms of ASD are present at an early age and ASD often occurs in families, suggesting a genetic basis. Intensive efforts to identify a common genetic mechanism suggest that a very small fraction of ASD diagnoses can be attributed to single gene mutations. Complex combinations of common allelic variants may account for up to half of ASD cases, with the remaining cases due to other factors. It is also suspected that genetic predisposition acts in combination with environmental influences. Maternal immune events during pregnancy are among the most pronounced non-genetic risks and interactions between single gene risk factors and gestational immune events are beginning to illustrate how a mild genetic risk may combine with a mild environmental risk to cause autism. Single nucleotide polymorphisms and disruptive mutations in the GABAA receptor beta-3 subunit gene (GABRB3) are among the high-confidence recurrent mutation in ASD. Here we show that GABRB3 heterozygosity in mice shows striking synergy with the activation of a maternal immune response during pregnancy. Offspring exhibit pronounced ASD and intellectual disability-like behaviors, including absence of social interaction, increased repetitive behavior, and impaired cognitive function. Global physiological aberrations are also noted in medial prefrontal cortex (mPFC). Both excitatory and inhibitory synaptic transmission of layer 2/3 neurons was markedly attenuated in conjunction with reduced dendritic spine density. Mice also exhibit a reduction in NMDAR function within mPFC layer 2/3 neurons. In multichannel extracellular recording, both synaptic sinks and sources are globally diminished in the mPFC layer 2/3. These results strongly suggest that partial loss of GABRB3 potently

interacts with gestational immune events to elevate the severity of ASD-like symptoms and extensively alter synaptic structure and neurotransmission.

Disclosures: **H. Lee:** None. **T. Weerakkody:** None. **G.C. Nastarin:** None. **Y. Wu:** None. **J. Huguenard:** None. **J.B. Ding:** None. **T.D. Palmer:** None.

Poster

776. Autism: Neuromimmune, Microbiota, and Environmental Factors

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 776.16/C2

Topic: A.07. Developmental Disorders

Support: Dr. Miriam and Sheldon G. Adelson Medical Research Foundation

NICHD U54 11891046

Title: Rapidly reversible altered functional connectivity and autism-like behaviors in a model of maternal inflammation-induced mild brain overgrowth

Authors: J. E. LE BELLE[1], N. G. HARRIS[2], A. J. SILVA[3], *H. KORNBLUM[4];
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Abstract: Autism spectrum disorders (ASD) affect up to 1 in 68 children and are associated with a broad array of genetic alterations, making an understanding of ASD a daunting task. Additionally, while autism is clearly heritable, there is also a strong environmental component to ASD pathogenesis. Despite this complexity, there are common themes that have emerged from studying children with ASD and animal models. One such theme is that autism is associated with altered neuronal connectivity. Another is that many mutations merge onto common molecular pathways, including the PI3K/AKT/mTOR pathway. Within this pathway, there are autism-associated mutations in PTEN. Mutations in PTEN and other negative regulators of the pathway are also associated with brain overgrowth, suggesting a potential role for enhanced neural stem proliferation in the development of autism. Additionally, a significant consensus is emerging that maternal inflammation is a common environmental exposure that could interact with genetic risk factors to cause autism. We found that mild maternal inflammation at midgestation in the mouse leads to activation of PI3K/NOX/AKT/mTOR signaling in the brain, enhanced neural stem cell proliferation, enlarged brains, and behaviors consistent with an “autistic” phenotype in the offspring (Le Belle et al., 2014). The effect on brain size was even more profound in PTEN heterozygotes due to a more complete oxidative inactivation of PTEN function. Our new data

demonstrate that MIR-exposed offspring in our model have altered functional brain connectivity (fMRI) in mice with the largest behavioral changes. Furthermore, the long-term activation of the PI3K/AKT/mTOR signaling pathway observed in our model following MIR exposure led us to test the effects of an mTOR inhibitor, Rapamycin. We found that Rapamycin produces dramatic rescue of the autism-associated behaviors and functional brain connectivity in adult mice within 2 hours, despite the persistence of their enlarged brain size. This exciting result indicates that inhibition of the abnormal signaling pathway activation in adult mice can rapidly reverse neuronal dysfunction without needing to alter aberrant structural changes.

Disclosures: **J.E. Le Belle:** None. **N.G. Harris:** None. **A.J. Silva:** None. **H. Kornblum:** None.

Poster

776. Autism: Neuromimmune, Microbiota, and Environmental Factors

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 776.17/C3

Topic: A.07. Developmental Disorders

Support: Deanship of Academic Research, The University of Jordan. Amman, Jordan (grant to Loai Alzghoul)

Title: The association between blood levels of inflammatory markers and autism in Jordan

Authors: *L. ALZGHOUL[1], A. H. I. YANIS[2], S. S. N. MAHMOUD[2], Y. Z. S. QWAIDER[2], M. ELDAHABI[3], S. ALBDOUR[3];
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Abstract: Almost one percent of the world's population has been diagnosed with Autism Spectrum Disorder (ASD) with a male predominance. Although the various studies aiming to understand the pathophysiology of ASD, there is still many to reveal especially in middle and low-income countries, such as Jordan, which might help in early detection and hence better prognosis. Recently, several studies have demonstrated a link between abnormal immune activation and ASD. For instance, Epidemiological studies have established a correlation between ASD and family history of autoimmune disease, and allergic disorders such as celiac disease. In addition, several studies found higher immune system markers in autistics compare to controls. Cytokines are molecules that function as signaling chemicals by the body's immune system. They participate in many complex physiological functions, including inflammation and immunity. Also, they have an important role in proper brain and nervous system development, which is dependent on the correct balance of cytokine levels and other regulatory molecules.

While several researches have demonstrated an increase pro-inflammatory cytokines levels with decreased anti-inflamatory cytokines levels in autistics compare to controls, these finding might be variable between different regions and ethnicities. For example, a study based in Saudi Arabia did found a lower incidence of Il-6 hyperactivity among autistic patients compared to a control group, and another study did not found any correlation between degree of autism severity and the level of cytokines. Hence, the goal of this study was to test several pro interleukins levels and blood markers of gluten sensitivity in autistic patients in Jordan compared to controls. To test that, blood samples were collected from autistics, their unaffected siblings, and healthy unrelated controls. Later on, the plasma levels of IL-6, IL-8, IL-9, and IL-10 was measured by ELISA and compared between groups. For Gluten sensitivity, serum levels of IgA and IgG against gliadin and anti tissue transglutaminase was also measured by ELISA among the three groups. Furthermore, the association between immunological markers with age and symptoms was also investigated. Our preliminary data revealed increase pro-inflammatory cytokines, mainly IL-6 in autistic group compare to controls. Furthermore, while autistics did not have higher incidences of positive IG levels for anti tissue transglutaminase, they have a higher IG levels against gliadin compare to the control group.

Disclosures: L. Alzghoul: None. **A.H.I. Yanis:** None. **S.S.N. Mahmoud:** None. **Y.Z.S. Qwaider:** None. **M. Eldahabi:** None. **S. Albdour:** None.

Poster

776. Autism: Neuromimmune, Microbiota, and Environmental Factors

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 776.18/C4

Topic: A.07. Developmental Disorders

Support: NYU Challenge Grant 2014-15

Title: Increased microglial priming in autism spectrum disorder, an immunocytochemical study in postmortem human temporal cortex

Authors: *A. S. LEE[1,3,4], M. A. MOORE[1], Z. T. SACCOMANO[3], E. C. AZMITIA[3], P. M. WHITAKER-AZMITIA[1,2];
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Abstract: Microglia can shift into different complex morphologies depending on the microenvironment of the central nervous system (CNS). The distinct morphologies correlate with specific functions and indicate the pathophysiological state of the CNS. Previous postmortem

studies of autism spectrum disorder (ASD) showed regions of neuroinflammation in ASD resulting in changes in microglia number. These change in the microglia density can be accompanied by changes in microglia phenotype but the individual contribution of different microglia phenotypes to the pathophysiology of ASD remains unclear. Here, we used an unbiased semi-stereological approach to quantify six structurally and functionally distinct microglia phenotypes in postmortem human temporal cortex, which were immuno-stained with an antibody against Iba1. In addition to stereological measures, we used three different methods to quantify Iba1-immunoreactive microglia. We now report in human postmortem cortex measures on six distinct phenotypes including ramified, primed, reactive, amoeboid, rod and dystrophic. The total density of all microglia phenotypes did not differ between ASD donors (n=10, 14.6 yrs, range 2.8-29 yrs) and typically developing individual donors (controls, n=9, 14.9 yrs, 1.8-32 yrs). However, there was a significant decrease in ramified microglia in both gray matter and white matter of ASD, and a significant increase in primed microglia in gray matter of ASD compared to controls. This increase in primed microglia showed a positive correlation with donor age in both gray matter and white of ASD, but not in controls. Our results provide evidence of a shift in microglial phenotype that may indicate impaired synaptic plasticity, and a chronic vulnerability to exaggerated immune responses. We suggest the priming of microglia is most likely due to the disruption of maternal environment during pregnancy and developmental influences rather than genetic predispositions, but the exact mechanism is unclear. Further investigation in the underlying mechanism of the shift in microglia phenotype may be a step forward in understanding the significance of maternal environment and microglial pathology in ASD. Quantitative methods of measuring Iba1-immunoreactive microglia did not show significant difference between ASD and controls, which suggests the importance of using visual categorization or finer and/or more sensitive methods when neuroinflammation is subtle to delineate the complex morphology of microglia.

Disclosures: **A.S. Lee:** None. **M.A. Moore:** None. **Z.T. Saccomano:** None. **E.C. Azmitia:** None. **P.M. Whitaker-Azmitia:** None.

Poster

777. Adolescents: Mechanisms of Vulnerability

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 777.01/C5

Topic: A.09. Adolescent Development

Support: Wellcome Trust Neuroscience in Psychiatry Network

Title: Age dependent response to simulated brain injury in the functional connectome

Authors: *M. HART[1], E. BULLMORE[2], R. DOLAN[3], I. GOODYER[2], P. B. JONES[2], J. SUCKLING[2];
[1]Univ. of Cambridge, Cambridge, United Kingdom; [2]Dept. of Psychiatry, University of Cambridge, United Kingdom; [3]Wellcome Trust Ctr. for Neuroimaging, University College London, United Kingdom

Abstract: Introduction Brain robustness and recovery from injury is believed to be maximal in infancy, and then reduce during development. Despite corroboration of this theory in animal models, clinical evidence in humans is suggestive of a more complex relationship. We sought to model this process with a percolation theory analysis of the functional connectome to clarify the relationship between age and response to brain injury. **Methods** We recruited 100 healthy participants aged 14 to 24 years (50 female) and acquired multi-echo, BOLD sensitive, echo-planar imaging at 3 Tesla. Functional connectomes were formed using an anatomical template of 116 regions and Pearson correlations without thresholding. Brain injury was simulated through removal of nodes individually or sequentially (in either a random or targeted manner). Gender and age specific changes were analysed with a general linear model and permutation testing, corrected for the false discovery rate. **Results** Overall there was little significant change with age in resistance to sequential node removal (either targeted or random). However, the effects of removal of individual brain regions did changes with age, with approximately 10% of all nodes demonstrating either an increase or decrease in their vulnerability. Regions of increased vulnerability with age included deep nuclei and the cerebellum, while regions of decreased vulnerability were predominantly on the medial surfaces (for example the posterior cingulate cortex).**Conclusions** Age dependent response to brain injury during the adolescent to adult period involves a reorganisation of individual components rather than reflecting an overall feature of connectome or brain network organisation. This process suggests a parsimonious explanation for divergent clinical effects whereby the effects of injury vary with location and age. Further directions could include determining the effects of potential age-dependent plasticity on recovery and relating this to concurrent developmental processes such as synaptic refinement. Clarifying the mechanisms underlying how the brain responds to injury may allow us to better tailor neurosurgical approaches to lesion resections, for instance by avoiding vulnerable areas or those that have potential for recovery.

Disclosures: **M. Hart:** None. **E. Bullmore:** None. **R. Dolan:** None. **I. Goodyer:** None. **P.B. Jones:** None. **J. Suckling:** None.

Poster

777. Adolescents: Mechanisms of Vulnerability

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 777.02/C6

Topic: A.09. Adolescent Development

Support: NIH Training Grant: 5T32GM008602-17

Katherine Deschner Family NARSAD Award

NIH BRAINS Award: MH101477

Yerkes National Primate Research Center: P51OD011132

Viral Vector Core: P30NS055077

Title: Inhibition of rho-kinase II has antidepressant-like efficacy in adolescent mice

Authors: L. P. SHAPIRO[1], *S. L. GOURLEY[2];
[1]Pharmacol., [2]Pediatrics, Neurosci. Program, Emory Univ., Atlanta, GA

Abstract: Adolescence represents a critical period of neurodevelopment, defined by structural reorganization and synaptic maturation within the prefrontal cortex. Although these processes are critical for the transition to adulthood, structural instability may open a window of vulnerability to neuropsychiatric disorders including depression. Interventions that facilitate activity-dependent neural remodeling, as occurs during adolescence, may be advantageous. Here we evaluated the therapeutic-like potential of Rho-kinase (ROCK) inhibition, which can expedite activity-dependent dendritic spine plasticity. The brain-penetrant ROCK inhibitor fasudil had antidepressant-like effects in the forced swim test in adolescent mice and was comparable to ketamine and fluoxetine. Fasudil also decreased the latency to approach a palatable food in the novelty suppressed feeding task, a rapid antidepressant-like effect. Within the adolescent ventromedial prefrontal cortex (vmPFC), fasudil increased levels of the post-synaptic marker PSD-95, while pruning dendritic spines, resulting in adult-like spine densities. Fasudil stimulated several neurotrophin-related signaling factors in the vmPFC, including increasing the ratio of full-length:truncated tyrosine kinase receptor B (TrkB). Subsequent experiments utilizing viral vector-based and pharmacological manipulations indicated, however, that the antidepressant-like actions of fasudil are nonetheless attributable to the inhibition of the neuronal ROCK isoform, ROCKII.

Disclosures: L.P. Shapiro: None. **S.L. Gourley:** None.

Poster

777. Adolescents: Mechanisms of Vulnerability

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 777.03/C7

Topic: A.09. Adolescent Development

Support: NSF GRFP (DGE - 1414475)

NIH ES024850

Title: Adolescent exposure to methylmercury and d-amphetamine produce comparable reversal-learning impairments in mice

Authors: *R. A. SAUER, S. R. BOOMHOWER, K. R. JOHNSON, M. C. NEWLAND; Psychology, Auburn Univ., Auburn, AL

Abstract: Adolescence is a dynamic period of neuronal development in which the dopamine (DA) neurotransmitter system matures. These changes to the DA system may cause adolescents to be especially susceptible to neurotoxicants and drugs that act on DA. One such neurotoxicant, methylmercury (MeHg), inhibits the dopamine transporter (DAT) and promotes DA efflux in vitro. Gestational exposure to MeHg is associated with lasting deficits in behavioral flexibility and increased sensitivity to dopamine agonists, but the impact of adolescent MeHg exposure remains to be explored. Moreover, it is unclear whether the interactions of MeHg with DA are a mechanism by which MeHg produces these behavioral deficits. To assess the role of DA in MeHg's developmental neurotoxicity, we compared adolescent MeHg exposure to that of a drug that inhibits DAT and induces DA efflux, *d*-amphetamine (*d*-AMP). Adolescent male C57Bl/6n mice were randomly assigned to two MeHg-exposure groups (0 ppm and 3 ppm) and two *d*-AMP-exposure groups (saline and 1 mg/kg), producing four treatment groups (n = 10-12/group): Control, MeHg, *d*-AMP, and MeHg + *d*-AMP. MeHg exposure (via drinking water) spanned postnatal day 21 to 60 (the murine adolescent period), and once daily i.p. injections of *d*-AMP or saline spanned postnatal day 28 to 42. As adults, mice were trained on a spatial-discrimination-reversal task in which trials were response-initiated and the spatial location of a lever press (left or right) predicted reinforcement. Following two spatial discrimination reversals, a visual-discrimination task (extradimensional shift) was instated in which the presence of a stimulus light above a lever (lit or unlit) predicted reinforcement. Responding was modeled using a logistic function, which estimated the rate (slope) of a behavioral transition and trials required to complete half a transition (half-max). Adolescent exposure to MeHg alone, *d*-AMP alone, and MeHg + *d*-AMP increased estimates of half-max on the second reversal. MeHg exposure alone also increased half-max and decreased the rate of the transition following the extradimensional shift. Conjoint exposure to MeHg and *d*-AMP produced more perseverative errors and omissions following a reversal. The similar effects of MeHg and *d*-AMP exposure, alone and in combination, on reversal performance provide indirect evidence for the hypothesis that disruption of DA neurotransmission is a mechanism of MeHg-induced behavioral toxicity. Additionally, these data suggest that adolescence is a time during which the brain and behavior may be especially susceptible to MeHg exposure and its interaction with psychomotor stimulant drugs.

Disclosures: R.A. Sauer: None. **S.R. Boomhower:** None. **K.R. Johnson:** None. **M.C. Newland:** None.

Poster

777. Adolescents: Mechanisms of Vulnerability

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 777.04/C8

Topic: A.09. Adolescent Development

Support: NSF GRFP Fellowship DGE1414475

NIH Grant ES024850

Civitan International Research Center Emerging Scholar Award

Title: Epigenetic and behavioral influences of adolescent methylmercury exposure in mice

Authors: *S. R. BOOMHOWER[1], S. V. BACH[2], J. J. DAY[2], M. C. NEWLAND[1]; [1]Psychology, Auburn Univ., Auburn, AL; [2]Neurobio., Univ. of Alabama at Birmingham, Birmingham, AL

Abstract: Environmental stressors during critical developmental periods can have long-lasting, epigenetic consequences on neural and behavioral development. Exposure to the environmental neurotoxicant, methylmercury (MeHg), produces neurobehavioral dysfunction that persists long after exposure ceases. In animal models, gestational MeHg exposure disrupts cortical development, impairs reversal learning, and distorts the impact of reinforcing events on behavior in adulthood. The enduring impact of MeHg exposure supports a hypothesis that epigenetic dysregulation is a key mechanism underlying MeHg's toxicity. Perinatal MeHg exposure has been linked to decreased gene expression and deacetylation of histone N-terminals, a classic epigenetic mark, in the prefrontal cortex of adult animals. The impact of MeHg exposure during other sensitive periods of development, such as adolescence, has not been examined. Male C57Bl/6n mice were randomly assigned to three MeHg exposure groups (n = 12 in each): 0, 0.3, and 3.0 ppm MeHg (via drinking water). Exposure lasted from postnatal day 21 to 60, the murine adolescent period. As adults, lever-pressing was maintained under a multiple fixed-ratio (FR) schedule of reinforcement for sweetened-condensed milk. The response-to-reinforcer ratio increased within a session: FR 1, 5, 15, 30, 60 and 120. Responding was analyzed using Mathematical Principles of Reinforcement, a theoretically-driven model of reinforcement-based learning whose parameters reveal information about motor function, reinforcer efficacy, and saturation rate—a measure of the effects of delayed reinforcement. To examine the genome-wide transcriptional impact of adolescent MeHg exposure, directional poly(A)$^+$ RNA sequencing was performed on prefrontal-cortex samples from a separate cohort of animals exposed to 0 ppm (n = 7) and 3 ppm MeHg (n = 7) during adolescence. Adolescent MeHg exposure decreased estimates of minimum response time thereby increasing maximum response rates. MeHg also increased saturation rate, indicating that temporally distal responses were less likely to be strengthened by

reinforcement. Further, adolescent MeHg exposure suppressed expression of fourteen genes, including a number of immediate early genes implicated in neural development, learning, and motor function (e.g., *Btg2*, *Arc*, and *Fos*). Adolescence represents a vulnerable developmental window for long-lasting behavioral and epigenetic effects of neurotoxicant exposure. Neuroepigenetic markers coupled with detailed, theory-driven behavioral analyses provide a deeper understanding of brain-behavior relations with MeHg exposure.

Disclosures: S.R. Boomhower: None. **S.V. Bach:** None. **J.J. Day:** None. **M.C. Newland:** None.

Poster

777. Adolescents: Mechanisms of Vulnerability

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 777.05/C9

Topic: A.09. Adolescent Development

Support: MH099625

T32 ES007326

Title: Pubertal stress exerts sex-specific deficits on pre-pulse inhibition and forced swim test performance in adulthood

Authors: *C. DRZEWIECKI, J. WILLING, L. CORTES, J. JURASKA;
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Abstract: Adolescence, the period between childhood and adulthood, is a peak time for the onset of various mental illnesses, including depression, anxiety, and schizophrenia. Additionally, numerous neuroanatomical changes occur across adolescence, particularly within the medial prefrontal cortex (mPFC), a region implicated in these disorders. Previous research from our laboratory has demonstrated that the onset of puberty in both male and female rats may affect neuronal and/or synaptic pruning within the mPFC, suggesting puberty is a critical time for development of this region. While research suggests that adolescent stress during adolescence may contribute to symptoms of mental illness, no research to date has examined the role of pubertal onset in sex-specific effects of stress. We exposed male and female rats to a combination of isolation and restraint stress during the onset of puberty or during the post-pubertal period of adolescence, with an additional unstressed control group. At young adulthood, all subjects were tested in an Elevated Plus Maze (EPM), Forced Swim Task (FST), Pre-pulse Inhibition (PPI), Open Field Task, and a Novel Object Recognition task. While we found no

effects of stress on Open Field or Novel Object Recognition performance, we did find sex-specific effects of pubertal stress on EPM, FST, and PPI. Females stressed during the window of pubertal onset displayed an increased latency to enter an open arm in the EPM, as well as increased time spent immobile during the FST. Males stressed during pubertal onset showed deficits on a PPI task. These results demonstrate sex-specific effects associated with pubertal, but not post-pubertal, stressors during adolescence, which may contribute to peak onset of mental illnesses during this time.

Disclosures: **C. Drzewiecki:** None. **J. Willing:** None. **L. Cortes:** None. **J. Juraska:** None.

Poster

777. Adolescents: Mechanisms of Vulnerability

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 777.06/C10

Topic: A.09. Adolescent Development

Support: NIDA/NIH Grant R01 DA-026485

NIDA/NIH Grant R01 DA-015403

Title: Novelty preferences are associated with blood flow changes in addiction regions of the brain of female juvenile rats

Authors: ***A. N. ROCK**[1], M. ROHAN[2], S. B. LOWEN[2], K. J. NORMAN[3], S. L. ANDERSEN[3]; [1]McLean Hospital; Harvard Med. Sch., Belmont, MA; [2]McLean Imaging Center; Dept. of Psychiatry, [3]Lab. of Developmental Neuropharmacology; Dept. of Psychiatry, McLean Hospital; Harvard Med. Sch., Belmont; Boston, MA

Abstract: Adolescence is a critical neurodevelopmental period rife with novelty-seeking and impulsive behaviors that facilitate drug use and increase vulnerability to addiction. Concurrent with and related to these changes, the adolescent prefrontal cortex overexpresses dopamine D1 receptors (D1r) in glutamatergic neurons that project to the reward area of the nucleus accumbens. These D1rs are associated with an increased sensitivity to drug cues. We investigated whether the overexpression of D1rs within the female adolescent rat brain would increase either novelty-preferring behaviors and/or preferences to cocaine-associated environments. We also assessed whether conditioned odor cues would change blood flow in addiction-relevant brain areas. On postnatal day (P) P16, a lentiviral vector that overexpressed D1r was injected into the prelimbic prefrontal cortex of female rats, while a control group received only the green fluorescent protein-expressing vector. Rats were then behaviorally tested

for novelty preference on P19-P23. Afterwards, rats were administered two cocaine injections (10 mg/kg, i.p.) on P24-P27 paired with an odor stimulus to condition a place preference to the setting in which they received the drug. Employing the methods of Lowen et al (2015), the same cocaine conditioned odor stimulus was used in conjunction with whole-brain functional magnetic resonance imaging (fMRI) at 9.4T on P28 to determine blood flow responses to the drug cue. Contrary to our hypothesis, post-conditioning trials revealed a trend (P=0.08) in which the control group spent the majority of time in the drug-paired chamber, while the rats overexpressing D1r demonstrated no preference. Functional MRI responses to the conditioned odor in both the rats with increased preference to novel environments and those treated to overexpress D1rs indicated increased activation in the prefrontal cortex and the dorsal striatum, and a concurrent decrease of activity in the insula.The strong activation in the dorsal striatum observed in female adolescent rats suggests that blood flow increases in this region, which are associated with habit formation and cue reactivity rather than reward per se, might place adolescent females at elevated risk for addiction. The decrease in activation in the insula in these rats suggests a corresponding decrease in response inhibition. These two imaging observations in this two-day cocaine and odor stimuli conditioning experiment suggest increased vulnerability to psychostimulant addiction in adolescent females may be related to novelty preferences.

Disclosures: A.N. Rock: None. **M. Rohan:** None. **S.B. Lowen:** None. **K.J. Norman:** None. **S.L. Andersen:** None.

Poster

777. Adolescents: Mechanisms of Vulnerability

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 777.07/C11

Topic: A.09. Adolescent Development

Support: East Tennessee State University Honors College

Title: Adolescent methylphenidate exposure alters nicotine self-administration and the accumbal firing response to nicotine

Authors: *C. C. DE PRETER[1], L. J. HERNANDEZ[1], S. L. KIRBY[1], R. B. CAMPBELL[2], E. BEAUMONT[2], C. A. BRADLEY[1], M. I. PALMATIER[1], R. W. BROWN[2];
[1]Psychology, [2]Biomed. Sci., East Tennessee State Univ., Johnson City, TN

Abstract: This study was designed to analyze the effects of adolescent exposure to methylphenidate (MPH; trade name: Ritalin) on nicotine self-administration, the motivation to obtain nicotine, and accumbal neuronal firing rate in female adolescent rats. MPH is the most

commonly prescribed medication for Attention Deficit-Hyperactivity Disorder (ADHD) which is diagnosed in 3-5% of adolescents in the United States. However, this disorder is often misdiagnosed, and MPH is often prescribed to individuals not diagnosed with ADHD. Adolescent female Sprague-dawley rats were ip administered 1 mg/kg MPH or saline using a "school day" regimen of five days on, two days off, beginning on postnatal day (P)28 and this regimen was maintained throughout testing. A 1 mg/kg dose of MPH has been shown to result in brain plasma levels equivalent to clinical dosing in humans. Indwelling catheters were implanted in the jugular vein at P35, and one week later on P42, animals began nicotine self-administration. MPH (1 mg/kg) was administered each day approximately 6 h before each self-administration session began, which allows for nearly full plasma clearance of MPH (half-life = 1 h) before self-administration commenced. Rats were reduced to 85% of their free-feeding body weight and sipper tubes were made available to the rats in this paradigm, and responses to licking the tube produced an infusion of nicotine solution (15μg/kg) over a range of fixed ratio (FR) reinforcement schedules followed by a progressive ratio (PR) schedule, a measure of motivation. The schedule of reinforcement during 60 min sessions was increased from an FR5 to FR15 over approximately a three-week period. Results revealed that MPH pre-exposed rats self-administered significantly higher amounts of nicotine as compared to animals treated with saline throughout the FR5 and FR10 schedules. Further, MPH enhanced the motivation to self-administer nicotine on the PR schedule compared to controls, demonstrating an enhanced motivation to obtain nicotine produced by MPH. Finally, animals that had been pre-exposed to MPH and self-administered nicotine demonstrated a lower rate of basal accumbal firing as compared to controls, but a burst firing in response to nicotine that was higher than rats pre-exposed to saline. In conclusion, MPH altered the behavioral and neural response to nicotine in the nucleus accumbens.

Disclosures: C.C. De Preter: None. **L.J. Hernandez:** None. **S.L. Kirby:** None. **R.B. Campbell:** None. **E. Beaumont:** None. **C.A. Bradley:** None. **M.I. Palmatier:** None. **R.W. Brown:** None.

Poster

777. Adolescents: Mechanisms of Vulnerability

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 777.08/C12

Topic: A.09. Adolescent Development

Support: NIMH R01 MH096093

NIMH R01 MH087660

Title: Epigenetic alterations apparent in brain-expressed genes after severe childhood trauma

Authors: *A. ZIMMERMAN[1], F. E. MENNEN[2], E. L. BEARER[1];
[1]Univ. of New Mexico Hlth. Sci. Ctr., Albuquerque, NM; [2]Sch. of Social Work, USC, Los Angeles, CA

Abstract: Childhood maltreatment is a major risk factor for poor physical outcomes in adulthood including depression, anxiety and cognitive dysfunction. Therefore, it is necessary to develop biomarkers as indicators of maltreatment at an early age, before later-life clinical outcomes present themselves. For a preliminary study, we used children who were referred by Los Angeles County Child Protective Services to Children's Institute Inc. for recruitment into a trauma therapy program. Children, exposed to documented trauma at some point before entry into therapy, were followed for 6 to 8 months. Between their intake and one-month follow-up after therapy, only a portion of these children continued to experience traumatic events. At entry into therapy and one-month post therapy, three centimeters of hair were taken to measure average cortisol as a representative marker of long-term stress. Using an Illumina Infinium MethylationEPIC BeadChip we measured genome wide DNA methylation from saliva for over 850,000 methylation sites for six children to observe differences in children recently exposed to severe trauma, compared to children with no recent report of severe trauma. While average cortisol was not significantly correlated with caregiver-reported trauma, we found significant alterations in DNA methylation were apparent after traumatic experiences, such as domestic or sexual violence, especially in cases with no reported traumatic event in the previous month. These significant changes were primarily in genes involved in immune response and regulation of DNA methylation, while a few methylation sites were altered for genes over-expressed in the brain. While global methylation levels from one time point to another were not drastically changed, a subset of promoter regions and gene bodies were significantly altered indicating that significant methylation changes can occur in a period of only a few months. It also appears that the duration and intensity of the trauma may play a role in the amount of change seen in methylation levels. After seeing significant methylation changes in individuals with a similar trauma history, we hope to validate this finding in children from a different fifteen-year study to determine long-term effects that severe childhood maltreatment has on DNA methylation from early childhood into adulthood.
Supported by: NIMH R01 MH096093 (Bearer) and NIMH R01 MH087660 (Jacobs)

Disclosures: A. Zimmerman: None. **F.E. Mennen:** None. **E.L. Bearer:** None.

Poster

777. Adolescents: Mechanisms of Vulnerability

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 777.09/C13

Topic: A.09. Adolescent Development

Support: This Research was funded by the Leverhulme Trust [F/07134/CZ (P12835)] and a Wellcome Trust/MRC Joint Call in Neurodegeneration Award (WT089698)This Research was funded by the Leverhulme Trust [F/07134/CZ (P12835)] and a Wellcome Trust/MRC Joint Call

EJK is supported by an MRC studentship

SJB is a Royal Society University Research Fellow and receives funding from the Wellcome Trust, the Nuffield Foundation and the Jacobs Foundation

Title: Developmental changes in the influence of COMT genotype on the flexible processing of self-generated information and trait anxiety

Authors: *E. J. KILFORD[1], I. DUMONTHEIL[2], S.-J. BLAKEMORE[3];
[1]UCL Inst. of Cognitive Neurosci., London, United Kingdom; [2]Dept. of Psychological Sci., Birkbeck, Univ. of London, London, United Kingdom; [3]Inst. of Cognitive Neurosci., Univ. Col. London, London, United Kingdom

Abstract: The catechol-O-methyltransferase enzyme (COMT) is a major determinant of prefrontal dopamine levels. The Val[158]Met polymorphism of the *COMT* gene has previously been associated with reciprocal variation in executive function and affective reactivity, hypothesised to represent a trade-off between cognitive efficiency and affective resilience. In adults, the Met allele, which results in lower enzymatic activity and higher dopamine availability, has been associated with superior executive function and working memory, whereas the Val allele has been associated with advantages in affective processing and lower levels of anxiety disorders and related traits. Dopamine effects on prefrontal function follow an inverted U-shape curve, with both deficient and excessive levels resulting in poor cognitive performance. A recent study demonstrated that Met allele advantages on working memory emerge during adolescence, consistent with developmental changes in the dopaminergic system that are hypothesised to shift the relative position of each *COMT* genotype group on the dopamine curve. We investigated developmental changes in the influence of *COMT* genotype on both executive function, specifically the flexible processing of self-generated information, and trait anxiety. A cross-sectional sample of healthy adults and adolescents (N=307, aged 9 to 37 years) performed a behavioural task in which they processed alternating blocks of self-generated and stimulus-oriented information, and completed measures of self-reported trait anxiety. We hypothesised that associations between *COMT* genotype and cognition would be moderated by developmental

stage.
Age group x *COMT* genotype interactions were found for both task accuracy and trait anxiety. Met/Met adults were more accurate and had higher trait anxiety relative to adult Val carriers, whereas Met/Met adolescents were relatively less accurate and had lower trait anxiety than adolescent Val carriers. These results extend previous findings of developmental variation in the association between *COMT* genotype and prefrontal cognition to other aspects of executive function and to individual differences in trait anxiety, consistent with trade-off models of *COMT* genotype effects.

Disclosures: **E.J. Kilford:** None. **I. Dumontheil:** None. **S. Blakemore:** None.

Poster

777. Adolescents: Mechanisms of Vulnerability

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 777.10/C14

Topic: A.09. Adolescent Development

Support: National Health and Medical Research Council (NHMRC) Career Development Fellowship APP1083309

National Health and Medical Research Council (NHMRC) Principal Research Fellowship 1020737

Melbourne International Research Scholarship (MIRS)

Title: Escalation of methamphetamine intake in adolescent rats compared to adults

Authors: *S. J. LUIKINGA[1,2], H. B. MADSEN[1,2], I. C. ZBUKVIC[1,2], A. J. LAWRENCE[1,2], J. KIM[1];
[1]Behavioural Neurosci., Florey Inst. of Neurosci. and Mental Hlth., Parkville, Australia; [2]Univ. of Melbourne, Melbourne, Australia

Abstract: Methamphetamine (Meth) abuse is a growing problem in Australia, with the rise in its purity as a main concern. Additionally, the age of Meth abusers has significantly dropped over the past few years with children as young as 10 years admitted to hospital on Meth. Therefore, we used the intravenous self-administration paradigm to compare Meth abuse-related behaviour in adolescent (postnatal day 35) and adult (postnatal day 70) rats. Rats were trained to lever press for Meth at a dose of 0.03 mg/kg/infusion. It was found that both adults and adolescents acquired in a similar manner however, after acquisition, adolescent rats escalated their intake when the dose was increased (0.1mg/kg/infusion, $p<0.05$). To test whether this escalation was due to pre-

exposure to Meth or due to a particular affinity for 0.1mg/kg/infusion, a new group of rats acquired at 0.1mg/kg/infusion, and then were tested on 0.3mg/kg/infusion. Interestingly, both age groups acquired in a similar manner and again an escalation of intake was seen in the adolescent group on the high dose ($p<0.05$). We also investigated the effects of meth vs saline on the number of interneurons in adolescent and adult rats using immunofluorescent staining of Parvalbumin (PV) and Somatostatin (SST). Preliminary data suggest that meth self-administration reduces the number of PV-positive interneurons in the infralimbic cortex in adolescents more dramatically compared with adult rats.

Disclosures: S.J. Luikinga: None. **H.B. Madsen:** None. **I.C. Zbukvic:** None. **A.J. Lawrence:** None. **J. Kim:** None.

Poster

777. Adolescents: Mechanisms of Vulnerability

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 777.11/C15

Topic: A.09. Adolescent Development

Support: NIH AA019967

NIH AA020537

NIH T32DA007288

Title: The impact of adolescent alcohol exposure on fear memory acquisition, extinction, consolidation, and recall in adulthood

Authors: *R. J. NEWSOM, E. GLOVER, J. CHANDLER, J. GASS;
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Abstract: Ethanol is the most commonly used drug among adolescents in the United States, and is frequently ingested in repeated binge-like episodes involving large amounts consumed over short periods of time. The lasting effects of these binge-like exposures are not well understood. In the present study, we examined the effects of adolescent intermittent ethanol (AIE) vapor exposure (postnatal days 28-44) on fear conditioning and extinction in adulthood. AIE-exposed and air-exposed controls received 3 daily sessions of fear conditioning in which an auditory tone was paired with a moderate (0.75 mA) foot shock. Following conditioning, all rats were given 5 daily extinction sessions in which the visual context was altered and the auditory tone was no longer followed by a foot shock. All rats had reached extinction criteria on the 5th day of extinction. Following extinction, rats were tested in multiple conditions to allow for examination

of context-induced freezing behavior, retention of extinction learning, and spontaneous recovery of conditioned freezing behavior. The results indicated that AIE-exposed rats acquired fear conditioning more quickly when compared to air-exposed controls. Additionally, AIE-exposed rats exhibited significantly less freezing in response to the fear context. However, when tested in a retention trial to assess their ability to retain the extinction memory of the tone AIE-exposed rats display significantly higher freezing rates in response to the tone. Furthermore, AIE-exposed rats demonstrated higher freezing rates during a spontaneous recovery test of conditioned freezing three weeks later. These data suggest that AIE exposure results in lasting neural alterations that increase susceptibility to fear memory acquisition and disrupt consolidation of contextual and extinction memories in adulthood. These behavioral alterations are possibly due to AIE-induced disruptions in multiple neural mechanisms related to memory formation and consolidation. We are currently examining the impact of AIE exposure on stress reactivity measures and exploring potential mechanisms to attenuate AIE-induced deficits in fear-related memories.

Disclosures: **R.J. Newsom:** None. **E. Glover:** None. **J. Chandler:** None. **J. Gass:** None.

Poster

777. Adolescents: Mechanisms of Vulnerability

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 777.12/C16

Topic: A.09. Adolescent Development

Support: NIH/NIAAA 2U01 AA019969-06

NIH/NIAAA 5R01 AA006059-22

Title: Effects of chronic intermittent adolescent ethanol exposure on early and late modulation of Ox/Hcrt system

Authors: *M. SANCHEZ-ALAVEZ, W. NGUYEN, S. MORI, D. N. WILLS, B. CONTI, C. L. EHLERS;
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Abstract: Recently it has been shown that the orexin/hypocretin (Ox/Hcrt) system is involved in the mediation of sleep as well as the reward aspect of ethanol intake. However the effect of ethanol itself on the Ox/Hcrt system has been poorly explored. Here we investigated the effects of chronic intermittent ethanol (CIE) exposure on early (0h and 24h) and late modulation (4 weeks) of Ox/Hcrt system after CIE exposure in adolescent rats. 48 rats (P22) were divided in

two groups, the control group (n=24) and EtOH group (n=24) that was exposed to CIE for 5 weeks (P22-P56). Control and CIE groups were subdivided in three subgroups (n=8) and sacrificed at P57 (0h), P58 (24h) and P85 (4 weeks) after CIE exposure. Ox/Hcrt levels and the expression of prepro Ox/Hcrt mRNA and GABARα1 mRNA on lateral hypothalamus were investigated using an enzyme link immunoassay (EIA) and SQPCR respectively. In addition, Ox/Hcrt 1 and 2 receptors mRNA, GAD65 mRNA, GAD67 mRNA were evaluated in the anterior hypothalamus, which includes the median preoptic area (MnPO). Results show that CIE did not change Ox/Hcrt peptide levels on lateral hypothalamus although expression of prepro Ox/Hcrt mRNA increased on P57 (0h, $p<0.05$) returning to control expression levels on P58 and P85. GABARα1 mRNA was upregulated at P85 compared to control ($p<0.05$). No significant changes were observed in the expression of GAD65, GAD67 and Ox/Hcrt 1 and 2 receptors mRNA in the anterior hypothalamus. These data indicate that CIE during 5 weeks disrupt the early modulation of prepro Ox/Hcrt mRNA expression and late modulation of GABARα1 mRNA on lateral hypothalamus.

Disclosures: **M. Sanchez-Alavez:** None. **W. Nguyen:** None. **S. Mori:** None. **D.N. Wills:** None. **B. Conti:** None. **C.L. Ehlers:** None.

Poster

777. Adolescents: Mechanisms of Vulnerability

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 777.13/C17

Topic: A.09. Adolescent Development

Support: U01 AA019972

Title: Developmental effects of the AMPA receptor antagonist NBQX differ from adolescent-specific effects of ethanol on social interactions

Authors: *C. DANNENHOFFER, E. I. VARLINSKAYA, L. P. SPEAR;
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Abstract: Adolescent and adult rats respond differently to drugs of abuse, including ethanol. We have previously shown pronounced age differences in sensitivity to the social consequences of acute ethanol challenge. Adolescents, but not adults, display increases in social activity in a modified social interaction test following a low dose of ethanol, and are less sensitive than adults to the social inhibitory effects of higher doses of ethanol. Among the prominent neural effects of ethanol are its glutamate antagonistic-like effects, raising the possibility that age dependent effects of ethanol on social behavior may be related to developmental alterations in

glutamatergic function. Indeed, reminiscent of the developmental data with ethanol, adolescents show age-specific induction of social facilitation by the selective NMDA NR2B antagonist ifenprodil, and are less sensitive than adults to the social inhibitory effects of this NMDA antagonist. The purpose of the current experiment was to determine whether an ontogenetic pattern similar to those of ethanol and ifenprodil will be evident following antagonism of another type of glutamate receptor, namely AMPA receptors. The effects of a specific AMPA1 receptor antagonist, NBQX, were assessed in a social interaction test in adolescent and adult male and female Sprague Dawley rats. Animals were injected i.p. with a dose of NBQX (0.0, 1.0, 2.0, 4.0, 6.0 and 8.0 mg/kg) and placed alone into a two-compartment apparatus for a 30-min habituation period. A non-familiar social partner was then placed into the chamber for 10 min, and the session was videotaped for later scoring of the social behaviors. There were significant main effects of age and dose for all social measures (social investigation, contact behavior, play fighting, and the preference/avoidance coefficient), with adolescents generally showing more social behavior than adults. Unlike effects shown previously with ethanol and ifenprodil, no stimulatory effect of NBQX emerged at any dose in adolescents. Both adolescents and adults were sensitive to the social inhibitory effects of the two highest doses of NBQX, with few age differences in this social inhibition. Taken together, the data provide little evidence for notable differences between adolescents and adults in response to NBQX in a social interaction test, findings that vary considerably from the adolescent-specific effects of ethanol and the NR2B antagonist ifenprodil on social behavior. Results from this study further our understanding of the potential role of specific glutamate receptor systems during ontogeny in contributing to age-specific effects of ethanol on social behavior during adolescence.

Disclosures: C. Dannenhoffer: None. **E.I. Varlinskaya:** None. **L.P. Spear:** None.

Poster

777. Adolescents: Mechanisms of Vulnerability

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 777.14/C18

Topic: A.09. Adolescent Development

Support: NIH Grant AA020022

Title: Adolescent intermittent binge ethanol alters ERK1/2 phosphorylation expression in the different brain regions of adult rat

Authors: *W. LIU, F. T. CREWS;
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Abstract: Adolescence is a vulnerable developmental period when many binge drink. We previously found that adolescent intermittent binge ethanol (AIE) decreased ERK1/2 phosphorylation (pERK1/2) immunoreactivity (pERK1/2+IR) in the frontal cortical regions of adult rat brain. AIE blunted acute ethanol-induced decrease in the prelimbic and infralimbic cortex. In the current study, we determined the effect of AIE on pERK1/2+IR in other brain regions of adult (P80) rats. Male Wistar rats were bred and reared in our vivarium. On the day following birth (P1), litters were culled to 10 pups. At weaning on P21, male offspring were weight matched and pair-housed. Two groups, water control and ethanol (AIE, 5 g/kg/day, i.g., P25-P54; 2 days ethanol, 2 days off) were further divided at P80 following 26 days without ethanol, into water or ethanol (4 g/kg, i.g.) challenge separately, and sacrificed 2 hours later. At P80, in non-ethanol treatment control, ethanol challenge decreased pERK1/2+IR about 50~90% in most brain regions, including agranular insular (AI), forceps minor of the corpus callosum (fmi), ectorhinal (Ect), perirhinal (PRh) and lateral entorhinal (LEnt) cortex; amgydala, the ventral part of lateral septal nucleus (LVS), granular cell layer (GCL), lateral habenular nucleus(LHb), rostral linear nucleus of the raphe (RLi), anterior (aVTA) and posterior (pVTA) ventral tegmental area, except the nucleus accumbens (NAc) and medial habenular nucleus (MHb) which were not changed. In AIE treated group, AIE decreased adult pERK1/2+IR baseline (of control) in AI (19%, $p<0.001$); Ect (15%, $p<0.001$), PRh (27%, $p<0.001$), LEnt (10%); LVS (41%, $p<0.01$); amgydala (Lateral: 13%, $p<0.001$; Basolateral: 17%, $p<0.01$; Central: 34%, $p<0.01$); RLi (57%, $p<0.01$); aVTA (24%, $p<0.001$) and pVTA (24%, $p<0.001$) except NAc shell and GCL which pERK1/2+IR were increased about 216% and 166% (of control), separately, and NAc Core, the habenular nucleus and fmi which were not changed. In contrast, AIE blunted acute ethanol-induced decrease in the fmi ($p<0.05$); and AIE had a trend to blunt acute ethanol-induced increase in NAc shell (p=0.068). In the some brain regions, baseline was near zero suggesting a long lastly effect to AIE. These findings indicate that adolescent intermittent binge ethanol has a long lastly impacts on the activation of extracellular signal-regulated kinase in nucleus accumbens shell and granular cell layer of hippocampus of adult rat brain. ERK1/2 pathways involved in AIE effect on brain functions will further be investigated. (Supported by the NADIA from NIAAA).

Disclosures: W. Liu: None. **F.T. Crews:** None.

Poster

777. Adolescents: Mechanisms of Vulnerability

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 777.15/C19

Topic: A.09. Adolescent Development

Support: NIH Grant U01AA024599

NIH Grant R01AA021121

NIH Grant T32AA07455

Title: Arrested development following adolescent alcohol intake? Investigation of risky behavior and NAcc phasic dopamine release during development

Authors: *L. KRUSE, A. SCHINDLER, K. REICHARD, J. J. CLARK;
Univ. of Washington, Seattle, WA

Abstract: Adolescence is characterized by increased sensation seeking and risk taking, often including initial experimentation with alcohol. Adolescent alcohol use is a major public health concern given that age of onset of alcohol use is one of the best predictors of development of alcohol use disorders in adults. Using a preclinical model of risky decision making, we have previously demonstrated that voluntary alcohol intake during adolescence, but not adulthood, promotes maladaptive, risky choice behavior in adulthood. These data indicate a unique vulnerability of adolescents to the long-term effects of alcohol on decision making. Using fast scan cyclic voltammetry (FSCV), we further demonstrated increased phasic dopamine release in the nucleus accumbens core (NAcc) in response to risky, but not safe, options in adults exposed to alcohol as adolescents. Consistent with this data, we recently showed that pedunculopontine tegmental nucleus (PPT), but not median forebrain bundle (MFB), stimulated dopamine release is greater in the NAcc of adults exposed to alcohol during adolescence compared to controls. We hypothesize that exposure to alcohol during this critical developmental period arrests normal brain development "locking in" an adolescent phenotype of risk taking behavior and increased phasic dopamine release that persists into adulthood. Here, we utilize *in vivo* FSCV, as well as probability discounting as a preclinical model of risky decision making, to begin to examine this hypothesis. Briefly, the probability discounting task involves a choice between a 'safe' lever that consistently delivers a low reward or a 'risky' lever that delivers a high reward at decreasing probabilities. Risky decisions are those where a large but uncertain reward is favored over a smaller certain reward of equal or expected value. Our results demonstrate that adolescent animals show a risk preference comparable to that of adult animals that voluntarily consumed alcohol during adolescence. In further support of our hypothesis, we show that PPT, but not MFB, stimulated phasic dopamine signaling in the NAcc peaks in late adolescence (PND50-55) and closely resembles PPT stimulated dopamine release in adult animals that were exposed to alcohol as adolescents. Present studies are utilizing *in vivo* FSCV in freely behaving animals to examine risky choice in late adolescence versus adulthood and associated phasic dopamine signaling to a risky decision. Together, our results provide novel insight into the long-term effects of adolescent alcohol exposure on maladaptive decision making and the underlying neurocircuitry.

Disclosures: **L. Kruse:** None. **A. Schindler:** None. **K. Reichard:** None. **J.J. Clark:** None.

Poster

777. Adolescents: Mechanisms of Vulnerability

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 777.16/C20

Topic: A.09. Adolescent Development

Support: AA024612

AA020908

AA022167

AA07611

AA07462

AA012262

Title: Voluntary ethanol consumption during adolescence enhances the sensitivity and response to nicotine within the mesolimbic dopamine system during adulthood

Authors: *Z. A. RODD, A. L. BRACKEN, G. A. DEEHAN, Jr, C. P. KNIGHT, R. A. WAIESS, W. J. MCBRIDE, R. L. BELL, S. R. HAUSER;
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Abstract: The age of onset of alcohol consumption in adolescents is associated with an increased risk of alcoholism during adulthood. The negative consequence of adolescent alcohol consumption is not specific to alcoholism, since there is a link to an increase risk of addiction to other drugs of abuse. Very little preclinical data has examined the effects of adolescent alcohol consumption on the response to other drugs of abuse during adulthood. Previous work from our laboratory has indicated that microinjection of nicotine directly into the posterior VTA stimulates dopamine (DA) release in the nucleus accumbens shell (AcbSh). The current study examined the effects of voluntary adolescent ethanol consumption on the ability of nicotine microinjected directly into the posterior VTA to stimulate (DA) release in AcbSh. Alcohol-preferring (P) male rats were allowed to consume EtOH (concurrent 15 and 30%) during post-natal day 30-60. After adolescent exposure, all rats were maintained without further treatment until at least post-natal day 90. Rats were implanted with ipsilateral guide cannulae aimed at the posterior VTA and the AcbSh. Microinjections were administered at a volume of 100 nl over a 5-sec period 3 times a minute (every 20 sec) during the first 10 min of the sample (30 microinjections total). This injection protocol mirrored self-administration for nicotine into the pVTA. Following microinjections, a minimum of 5 additional samples were collected. Rats were microinjected with aCSF, 1, 10 or 50 μM nicotine. Microinjection of 10 or 50 μM nicotine into the posterior

VTA of adolescent naïve P rats increased DA levels in the AcbSh (maximum response approximately 43 and 78%, respectively). The data indicated that lower concentrations of nicotine stimulated DA release in P rats that consumed ethanol during adolescence. In addition, the amount of DA released by 1, 10, or 50 μM nicotine microinjected into the posterior VTA was larger in the adolescent drinkers (48, 105, and 187%, respectively). The data indicate that adolescent ethanol consumptions results in a persistent alteration in the response to nicotine within the mesolimbic DA system. This cross sensitization produced by adolescent ethanol consumption could be the biological basis for the heightened rate of addiction to other drugs of abuse observed in adolescents who consume alcohol at an early age.

Disclosures: Z.A. Rodd: None. **A.L. Bracken:** None. **G.A. Deehan:** None. **C.P. Knight:** None. **R.A. Waiess:** None. **W.J. McBride:** None. **R.L. Bell:** None. **S.R. Hauser:** None.

Poster

777. Adolescents: Mechanisms of Vulnerability

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 777.17/C21

Topic: A.09. Adolescent Development

Support: AA024612

AA0200908

AA022167

AA013522

AA019366

AA007611

Title: Exposure to nicotine during adolescence increases the neurochemical response to nicotine within the mesolimbic dopamine system during adulthood.

Authors: *S. R. HAUSER[1], A. L. BRACKEN[2], C. P. KNIGHT[3], G. A. DEEHAN, Jr.[2], R. A. WAEISS[2], W. J. MCBRIDE[2], R. L. BELL[2], Z. A. RODD[2];
[1]Inst. of Psychiatric Res., Indiana Univ. Sch. of Med., Indianapolis, IN; [2]Indiana Univ. Sch. of Med., Indianapolis, IN; [3]Indiana Univ. Sch. of Med., Indianapolis, United States Minor Outlying Islands

Abstract: There is a positive correlation between the onset of drug use during adolescence with drug dependency during adulthood. The biological basis for this alteration in risk for addiction is unknown. Therefore, determining the biological consequences of adolescent exposure to nicotine on adult responsiveness to nicotine is of particular importance. Previous work from our laboratory has indicated that nicotine treatment during adolescence increased the onset of nicotine-induced locomotor activity during adulthood. The current study examined the effects of adolescent nicotine exposure on the ability of nicotine microinjected directly into the posterior VTA to stimulate dopamine (DA) release in the nucleus accumbens shell (AcbSh). Wistar male rats were administered 0 or 0.5 mg/kg nicotine during post-natal day 30-55. After adolescent exposure, all rats were maintained without further treatment until at least post-natal day 90. Rats were implanted with ipsilateral guide cannulae aimed at the posterior VTA and the AcbSh. Microinjections were administered at a volume of 100 nl over a 5-sec period 3 times a minute (every 20 sec) during the first 10 min of the sample (30 microinjections total). This injection protocol mirrored self-administration for nicotine into the pVTA. Following microinjections, a minimum of 5 additional samples were collected. Rats were microinjected with aCSF, 100 or 200 μM nicotine. Microinjection of 100 or 200 μM nicotine into the posterior VTA of adolescent naïve Wistar rats increased DA levels in the AcbSh (maximum response approximately 55 and 62%, respectively). The neurochemical response to nicotine microinjected into the posterior VTA in Wistar rats treated with nicotine during adolescence was significantly greater (maximum response approximately 188 and 239%, respectively). In addition, the effects of nicotine microinjection into the posterior VTA were more prolonged in nicotine treated adolescent rats compared to controls (80 min compared to 40 min). The data indicate that adolescent exposure to nicotine results in a persistent alteration in the response to nicotine within the mesolimbic DA system. This increase responsiveness to, and effectiveness of, nicotine within this system may be part of the biological basis for the increase propensity for nicotine dependency during adulthood following nicotine use during adolescence.

Disclosures: **S.R. Hauser:** None. **A.L. Bracken:** None. **C.P. Knight:** None. **G.A. Deehan:** None. **R.A. Waeiss:** None. **W.J. McBride:** None. **R.L. Bell:** None. **Z.A. Rodd:** None.

Poster

777. Adolescents: Mechanisms of Vulnerability

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 777.18/C22

Topic: A.09. Adolescent Development

Support: NIH Grant AA019967

Title: Adolescent alcohol exposure produces resistance to habit formation in adulthood

Authors: J. I. OBSORNE, J. M. BARKER, *L. CHANDLER;
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Abstract: Adolescence is a period of significant cortical development and refinement of neural circuits. Binge drinking patterns, which are common in adolescents, may result in aberrant remodeling of these circuits and potentially promote addiction in adulthood. Addiction is a chronic relapsing disorder characterized by inflexible drug seeking and may involve a transition from goal-directed behaviors, where drugs and alcohol are sought for their reinforcing properties, to automatic habitual behaviors. Here, we investigated how a model of binge-like alcohol exposure (intermittent ethanol exposure in adolescence; AIE) may result in dysregulation of behavioral flexibility in adulthood. To determine how adolescent alcohol exposure impacts habitual reward seeking in adulthood, male and female Long Evans rats were exposed to ethanol via vapor inhalation in the AIE paradigm. Subsequently, adult rats that had been exposed to AIE were trained to lever press for a 20% liquid sucrose reward on random interval (habit-promoting) and random ratio (action-promoting) schedules. Because habits are insensitive to changes in action-outcome contingencies, the expression of goal-directed or habitual reward seeking strategies can be assessed using contingency degradation paradigms. Contrary to our hypothesis that binge alcohol exposure during adolescence would facilitate habitual behavior in adulthood, we observed that at a time point where control adult rats exhibited habitual reward seeking on the interval (habit-promoting) lever, AIE-exposed adult rats exhibited goal-directed response strategies. Current studies are investigating c-fos induction after the expression of either goal-directed or habitual behavior in brain areas known to mediate behavioral flexibility.

Disclosures: J.I. Obsorne: None. **J.M. Barker:** None. **L. Chandler:** None.

Poster

777. Adolescents: Mechanisms of Vulnerability

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 777.19/C23

Topic: A.09. Adolescent Development

Support: NIH P60 AA011605

NIH T32 AA007573

NIH R00 DA031790

Title: Sex and adolescent intermittent ethanol promote Pavlovian conditioned approach to cue, no contribution of GLT-1

Authors: A. C. MADAYAG[1], S. J. STRINGFIELD[1], K. J. REISSNER[2], B. C. RILEY[1], C. A. BOETTIGER[1], *D. L. ROBINSON[1];
[1]Bowles Ctr. for Alcohol Studies, [2]Dept. of Psychology and Neurosci., Univ. of North Carolina, Chapel Hill, NC

Abstract: Ethanol binge drinking during adolescence has been associated with maladaptive behavior in adulthood such as disinhibition, addiction, and cognitive impairment. It is difficult to determine if people who binge drink during adolescence later exhibit behavioral deficits in adulthood due to preexisting traits, or as a consequence of adolescent ethanol consumption. Preclinical models provide the opportunity to manipulate ethanol exposure in otherwise homogeneous populations to identify ethanol's persistent neurobiological effects. We hypothesize that binge levels of adolescent intermittent ethanol (AIE) disrupt developing meso-cortico-limbic circuitry, which in turn alters reward-associated learning in adulthood. Previous studies show sex-specific differences in AIE-induced changes to basal and evoked glutamate levels in the nucleus accumbens in adulthood. Thus, we hypothesize that one mechanism by which AIE alters reward processing is via glutamate signaling in accumbens, particularly by changes in astrocytic glutamate transport. To test these hypotheses, we exposed rats to AIE then used Pavlovian conditioning in adulthood to assess reward-associated learning. Male and female rats received intermittent 5g/kg gavage ethanol or equivalent water volume from P25 to P54. Around P70, rats began Pavlovian conditioning (20 sessions, 15 trials/session). During a trial, an inactive lever extended and a cue light illuminated; this compound stimulus was the conditioned stimulus (CS). After 30 s, the CS ended and 0.1mL of 20% sucrose was delivered to the receptacle. Sign tracking (ST, CS approach behavior) has been suggested to indicate vulnerability to addictive and impulsive behavior. ST was indicated as lever presses, latency to lever press, and the probability to press the lever in a given trial; goal tracking (GT, approach to the receptacle) was indexed by reward receptacle entries, latency to enter the receptacle, and the probability to enter the receptacle in a given trial. Five days after the last session, fractionated nucleus accumbens tissue was analyzed for membrane expression of GLT-1, the astrocytic glutamate transporter. We observed main effects of both AIE and sex on adult lever presses, with female sex and AIE history both promoting lever pressing. Other ST indices were higher in females (main effects of sex), whereas metrics of GT were lower in AIE-exposed animals (main effects of AIE). However, these behavioral effects were not associated with GLT-1, as western blot analysis of GLT-1 yielded no differences among groups. Collectively, these findings show that females exhibit higher ST, whereas AIE shifted behavior from GT to ST in both sexes.

Disclosures: A.C. Madayag: None. **S.J. Stringfield:** None. **K.J. Reissner:** None. **B.C. Riley:** None. **C.A. Boettiger:** F. Consulting Fees (e.g., advisory boards); BlackThorn Therapeutics, Inc.. **D.L. Robinson:** None.

Poster

777. Adolescents: Mechanisms of Vulnerability

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 777.20/C24

Topic: A.09. Adolescent Development

Support: NIAAA U01AA020023

NIAAA F32AA021040

Title: Voluntary exercise prevents adolescent binge ethanol-induced loss of hippocampal neurogenesis by creating resiliency against innate immune activation

Authors: *R. P. VETRENO, C. LAWRIMORE, F. T. CREWS;
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Abstract: Adolescence is a developmental period of heightened neuroplasticity. Alcohol abuse and binge drinking are common during human adolescence. Using a rodent model of adolescent intermittent ethanol (AIE; 5.0 g/kg, i.g., 2-day on/2-day off from postnatal day [P] 25 to P55), we discovered a persistent loss of neurogenesis in the adult hippocampus that we tied to increased expression of innate immune signaling molecules. In the present study, we tested the hypothesis that voluntary wheel running (24 hr/day from P24 - P80) would prevent the AIE-induced reduction of adult hippocampal neurogenesis by blocking upregulation of innate immune signaling molecules. Voluntary exercise in the form of wheel running prevented the AIE-induced reductions of hippocampal neurogenesis (i.e., doublecortin-immunoreactive [DCX+IR] cells) and progenitor cell marker expression (Ki-67 and nestin) as well as the increase in cell death (cleaved caspase-3) in adulthood (P80). Expression of phosphorylated (activated) NF-κB p65, which is essential for NF-κB nuclear translocation and induction of proinflammatory cytokines, was upregulated in the post-mortem human alcoholic and adult AIE-treated hippocampus, an effect that was prevented by exposure to voluntary wheel running. Adolescent intermittent ethanol upregulated innate immune gene expression in the adult brain, which was prevented by voluntary wheel running exposure. Treatment with indomethacin (non-steroidal anti-inflammatory drug) prevented the AIE-induced loss of hippocampal neurogenesis, supporting a role for innate immune signaling molecules in the loss of neurogenesis following adolescent binge ethanol exposure. Together, these data reveal that exercise prevents the deleterious effects of AIE on adult hippocampal neurogenesis through an innate immune mechanism. (Supported by the NADIA of the NIAAA)

Disclosures: **R.P. Vetreno:** None. **C. Lawrimore:** None. **F.T. Crews:** None.

Poster

777. Adolescents: Mechanisms of Vulnerability

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 777.21/C25

Topic: A.09. Adolescent Development

Support: NIAAA NADIA Grant U01AA019972 to LPS

Title: The effects of the oxytocin agonist way 267464 on social behavior in adult male and female rats following adolescent intermittent ethanol exposure

Authors: *J. SAALFIELD, C. DANNENHOFFER, D. WERNER, E. VARLINSKAYA, L. SPEAR;
Psychology, Binghamton Univ., Binghamton, NY

Abstract: We have previously demonstrated lasting, sex-specific adverse social consequences of early adolescent intermittent ethanol exposure (AIE), with male, but not female, rats exhibiting social anxiety-like alterations when tested as adults. Oxytocin (OXT) has long been implicated in social behavior, with diverse lines of evidence supporting the suggestion that OXT increases approach and decreases avoidance to social stimuli. The current study aimed to determine if administration of the selective non-peptide OXT receptor agonist WAY 267464 (WAY) restores social behavior disrupted by AIE in male rats. Same-sex group-housed (4 to a cage) male and female Sprague-Dawley rats were given 4 g/kg ethanol (25%) or water intragastrically (i.g.) every 48 hr for a total of 11 exposures during postnatal days (P) 25-45. On P70-72, animals were assessed in a modified social interaction test. Experimental animals were injected interperitoneally (i.p.) with one of the three doses of WAY (0.0, 2.5, or 5 g/kg), and were placed individually for a 30-min habituation period in a two-compartment testing apparatus with an aperture connecting the two sides. A social partner of the same age and sex was then introduced for a 10-min test period. During the test session, the behavior of the animals was recorded by a video camera for later scoring. Behaviors scored included two social behaviors that are sensitive to anxiogenic stimuli: social investigation and the coefficient of social preference/avoidance. Social investigation was defined as the sniffing of any part of the body of the partner. Social preference/avoidance was analyzed by separately measuring the number of crossovers demonstrated by the experimental subject towards as well as away from the social partner and assessed by means of a coefficient [coefficient (%)= (crossovers to the partner – crossovers away from the partner)/(total number of crosses) X 100]. Consistent with prior findings, the results revealed sex-dependent baseline effects of AIE on social anxiety, with males, but not females, demonstrating greater social anxiety-like alterations, indexed through decreases in social investigation and social preference. Importantly, this AIE-induced social anxiety was reversed by WAY267464. Experiments are also currently assessing neuropeptide and OXT receptor levels

within hypothalamic and limbic structures. Determining the efficacy of pharmacological agents such as WAY for reversing behavioral phenotypes produced by AIE will be of importance in future translational efforts designed to mitigate lasting consequences of adolescent binge-level ethanol exposures.

Disclosures: J. Saalfield: None. **C. Dannenhoffer:** None. **D. Werner:** None. **E. Varlinskaya:** None. **L. Spear:** None.

Poster

777. Adolescents: Mechanisms of Vulnerability

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 777.22/C26

Topic: A.09. Adolescent Development

Support: NIAAA Grant U01-AA019972

Title: The role of pubertal timing in the social and neural consequences of early adolescent intermittent ethanol exposure

Authors: *E. U. KIM, L. P. SPEAR;
Binghamton Univ., Binghamton, NY

Abstract: Alcohol use is typically initiated in adolescence with earlier use being a major predictor for the development of alcohol use disorders (AUDS). Studies have also reported that pubertal timing in early adolescence plays a role in the initiation and escalation of alcohol use. Our lab has previously shown that males exposed to adolescent intermittent ethanol exposure (AIE) prior to and throughout puberty (P25-45) were more socially anxious and sensitive to ethanol-induced social facilitation than males given comparable exposure later in adolescence (P45-65). Thus, early AIE could potentially elevate adult use for its anxiolytic effects or to enhance positive social experiences, changes which may be attributable to alterations in neural expression of oxytocin (OXT) and vasopressin (AVP). The goal of this study was to determine the role of pubertal timing in the development of social and neural vulnerabilities in adulthood after early AIE. Male and female Sprague-Dawley rats were intubated with 4g/kg of EtOH (25% v/v) or water (H20) every other day from P25-45. Non-intubated (NI) and non-handled (NH) groups were included to control for intubation effects and experimenter handling, respectively. EtOH, H2O, and NI rats were weighed and checked daily until P50 for indices of puberty (age of vaginal opening [VO] in females and partial or complete balano-preputial skinfold separation [BPS] in males). While no differences were seen in age of partial BPS, EtOH and H2O males completed BPS earlier than NI males. Females in the H2O group exhibited VO at a younger age

than NI females, an effect that was reversed in the EtOH group. On P70, animals were tested with social partners for changes in play fighting, social investigation, contact and preference. Brain were collected immediately after testing for determination of OXT and AVP 1a receptor mRNA (OXTR, AVP-1aR) expression in the central amygdala (ceA) and lateral septum (LS). Although no AIE-induced changes in behavior were evident, OXTR expression was increased in the ceA and LS for males and females following social testing relative to non-tested controls. AVP-1aR expression was greater in the socially than non-tested females in the ceA but lower for socially-tested males in the LS. A main effect of adolescent exposure was seen in AVP-1aR and OXTR expression in the LS for males and females, respectively, with greater expression in the NH relative to all other groups. Furthermore, individual differences in gene expression were correlated with sexual development and social test behaviors. These data suggest that the OXT/AVP system is influenced by pubertal development and associated with the expression of adult social behaviors.

Disclosures: E.U. Kim: None. **L.P. Spear:** None.

Poster

777. Adolescents: Mechanisms of Vulnerability

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 777.23/C27

Topic: A.09. Adolescent Development

Support: NIAAA K01022475

NIAAA U01019967

Title: Binge-like alcohol exposure during adolescence disrupts dopaminergic neurotransmission in the adult prefrontal cortex.

Authors: *H. TRANTHAM-DAVIDSON[1], L. CHANDLER[2];
[1]Neurosci., [2]Med. Univ. of South Carolina, Charleston, SC

Abstract: The prefrontal cortex (PFC) is critically involved in cognitive function and inhibitory control. Adolescence represents a critical period of continued development of this region that parallels the maturation of its cognitive function. This extended period of developmental plasticity is thought to render the PFC, and its underlying circuitry, especially vulnerable to environmental insults that may result in deficits that persist well into adulthood. Alcohol drinking typically begins during adolescence when consumption of large quantities, in binge-like episodic patterns, is common. A primary function of dopamine (DA) in the PFC is to maximize

the efficient processing and transfer of information within the neurocircuitry that mediates decision-making. Dopamine innervation of the medial PFC peaks in early adolescence and then undergoes pruning and changes in DA receptor function during the transition to adulthood. These changes appear to play a critical role in the maturation of the executive function of the PFC. To determine adolescent alcohol-mediated changes in dopamine transmission, we performed whole cell patch clamp recordings in acute PFC slices from adult rats (PD90-PD110) that received five 14 hour cycles of intermittent vapor exposure to alcohol during adolescence (PD28-PD44). Recordings targeted PrL layer V pyramidal neurons labeled with a retrograde tracer to isolate specific prefrontal projections to subcortical structures (BLA, NAcc core and NAcc shell). These studies revealed that AIE exposure resulted in a loss of D1 receptor modulation of intrinsic excitability and synaptic transmission in mPFC projections to NAcc core, but had no effect on D2 or D4 receptor function in this pathway. Interestingly, treatment with the D2 agonist eticlopride during AIE exposure prevented the loss of D1 receptor function. In contrast, eticlopride treatment had no effect in the control air exposed rats. Taken together, these findings demonstrate that binge-like alcohol exposure during adolescence compromises D1 receptor function and co-administration of a D2 receptor agonist during AIE exposure can protect against these deficits and may prevent AIE induced deficits in the cognitive function of the PFC.

Disclosures: H. Trantham-Davidson: None. **L. Chandler:** None.

Poster

778. Comparative Anatomy

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 778.01/C28

Topic: A.10. Development and Evolution

Title: Intrinsic connectivity of the hippocampal formation of pigeons: an *In vitro* tracing study

Authors: *N. ROOK[1], M. STACHO[1], A. SCHWARZ[1], V. P. BINGMAN[2], O. GUNTURKUN[1]; [1]Biopsychology, Ruhr-University Bochum, Bochum, Germany; [2]Dept. of Psychology, Bowling Green State Univ., Bowling Green, OH

Abstract: Pigeons have incredible navigational abilities and are able to return to their home loft when being displaced at distances over thousands of kilometers. Ablation experiments have shown that an intact hippocampus (HC) is important for this capability. Similar to mammals, birds with damage to the HC are severely impaired on a variety of spatial tasks including navigation or retention of spatial information. However, since avian and mammalian evolutionary lines have separated 300 million years ago, the organization of the avian and mammalian HC is vastly different. Information flow within the avian HC has been shown to be

rather bidirectional in contrast to the unidirectional trisynaptic pathway found in the mammalian HC. Given the similar role of the mammalian and avian HC in spatial navigation, the question arises of whether some characteristics of the avian and mammalian HC may be evolutionarily conserved.
We combined in vivo tracing with high resolution in vitro tracing in the HC of pigeons to address this issue. Using in vitro tracing, we were able to investigate the internal connectivity at a more specific level than previous studies, especially with respect to its topological organization.
We found that input to the HC is distributed to all hippocampal regions via dorsolateral subdivisions (DL; predominantly via its ventral part). Our data suggests that a dorsomedial and ventrolateral zone can be distinguished within the HC. The former might process the thalamic input in intrinsic reverbatory circuits and then transfer it to the ventrolateral zone from which the hippocampal output is generated. Moreover, we selectively targeted the medial (VM) and lateral (VL) ventral cell layers by performing in vitro injections and could show that connections arising from those two subdivisions are indeed intrinsic to the HC. This finding underpins the already proposed equivalence to the dentate gyrus of mammals. Additionally, our in vivo tracing data indicates that projections from the area corticoidea dorsolateralis (CDL) are possibly roughly topographic such that the more medial (proximal) part of CDL projects to more dorsal parts of the HC, whereas the distal part of CDL projects to more ventral parts of the HC.
Despite the large phylogenetic distance between birds and mammals, some features such as topographically organized intrinsic hippocampal connectivity are shared by those two taxa, and may be one explanation for the functional equivalence between the avian and mammalian HC in spatial navigation.

Disclosures: **N. Rook:** None. **M. Stacho:** None. **A. Schwarz:** None. **V.P. Bingman:** None. **O. Gunturkun:** None.

Poster

778. Comparative Anatomy

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 778.02/C29

Topic: A.10. Development and Evolution

Support: NIH Grant GM109817 (AMK)

UTEP ORSP Grand Challenges Grant (AMK)

NSF DEB-1145459 (EG, DFH)

NSF DEB-1457180 (PMG)

NSF EAGER 1450850 (PMG)

Keelung Hong Fellowship (DFH)

Title: Documenting brain diversity in field-caught lizards, from skull to cell: Initial development of a processing pipeline for top down, multi-scale structural analyses of a single brain by integrating specialized microcomputed tomography (diceCT), Nissl-based cytoarchitectonics, and immunohistochemistry

Authors: *D. F. HUGHES[1], P. M. GIGNAC[3], E. GREENBAUM[1], A. M. KHAN[2];
[2]Biol. Sci. and UTEP Systems Neurosci. Lab., [1]Univ. of Texas At El Paso, El Paso, TX;
[3]Oklahoma State Univ. Ctr. for Hlth. Sci., Tulsa, OK

Abstract: Diffusible iodine-based contrast-enhanced computed tomography (diceCT) is an emerging tool that facilitates the non-destructive visualization of gross neuroanatomical features at levels of detail previously unattainable with traditional computed tomography approaches. In remote field conditions, we tested a protocol to prepare specimens for diceCT scans using immersion fixation and prolonged storage in fixative. We experimentally developed this protocol (field-fixation followed by diceCT) using novel field-collection procedures for a lizard model. Our field-preservation approach was found to be tractable with diceCT, allowing for the preservation and detailed visualization of bony anatomy as well as muscular, epithelial, glandular, and neural tissues (i.e., differentiating myelinated from unmyelinated structures)—all in the same individual specimen.

In this study, we integrated this validated field-based protocol for diceCT imaging within a processing pipeline that aims to examine the tissue structures of the head (bone and nervous tissues) in 3-D space and ground truth these models with more fine-scale histological analyses of cellular distribution. The process involves first imaging field-collected specimens in their native state (unstained) to reconstruct high-density tissue structures (e.g., skull), which are 3-D rendered using Avizo software. The same specimens are next stained with Lugol's iodine (I_2KI) and re-scanned to visualize soft-tissue structures such as the brain and cranial nerves. Images of stained specimens are then also 3-D rendered to produce models of soft-tissue structures within the head. Models of both the skull and brain are pseudo-colored according to region and integrated to inform the interrelationships between central and peripheral components of the nervous system and cranium. These datasets, in turn, can be analyzed to quantify and compare neuroanatomical structures among different body regions and species. Finally, brain tissue stained with Lugol's iodine can be de-stained and used for subsequent histological preparations to visualize cytoarchitectural features at the microscopic level. Our results—a pipeline for reciprocal illumination of field-fixed brains from the gross anatomical to the cellular levels—set up the potential for a comprehensive mapping of brain interconnectedness in three dimensions across spatial scales for poorly known, and in this case, unknown lizard species.

Disclosures: D.F. Hughes: None. **P.M. Gignac:** None. **E. Greenbaum:** None. **A.M. Khan:** None.

Poster

778. Comparative Anatomy

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 778.03/C30

Topic: A.10. Development and Evolution

Support: FAPERJ

CNPq

The James S. McDonnell Foundation

Title: Invariant microglial cell densities in mammalian brains

Authors: S. E. DOS SANTOS, L. BOTELHO, M. MEDEIROS, J. PORFIRIO, J. BRITO, *S. HERCULANO-HOUZEL;
UFRJ, Rio de Janeiro, Brazil

Abstract: Brain structure mass scales as a universal function of numbers of non-neuronal cells across mammalian species, while brain structure mass scales differently with numbers of neurons across brain structures and across primate and non-primate clades. The universality of the relationship for non-neuronal cells suggests that similar scaling rules apply to endothelial cells and individual glial cell subtypes.
Here we aim to determine if the universal scaling rule found for non-neuronal cells as a whole applies to microglial cells in particular. In that case, brain structure mass should scale universally with their numbers of microglial cells across species, and microglial cell densities should be found to remain invariant across brain structures and species, as found previously for non-neuronal cells as a whole.
Microglial cells are the resident macrophages of the brain whose actions contribute to the maturation and plasticity of neural circuits that ultimately shape behavior. Invariant microglial cell densities across brain structures and species would be consistent with their key role in the construction and modeling of brain structures.
We quantify the total number of microglial cells, their proportion to non-neuronal cells as a whole, and the ratio of microglial cells to neurons in species belonging to several mammalian clades. We used the isotropic fractionator and immunocitochemistry to anti-Iba1 and anti-NeuN antibodies to estimate numbers of microglial cells and neurons in several brain structures. We examined the brains of 28 species of mammals (10 marsupials, 5 artiodactyls, 8 primates and 5 afrotherians).
Microglial cells represent between 1% of all cells in the cerebellum and 12% in the cerebral cortex and rest of brain, at densities between 1,000 and 10,000 cells/mg. Each brain structure gains microglial cells as a similar power function of its number of neurons across species.

Importantly, all brain structures vary in mass across all species as a single power function of the number of microglial cells in the structure with a joint exponent of 0.946±0.027 ($p<0.0001$) indicating that brain structures of similar size are composed of similar numbers of microglial cells across different mammalian clades. Additionally, the ratio between microglial cells and neurons decreases universally with increasing neuronal density across structures and species. The present finding that numbers of microglial cells scale in a similar manner across the wide range of mammals studied indicates that the addition of these cells to the brain is governed by conserved developmental and evolutionary mechanisms.

Disclosures: S.E. Dos Santos: None. **L. Botelho:** None. **M. Medeiros:** None. **J. Porfirio:** None. **J. Brito:** None. **S. Herculano-Houzel:** None.

Poster

778. Comparative Anatomy

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 778.04/C31

Topic: A.10. Development and Evolution

Support: NIMH IRP

Title: A new high resolution anatomical template for macaque MRI data analysis

Authors: *C. SPONHEIM[1], J. SEIDLITZ[4,2,1], F. Q. YE[3], D. A. LEOPOLD[3], L. G. UNGERLEIDER[1], A. MESSINGER[1];
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Abstract: Although published paper atlases of the macaque brain provide accurate renderings of an individual animal, they lack the generalizability and ease of use of a multi-subject digital template based on Magnetic Resonance Imaging (MRI). The use of standardized templates (e.g., the ICBM-152 template; Mazziotta et al., 2001) is common in human neuroimaging, where it has greatly facilitated comparisons across studies. Such a template of the macaque brain could similarly benefit the non-human primate imaging community. Indeed, macaque templates generated using iterative co-registration approaches are currently available (McLaren et al., 2009; Frey et al., 2011). However, there have recently been substantial improvements in non-linear deformation-based registration methods. To make use of these approaches, we developed a new high-resolution digital template of the macaque monkey brain. The template, dubbed the NIMH Macaque Template-35 (or NMT-35 for short), reflects the morphology of 35 adult

macaques (*Macaca mulatta*) scanned at the NIMH at 4.7T. Using both AFNI (Cox, 1996) and the Advanced Normalization Tools (ANTs) package (Avants et al., 2011), the individual anatomical scans were first rigidly aligned to stereotaxic space (Saleem and Logothetis, 2006), then recursively deformed in a non-linear fashion to locally match the group average, and lastly averaged together. The result is a high contrast template that preserves and even enhances the cytoarchitectonic and morphological details common to the group. The template, paired with tissue segmentation maps and atlases of anatomical regions, provides possibilities for precise single-subject brain extraction (i.e. skull-stripping) and segmentation, as well as accurate characterizations of functional and structural MRI results. For example, functionally defined areas (i.e. face and object responsive patches) could be combined across subjects and tasks, allowing for a probabilistic mapping of various brain specializations. Other utilities include the anatomical assessment of whole-brain structural and functional connectivity, as derived from T1-weighted sequences, and resting state-fMRI, respectively. Moreover, the template is a valuable platform for detailed evaluation of anatomical and functional homologies between humans and non-human primates, and for the interpretation of human research in light of studies conducted in non-human primates.

Disclosures: **C. Sponheim:** None. **J. Seidlitz:** None. **F.Q. Ye:** None. **D.A. Leopold:** None. **L.G. Ungerleider:** None. **A. Messinger:** None.

Poster

778. Comparative Anatomy

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 778.05/C32

Topic: A.10. Development and Evolution

Title: Cortical morphology can be predicted universally by a model with only three parameters: number of symmetric and assymetric cell divisions, and average neuronal cell volume

Authors: *B. MOTA, S. HERCULANO--HOUZEL;
Univ. Federal Do Rio De Janeiro, Rio de Janeiro, Brazil

Abstract: The mammalian cerebral cortex is extremely variable. Across species, grey and white matter volume (V_g and V_w), total (A_T) and exposed surface area (A_e), numbers of neurons (N_n) and neuronal density (D) vary by several orders of magnitude, and average cortical thickness (T) and folding index (F) vary by one order of magnitude.
Although it has been known for some time that these variables correlate to some extend, both universally and across phylla, only recently some strict universal relations have been found: By modelling the self-avoiding nature of the cortical surface and the plastic properties of axonal

elongation, we have proposed a model that predicts a power-law relation between A_e, A_T and T, and have verified that this relation holds true for both gyrified and lysencephalic cortices of dozens of different species [1]. Using the same data, we also verify that the overall outer shape of the cortex changes only slowly, and systematically with size. This implies a strict relation between A_e and total volume V [1]. Finally, we have also previously shown there is a universal relation between total number of neurons and glia numbers and average cell mass [2]
Cortical diversity is presumably generated in evolution as changes occur in some of the parameters that regulate those developmental processes that build the cerebral cortex. Taking these relations as a starting point, here we show that a three-parameter model predicts all major morphological features of the cerebral cortex (A_e, At, D, F, N_n, N_g, T, V_g and V_w) from variations in the number of symmetric (N_s) and asymmetric (N_a) divisions of progenitor cells in early development, and in the average volume (v_n) of neurons. Notably, we show that N_a varies much more across species than N_s, and the three parameters exhibit different relationships across mammalian orders. It is thus possible that evolutionary diversity in cortical morphology occurs simply through variations in these three parameters.
[1] Mota B and Herculano-Houzel S (2015) Science 349, 74-77[2] Mota B and Herculano-Houzel S (2014) Front. Neuroanat.8:127B

Disclosures: **B. Mota:** None. **S. Herculano--Houzel:** None.

Poster

778. Comparative Anatomy

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 778.06/C33

Topic: A.10. Development and Evolution

Support: Canada Research Chairs Program

CFI

NSERC

Title: Density and distribution of oxytocin and vasopressin receptors in male and female Richardson's ground squirrels

Authors: ***J. ARAUJO**[1], A. NGWENYA[1], G. PROUNIS[2], A. G. OPHIR[2], A. N. IWANIUK[1]; [1]Neurosci., Univ. of Lethbridge, Lethbridge, AB, Canada; [2]Psychology, Cornell Univ., Ithaca, NY

Abstract: The neuropeptides oxytocin (OT) and arginine vasopressin (AVP) affect many different behaviors, especially in relation to pair bonding. The neural expression of receptors for OT (OTR) and AVP (V1aR) has been of particular interest because the density and distribution of these receptors varies among species and individuals in relation to their degree of promiscuity. Little, however, is known about whether OTR and V1aR expression is also related to non-reproductive social interactions, such as those occurring in multi-male, multi-female social systems. Richardson's ground squirrel (*Urocitellus richardsonii*) is an excellent species in which to explore the relationship between receptor expression and social behaviour unrelated to pair bonding. Unlike previously studied polygamous and monogamous rodents, this species has a polygamous mating system, but there are social bonds among females. The objective of this study is therefore to investigate the anatomical distribution of OTR and V1aR in the brains of wild female and male Richardson's ground squirrels, and test for sex differences in receptor expression. Wild ground squirrels were trapped during the breeding season (Feb-Mar), their brains flash frozen, sectioned and processed using autoradiography. Compared to previously studied species, ground squirrels have different patterns of expression for OTR and V1aR. Specifically, there was much more V1aR than OTR and frequently V1aR was found in brain regions where OTR is typically found in voles and other rodents (such as nucleus accumbens and hippocampus). We also see expression of these receptors in parts of the midbrain (superior colliculus), hindbrain (spinal trigeminal nucleus and nucleus prepositus), which have been little explored in other species. The specific relationship between some of the regions expressing OTR and V1aR and social behaviour in this species is unclear, but our results lay the foundation for testing the roles of OT and AVP in modulating social behavior in ground squirrels and beginning to explore the evolution of social and mating system diversity across squirrel species.

Disclosures: J. Araujo: None. **A. Ngwenya:** None. **G. Prounis:** None. **A.G. Ophir:** None. **A.N. Iwaniuk:** None.

Poster

778. Comparative Anatomy

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 778.07/C34

Topic: A.10. Development and Evolution

Support: The James McDonnell Foundation

FAPERJ

CNPq

Title: Quantitative analysis of the distribution of neurons, glial cells and vasculature in the mouse brain.

Authors: *L. VENTURA ANTUNES[1], L. BOTELHO[1], J. MALDONADO[2], S. HERCULANO-HOUZEL[1];
[1]Federal Univ. of Rio De Janeiro, Rio De Janeiro, Brazil; [2]MBF Biosci., Williston, VT, VT

Abstract: Mammalian brains vary 100,000-fold in volume, with neuronal densities that are highly variable across brain structures and also across species. In contrast, non-neuronal cell densities are nearly invariant and shared across brain structures and species. The small variation in non-neuronal cell densities points to a universal set of rules determining how glial cells are added to brain tissue and distributed within it. Non-neuronal cells, however, comprise both glial cells and endothelial cells. It is thus possible that the shared scaling rules found for non-neuronal cells as a whole apply not to glial cells, but to the endothelium. It has been estimated that vasculature occupies no more than 4% of the cortical volume (Schuez and Palm, 1989). Finding that endothelial cells represent a similarly small proportion of all non-neuronal cells would support a conserved scaling of glial cells. Here we sought to quantify the proportions of endothelial and glial cells in different structures of the mice brain by using systematic random sampling of 3D stacks of microscopic images of tissue whose blood vessels were stained previously by venous injection of FITC-dextran. Neurons were identified by immunocytochemistry to NeuN, and all cell nuclei were visualized by staining with DAPI. Vascular fraction was determined by applying the area fraction fractionator. We find that the fractional microvascular volume is indeed small, but variable across brain structures. The relative vascular volume is highest in the gray matter of the cerebral cortex, at 2.24% of tissue volume, and lowest in the white matter, at 0.65%. Between these values we find the molecular layer of cerebellum (2.04%), the dentate gyrus of the hippocampus (1.71%), and thalamus, striatum, hypothalamus, cerebellar and hippocampal granular layers (1.3%-1.5%). In contrast, endothelial cells represent between 2.80% and 14.5% of all cells in these structures. Nevertheless, only 9.4-28.1% of non-neuronal cells are endothelial, meaning that about 80% of non-neuronal cells are glial cells. Neuronal and endothelial densities are correlated across brain sites, suggesting that local variations in neuronal density are accompanied by a corresponding variation in the density of endothelial cells, that is, by increased vascularization. Endothelial cells are thus more common than expected from the volume they occupy, which indicates that they are small cells compared to other cell types in the brain. Still, endothelial cells are uncommon enough amongst non-neuronal cells that we can safely conclude that the universal scaling rules that we have found to apply to non-neuronal cells also apply to glial cells in particular.

Disclosures: L. Ventura Antunes: None. **L. Botelho:** None. **J. Maldonado:** None. **S. Herculano-Houzel:** None.

Poster

778. Comparative Anatomy

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 778.08/D1

Topic: A.10. Development and Evolution

Support: NS-19620

NS-28721

NS-57722

Title: Neurochemical compartmentalization within the pigeon basal ganglia

Authors: *L. L. BRUCE[1], J. T. ERICHSEN[2], A. J. REINER[3];
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Abstract: The objectives of this study were to use multiple informative markers to define and characterize the neurochemically distinct compartments of the pigeon basal ganglia, especially striatum and accumbens. To this end, we used antibodies against 10 different neuropeptides, calcium-binding proteins or neurotransmitter-related enzymes that are enriched in the basal ganglia. Our results clarify boundaries between previously described basal ganglia subdivisions in birds, and reveal considerable novel heterogeneity within these previously described subdivisions. Sixteen regions were identified that each displayed a unique neurochemical organization. Four compartments were identified within the dorsal striatal region. The neurochemical characteristics support previous comparisons to part of the central extended amygdala, somatomotor striatum, and associational striatum of mammals, respectively. The medialmost part of the medial striatum, however, has several unique features, including prominent pallidal-like woolly fibers and thus may be a region unique to birds. Four neurochemically distinct regions were identified within the pigeon ventral striatum: the accumbens, paratubercular striatum, ventrocaudal striatum, and the ventral area of the lateral part of the medial striatum that is located adjacent to these regions. The pigeon accumbens is neurochemically similar to the mammalian rostral accumbens. The pigeon paratubercular and ventrocaudal striatal regions are similar to the mammalian accumbens shell. The ventral portions of the medial and lateral parts of the medial striatum, which are located adjacent to accumbens shell-like areas, have neurochemical characteristics as well as previously reported limbic connections that are comparable to the accumbens core. Comparisons to neurochemically identified compartments in reptiles, mammals, and amphibians indicate that, although most of

the basic compartments of the basal ganglia were highly conserved during tetrapod evolution, uniquely avian compartments may exist as well.

Disclosures: **L.L. Bruce:** None. **J.T. Erichsen:** None. **A.J. Reiner:** None.

Poster

778. Comparative Anatomy

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 778.09/D2

Topic: A.10. Development and Evolution

Support: FAPERJ

CNPq

James S. McDonnell Foundation

Title: Desert rodents have fewer neurons in their cerebral cortex: energetic constraints?

Authors: ***F. B. CUNHA**[1], D. MESSEDER[2], P. MANGER[3], S. HERCULANO-HOUZEL[2]; [1]Univ. Federal Do Rio De Janeiro, Rio De Janeiro, Brazil; [2]Univ. Federal do Rio de Janeiro, Rio de Janeiro, Brazil; [3]Univ. of the Witwatersrand, Johannesburg, South Africa

Abstract: Rodents are by far the most diverse order of mammals representing 40% of all current mammal species with more than 2,200 species. They occupy a huge range of ecological niches, from tropical forests to deserts and tundras. Using the isotropic fractionator to determine numbers of brain neurons in 11 species of rodents, we found previously that all of these species shared the same power law relating number of cortical neurons to the mass of the cerebral cortex, except for one: the naked mole-rat (*Heterocephalus glaber*), which has half the expected number of cortical neurons.

Why is this species an exception? One hypothesis raised by our group is that the strongly hypoxic, subterranean environment of this species puts these rodents under an extreme metabolic constraint that causes a reduction in its number of cortical neurons.

To test this hypothesis, we analyzed eight other African subterranean species and six African non-subterranean species, predicting reduced numbers of neurons in the subterranean compared to non-subterranean species of similar cortical mass. We determined the number of neuronal and non-neuronal cells through the isotropic fractionator method for the cerebral cortex, cerebellum, olfactory bulb and rest of the brain.

Our results show that, contrary to what we predicted, there is no systematic reduction in the number of cortical neurons in subterranean compared to nonsubterranean rodents. There is also

no systematic difference between African and American species. Rather, the results suggest that rodents - subterranean or not - inhabiting deserts or dry savannas present a number of neurons below the expected for their cerebral cortex mass, while those that inhabit forests match the predicted neuronal composition for non-African species.
In all species examined, however, cerebellum and other brain structures have numbers of neurons that match the expected for other rodents. Because cortical neurons cost on average 20 times more than other neurons, our results suggest that rodents living in severe environmental conditions have reduced numbers of neurons in their cerebral cortex due to energetic constraints.

Disclosures: F.B. Cunha: None. **D. Messeder:** None. **P. Manger:** None. **S. Herculano-Houzel:** None.

Poster

778. Comparative Anatomy

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 778.10/D3

Topic: A.10. Development and Evolution

Title: The orientation of regional expansion in the human cerebral cortex.

Authors: *D. S. MARGULIES[1], C. DELETTRE[1], S. OLIGSCHLÄGER[1], R. TORO[2], O. COULON[3,4], G. AUZIAS[3];
[1]Max Planck Inst. For Human Cognitive and Brain Sci., Leipzig, Germany; [2]Human Genet. and Cognitive Functions, Inst. Pasteur, Paris, France; [3]Inst. de Neurosciences de la Timone, [4]Lab. des Sci. de l'Information et des Systèmes, UMR 7296, Aix Marseille Université, CNRS, Marseille, France

Abstract: Phylogenetic theories of cortical expansion hypothesize growth along specific directions. While several studies have characterized local variation in expansion across individuals as well as species, here we instead investigated the orientation of variance in cortical morphometry. To address this question, we assessed where geodesic distance between a set of individually-specified cortical landmarks covaried with overall cortical surface area.
We conducted the analysis on a subset of the 1422 datasets made available by the Brain Genomics Superstruct Project. T1-weighted MRI images were processed using the standard FreeSurfer cortical surface extraction pipeline. FreeSurfer outputs were then imported to BrainVISA 4.5 for further processing through the Mars Atlas pipeline (BrainVISA Cortical Surface Toolbox), which derives a parcellation based on latitude and longitude lines derived from individual cortical morphology. The points at the corners of parcels provide consistent individual landmarks. The shortest geodesic distance between corners of the same parcels were

then computed along the cortical surface. The group-level statistical analysis was based on the ratio of the variance explained by a model including both cortical volume and total surface area versus a model containing only volume. The f-ratio values were thresholded at p-value < 0.01, Bonferroni-corrected for the number of distance segments. The results thus indicate how each distance segment covaries with overall surface area independent of cortical volume. Distance segments were categorized by longitude and latitude orientation, as well as their location within primary/unimodal or heteromodal cortex.
Significant distance segments were generally consistent across both hemispheres and predominantly aligned with sulcal lines. The ratio of longitude- to latitude-oriented segments was 2:1; however, the primary factor accounting for this orientation was the type of underlying cortical area (primary/unimodal or transmodal), which also demonstrate orthogonal sulcal orientation. Several exceptions of significant segments traversing gyri were also present within the operculum, prefrontal, and inferior parietal cortex.
The current results suggest that cortical expansion across individuals is primarily related to variance in expansion along sulci lines, with several notable exceptions in higher-order regions. We further consider these results in relation to theories of cortical phylogeny, which suggest that trends of areal differentiation are oriented orthogonal to sulci.

Disclosures: **D.S. Margulies:** None. **C. Delettre:** None. **S. Oligschläger:** None. **R. Toro:** None. **O. Coulon:** None. **G. Auzias:** None.

Poster

778. Comparative Anatomy

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 778.11/D4

Topic: A.10. Development and Evolution

Support: DFG Grant STR 1404/1-1

DFG Grant GU 227/21-1

Title: Figuring out why crows are smart - Area specific analysis of neuron numbers in corvid and non-corvid species

Authors: *F. STROECKENS[1], K. NEVES[2], S. HERCULANO-HOUZEL[2], O. GUNTURKUN[1];
[1]Inst. of Cognitive Neuroscience, Biopsychology, Ruhr-University Bochum, Bochum, Germany; [2]Federal Univ. of Rio de Janeiro, Rio de Janeiro, Brazil

Abstract: Over the recent years, growing evidence has been collected indicating that birds in the corvid family possess extraordinary cognitive skills matching those of non-human primates. However, little is known about how these species can achieve such impressive behaviors. It has been suggested that higher cognitive abilities in primates could be based on the total number of neurons within their telencephalon. Even though the anatomy of the avian telencephalon differs vastly from mammals, such an increase in neuron numbers could also be responsible for the advanced cognitive skills in corvids. Preliminary studies on cellular composition of bird brains have shown that neuronal densities in the whole avian telencephalon are higher than in mammals. However, it is unknown if numbers and densities of neurons are evenly distributed over the whole avian telencephalon. We assume that neuronal numbers in areas involved in higher cognitive functions (like Nido- and Mesopallium) scale to a greater extent with cognitive skills than in areas which are of lesser importance for cognition. To investigate this hypothesis, we delineated six telencephalic brain areas (Hyper-, Meso-, Nido-, and Arcopallium, Hippocampus, Striatum) in corvid (Carrion Crow, Hooded Crow, Rook) and non-corvid species (Chicken, Pigeon, Ostrich) and analyzed their cellular composition using the isotropic fractionator method. In this method, delineated brain areas were homogenized and samples were stained with DAPI to acquire total cell numbers or NeuN to obtain neuron numbers. Counts were performed using a Neubauer counting chamber and obtained numbers were used to calculate absolute numbers, cell densities, percentage of total telencephalic cells and neuron/glia ratios. Absolute cell and neuron numbers differed vastly between brain areas and species with a general correlation between size of an area and cell numbers. Overall, highest absolute cell numbers could be obtained in Hyper-, Meso- and Nidopallium of Ostriches and in Nidopallium of all corvids. In contrast, cell densities differed not that greatly between species for one area. Ostriches, however, showed massively reduced cell densities in comparison to all other species over all areas. In addition, there were slightly higher cell densities in the Meso- and Nidopallium of corvid species in comparison to non-corvid birds as well as a higher percentage of total telencephalic cells allocated to these areas in corvids. This data indicates that the cognitive abilities of corvids are at least to some extent based on higher relative cell and neuron numbers and densities in brain areas which are relevant for the execution of higher cognitive skills.

Disclosures: F. Stroeckens: None. **K. Neves:** None. **S. Herculano-Houzel:** None. **O. Gunturkun:** None.

Poster

778. Comparative Anatomy

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 778.12/D5

Topic: A.10. Development and Evolution

Title: A systematic relationship between intracortical myelin and functional connectivity in the human cerebral cortex

Authors: *J. M. HUNTENBURG[1], P.-L. BAZIN[2], A. GOULAS[3], D. S. MARGULIES[1];
[1]Max Planck Res. Group Neuroanatomy and Connectivity, [2]Dept. of Neurol., MPI for Human Cognitive and Brain Sci., Leipzig, Germany; [3]Inst. for Computat. Neurosci., Univ. Med. Ctr. Hamburg-Eppendorf, Hamburg, Germany

Abstract: Research in macaques suggests a systematic relationship between microarchitecture and interareal connections in the cerebral cortex, which has yet to be investigated in the human brain. Here we explore this link in the human cerebral cortex using two high-resolution MRI measures: resting state functional connectivity (FC), enabling non-invasive assessment of cortical connectivity, and quantitative T1 maps, which reflect intracortical myelin content and provide an in vivo proxy for cortical architecture.
MRI datasets of 8 subjects were acquired at 7 Tesla, comprising a T1 map (MP2RAGE, voxel=0.5mm³) and 4 resting state scans (BOLD, voxel=1.5 mm³, 300 volumes, TR=3s). After preprocessing, structural and functional data were sampled and smoothed (FWHM=3mm) on the individual's mid-cortical surface and projected onto a study-specific template. Whole brain FC was averaged across subjects and sessions. To determine the main gradients of variance in FC, nonlinear dimensionality reduction was performed using diffusion embedding, resulting in 10 components (FC 1 to 10) which are ordered by the amount of variance they explain. Each component represents a cortical map, in which similar values signify similar connectivity patterns. T1 values were sampled on 11 intracortical surfaces and averaged across subjects. To reduce partial volume effects only 5 central surfaces were averaged for intracortical T1. One or multiple FC components were used as predictors in a general linear model to fit T1.
The topography of FC 1 shows marked similarity to the distribution of intracortical T1 (Pearson's r=.56 , R^2=.31), but deviates in posterior cingulate, posterior temporal and inferior parietal cortex. A high overall fit is achieved when employing FC 1-10 to model T1 (Pearson's r=.81, R^2=.65). To rule out that every smooth cortical map can be explained by a linear combination of FC components, random, smoothed datasets were modelled in the same way as the T1 data. Even with large smoothing kernels the fit to the random data remains below that for the real T1 data.
We demonstrate a systematic relationship between intracortical T1 and FC in the human cerebral cortex. These findings are in line with extensive reports linking microarchitecture and connectivity in macaques and extend them to the human brain. It has been proposed that architectonic differentiation reflects the phylogenetic age of cortical areas. The observed relationship might thus be rooted in the simultaneous emergence of distributed areas upon a common environmental demand, resulting in a functional entity of strongly interconnected areas with comparable microarchitecture.

Disclosures: J.M. Huntenburg: None. **P. Bazin:** None. **A. Goulas:** None. **D.S. Margulies:** None.

Poster

778. Comparative Anatomy

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 778.13/D6

Topic: A.10. Development and Evolution

Support: AIHS

NSERC

Title: Comparison of estimates of neuronal number in the telencephalon of day old chicks (Gallus gallus domesticus) using the isotropic fractionator method and unbiased stereology

Authors: *A. NGWENYA, J. NAHIRNEY, E. STREIBEL, A. N. IWANIUK;
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Abstract: The isotropic fractionator (IF) method is a recently developed method of cell counting that allows for the rapid quantification of neurons and non-neurons in the nervous system (Herculano-Houzel and Lent, 2005). The method relies on immunocytochemical detection of neuronal nuclear antigen (NeuN) in homogenous suspensions of mechanically dissociated nuclei to estimate the proportion of neurons (i.e. NeuN-positive nuclei) from the total cell number. Homogenisation of tissue eliminates the need for extensive sampling and neuronal number can be obtained by counting relatively few cells. One of the criticisms of the method is that neuronal number may be underestimated as a result of dissociation/homogenisation of tissue. This may occur both in cases of over-homogenisation (when a large number of nuclei are disrupted and not included in the total cell number) and under-homogenisation (where nuclei form large clusters and individual nuclei are difficult to distinguish). Validation studies have demonstrated that this is not the case; similar estimates of neuronal number were obtained using the IF method and unbiased stereology. However, IF has only been validated in 3 primate species and whether it can provide accurate estimates of neuron numbers in non-mammalian species has yet to be tested. In this study we aimed to validate the IF method in a non-mammalian species by comparing estimates of the number of NeuN immunostained neurons in the telencephalon of day old chicks (*Gallus gallus domesticus*) using the IF method and unbiased stereology. In general, we found greater variation in neuron numbers obtained using the IF method when compared with stereology. The number of neurons estimated by the IF method was also generally lower than stereological estimates but, both methods produced similar averages of neuronal number. In addition, the IF allowed for neuron quantification in the optic lobes and cerebellum where heterogeneous neuronal distribution and high neuronal density (i.e., granule cells) make stereological counts more challenging. Our results suggest that the IF is a reliable method to estimate neuron numbers in birds. Further, our estimates of neuronal number lay the foundation for future developmental and experimental studies in chicks.

Disclosures: **A. Ngwenya:** None. **J. Nahirney:** None. **E. Streibel:** None. **A.N. Iwaniuk:** None.

Poster

778. Comparative Anatomy

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 778.14/D7

Topic: A.10. Development and Evolution

Support: Adelson Medical Research Foundation

Title: Comparative distributions and domains of human and mouse oligodendrocyte progenitor cells in the cortex and white matter

Authors: *J. OSÓRIO[1], K. HEFFERNAN[3], S. GOLDMAN[2,4];
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Abstract: When transplanted to the neonatal mouse brain, human oligodendrocyte progenitor cells colonize the host, and ultimately replace the murine glial progenitor population. To assess the anatomic correlates to these events, we evaluated the morphometric characteristics of human and mouse NG2-defined oligodendrocyte progenitor cells (OPCs) in the cortex and white matter, and asked whether the size or domain distributions of OPCs differed between mice and men, and whether any such differences might be a function of the brain compartment in which the cells were resident, whether cortical grey or subcortical white matter. To this end, we used thick sections of humanized chimeric mice (N=5, males, age 59,9 ± 0.1 weeks old) and control mice (N=5) to map individual NG2-stained and confocal imaged OPCs and analyse their volume and complexity. Human OPCs are more complex than murine cells in both the cortex (271.1 ± 25.2 vs 200.0 ± 9.1 ramifications, $p<0.05$, n=12) and corpus callosum (202.2 ± 14.6 vs 152.9 ± 11.7 ramifications, $p<0.05$, n=12) and they are larger than mouse cells within the cortex (168,419.4 ± 24,632.3 vs. 73,249.0 ± 7,358.1 μm^3, $p<0.05$, n=12), although displaying similar size within the corpus callosum (86,794.9 ± 8,024.4 vs 73,249.0 ± 7,358.1; $p>0.05$, n=12). The larger domain sizes and intradomain fiber complexity of human OPCs resembles what was previously observed with human astrocytes and might contribute to the competitive advantage of human OPCs over their murine counterparts. In both the cortex and white matter, the human and mouse OPCs each exhibited a domain architecture, with their fibers displaying minimal overlap. Both human OPCs in the chimeric mouse brain and murine OPCs occupy larger domains in the cortex than cells in the corpus callosum (168,419.4 ± 24,632.3 μm^3 vs 86,794.9 ± 8,024.4 μm^3, $p<0.01$ for human cells and 97,001.7 ± 6,269.3 μm^3 vs 73,249.0 ± 7,358.1 μm^3; $p<0.05$, n=12 for mouse cells) and

also exhibited more ramifications (271.7 ± 25.2 vs 202.2 ± 14.6 ramifications, $p<0.05$ for human cells and 200.0 ± 9.1 vs 152.9 ± 11.3 ramifications; $p<0.01$, $n=12$ for mouse cells). Whether such regional differences reflect distinct properties is to be determined. Overall, we showed that human OPCs in the chimeric mouse brain are larger and more complex than murine OPCs and that both human and mouse cells in the cortex occupy larger domains and exhibit higher complexity than in the corpus callosum. The prospective identification and selection of appropriate subpopulations of OPCs may prove an important consideration in the preparation of OPCs as cellular therapeutics for the disorders of central myelin.

Disclosures: J. Osório: None. **K. Heffernan:** None. **S. Goldman:** None.

Poster

778. Comparative Anatomy

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 778.15/D8

Topic: A.10. Development and Evolution

Support: MINECO Grant BFU2015-68537-R

Title: Is there a precursor of the entorhinal cortex in reptiles?

Authors: E. DESFILIS, A. ABELLÁN, *L. MEDINA;
Univ. Lleida-IRBLleida, Lleida, Spain

Abstract: The entorhinal cortex of mammals is considered the main gateway of the hippocampal formation. Together with the latter, the entorhinal cortex is involved in memory formation and navigation. There is some consensus about the homology between the mammalian hippocampal formation and parts of the medial pallium of sauropsids, which seems to be also involved in memory and spatial navigation. In contrast, there are very few data about the homologue of the entorhinal cortex in sauropsids. In mammals, the entorhinal cortex includes two subdivisions with apparently distinct embryonic origins. Based on gene expression patterns during development, a pallial area comparable to the medial entorhinal cortex has been identified in chicken. Data in other sauropsids, as lizards, may help to understand the evolutionary origin of the entorhinal cortex. Therefore, we analyzed the expression of several developmental regulatory genes (including *Lhx2*, *Lhx9*, *Emx1* and *Tbr1*) in the embryonic telencephalon of a lacertid lizard, and compared these results with our previous data on pallial connectivity. Our results highlight a specific area of the lizard pallium, the lateral cortical superposition, having a remarkably strong expression of *Lhx9*. This area appears to be part of the lizard medial pallium, and is strongly and reciprocally connected with the hippocampal formation. Based on these data,

the lizard lateral cortical superposition resembles and may be a precursor of the medial entorhinal cortex. Sponsor: Spanish Ministry of Economy and Competitivity (MINECO) BFU2015-68537-R

Disclosures: **E. Desfilis:** None. **A. Abellán:** None. **L. Medina:** None.

Poster

778. Comparative Anatomy

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 778.16/D9

Topic: A.10. Development and Evolution

Support: DFG GU227/16-1 G.-W.Labniz

Title: Functional network organization of the awake pigeon brain

Authors: ***M. BEHROOZI**, F. STROCKENS, X. HELLUY, E. GANC, O. GUNTURKUN; Psychology, Inst. of Cognitive Neurosci. , Biopsycholog, Bochum, Germany

Abstract: Despite the structural difference between the unlaminated avian brain and the laminated mammalian brain, there are striking parallels between the two species in function. Recent research on cognitive functions along with neurobiological discoveries in the avian brain demonstrated that the cognitive abilities of bird species are not inferior to mammalian species and that their brains' connectivity is functionally analogously organized. An important approach to investigate this functional analogy is the analyses of functional connectivity between forebrain sub-regions. Using resting state functional magnetic resonance imaging (rsfMRI) it is possible to analyze large-scale functional network including distinct modules. Here, we use rsfMRI along with graph theory in pigeons to identify for the first time of the avian functional connectome. MRI experiments were performed on 10 adult homing pigeons (*Columbia livia*). To assess the functional state of pigeon, resting data was acquired during 10 min. Resting state fMRI scans were performed using a RARE (Rapid Acquisition with Relaxation Enhancement) sequence to reduce the spatial distortions and signal losses due to magnetic effects of air-filled spaces inside the pigeon's skull. Functional images were preprocessed based on standard preprocessing procedures which included correction for head movement, slice time correction, temporal band-pass filtering ($0.01\ Hz < f < 0.1\ Hz$) and spatial smoothing (2 times the voxels size), regression of six parameters obtained by head movement correction, regression of whole brain signal. Functional scans were normalized to the pigeon brain atlas via individual 3D anatomical scan. Pearson correlation coefficient between pairs of averaged time courses within individual ROIs was used to form a 76×76 symmetric connectivity matrix. An average matrix across subjects was

utilized for graph definition. Computed graph characteristics of the correlation matrix were utilized for identifying subgraphs. The clustering coefficient was significantly higher than the clustering coefficient of the comparable random network. The results reveal the presence of between hemisphere correlation in visual, motor and somatosensory areas. We found the pigeon brain distinct functional network organization very similar to the ones found in mammalian brains. This similarity in functional network organization could be an explanation for the similar cognitive capacities in these two species and could represent a convergent evolution in the development of avian and mammalian complex cognition.

Disclosures: **M. Behroozi:** None. **F. Strockens:** None. **X. Helluy:** None. **E. Ganc:** None. **O. Gunturkun:** None.

Poster

778. Comparative Anatomy

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 778.17/D10

Topic: A.10. Development and Evolution

Title: Lateralized learning processes - Impact of commissural systems on one trial passive avoidance learning

Authors: ***A. SIMON**, R. KLOSE, O. GUNTURKUN;
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Abstract: Cerebral lateralization is a widespread organizational principle in the whole animal kingdom. It is assumed that hemispheric asymmetries enhance the cognitive capacities. Such a task sharing makes a communication between both hemispheres indispensable. Commissural systems can provide the necessary interhemispheric cooperation and regulate information transfer.
Pigeons and chickens are classical animal models within laterality research. In spite of several neuroanatomic differences, chickens and pigeons show nearly the same distinct asymmetrical organization of their visual perception and visual driven learning processes. Additionally their commissural systems are organized in a similar manner: At telencephalic level the hippocampal and anterior commissure interconnect both hemispheres whereas the tectal and posterior commissure are located within mesencephalon.
The single exposure of a novel food, coated with a bitter-tasting substance, leads to a permanent avoidance. This one trial passive avoidance learning (PAL) is a well-established paradigm in the juvenile chickens for investigating the neuronal foundations of memory consolidation. Lesion studies reveal that this visual driven learning process is left lateralized and it is assumed that

there is an information flow from the left to the right mesopallium and then bilateral to the medial striata.
In order to examine the impact of the commissural systems on visual driven learning processes several PAL experiments with normal (monocular and binocular conditions) and commissurectomized pigeons (anterior or posterior commissure) were conducted. The results of the binocular experiments show, that pigeons are excellent passive avoidance learners. Moreover the monocular testing confirms that PAL is a left-lateralized learning process. Furthermore, the findings of the commissurectomized pigeons indicate that the posterior commissure has no effect of the ability to avoid inedible food, whereas the anterior commissure plays a key role during this learning process. That supports the "memory flow theory" and shows that the integration of this process is organized exclusively at telecephalic level. We currently plan to examine the neuronal correlates of PAL with in situ hybridisation using the IEG arc. These results confirm the regulative and stabilizing character of commissural systems in general.

Disclosures: **A. Simon:** None. **R. Klose:** None. **O. Gunturkun:** None.

Poster

778. Comparative Anatomy

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 778.18/D11

Topic: A.10. Development and Evolution

Support: NSERC

Canada Research Chairs Program

Canada Foundaton for Innovation

Title: Relative size of the pontine nuclei in birds and its relation with their visual environment.

Authors: *A. N. IWANIUK[1], C. GUTIERREZ-IBANEZ[2], D. WYLIE[3];
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Abstract: As a bird flies through an environment cluttered with numerous objects, both global and local visual motion will occur across the retina. The global motion will occur simply because any form of self-motion will induce optic flow across the retina. The local motion is the motion parallax that occurs because objects and surfaces are at different distances from the observer. Global motion is processed by the accessory optic system, which is composed of two nuclei, the

nucleus lentiformis mesencephalic (LM) and the nucleus of the basal optic root (nBOR) and local motion is processed by the optic tectum (TeO). A prime candidate for the integration of global and local motion is the pontine nuclei. The medial (PM) and lateral pontine (PL) nuclei receive projections from nBOR and LM respectively and the PL receives projections from the TeO. Additionally, both pontine nuclei receive visual information from other sources, including the ventral thalamus, hyperpallium and arcopallium. Here we use a modern comparative approach to examine the relative size of the pontine nuclei, its main visual afferents (LM, nBOR, TeO, GLv), the telencephalon and the cerebellum across a wide variety of birds (107 species, 16 orders). Additionally we analyzed variation of the relative size of the medial spiriform nucleus (Spm), which receives visual projections from the telencephalon, projects to the cerebellum and has been considered a "displaced pontine nucleus". We predicted that the relative size of the pontine nuclei, particularly the lateral pontine, will be larger in species that live in environments that require obstacle avoidance during flight. Our results show that flightless species, but not birds that live in open environments, have relatively small PL when compared to birds that live in visually cluttered environments. Additionally our results suggest that the relative size of the pontine nuclei and Spm vary with the size of visual nuclei and the cerebellum, but not with the relative size of the telencephalon. This is in contrast with mammals where the size of the pontine nuclei and cerebellum seem to be closely related to the size of the telencephalon. Our results therefore have implications for understanding some of the differences between mammalian and avian brains and the evolution of the avian brain in relation to flight.

Disclosures: A.N. Iwaniuk: None. **C. Gutierrez-Ibanez:** None. **D. Wylie:** None.

Poster

778. Comparative Anatomy

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 778.19/D12

Topic: A.10. Development and Evolution

Support: Convergence International - Sorbonne Universités

Title: Continuous addition of neuronal cells during embryonic and postnatal cuttlefish development

Authors: *S. E. DOS SANTOS[1], B. IMARAZENE[2], L. BOTELHO[1], L. BONNAUD-PONTICELLI[2], S. HERCULANO-HOUZEL[1];
[1]Federal Univ. of Rio De Janeiro, Rio De Janeiro, Brazil; [2]UMR BOREA CNRS 7208/UPMC/IRD207/UCN/UA, Muséum Natl. d'Histoire Naturelle, Paris, France

Abstract: The neurogenesis process during development and growth gives organisms the capacity to increase its abilities and/or to renew old cells. Here we have chosen to study the dynamics of neurogenesis in a cephalopod, *Sepia officinalis*, because of its continuous growth throughout adult life and its highly centralized and hierarchical brain allowing rich behavioral repertoires comparable to those of several mammals.

To test the hypothesis of a relationship between the dynamics of brain neurogenesis and the cognitive abilities acquisition at different steps of the biological cycle, we used the isotropic fractionator and immunocitochemistry to NeuN and Nurr1 to determine how neurons numbers in the brain (N_{BR}) and the optic lobes (N_{OLs}) vary as structure mass increases in development (M_{BR} and M_{Ols}) in 58 animals between embryonic day (E)24 and adulthood (Ad), ranging in mass from 0.001g to 0.700g for M_{BR} and from 0.001g to 1.950g for M_{OLs}. For 54 animals, we also analyzed these parameters in the stellate ganglia (N_{SG}, M_{SG}), with mass increasing from 0.001g to 2.099g. We also examined the functional differentiation of neurons focusing on the dopaminergic system, which plays a key role in learning and memory processes. Additionally, we explored tissue expression of these markers by *in situ* hybridization in order to establish the cartography of their expression in the nervous system.

We find that the developing cuttlefish BR contains an average of 1,498,779±729,704 neurons at E24 and reaches an average of 20,082,662±11,044,194 at Ad, representing an increase in average N_{BR} of 13.5-fold. In the same period, N_{OLs} increases 39-fold from 2,804,026±1,620,741 to 108,425,664±24,488,997, and N_{SG} increases 186-fold, from 85,664.5±14,976 to 15,920,756±5,893,054. Ols and SG thus gain neurons faster than the BR, in relationships that can be described as $N_{BR}^{1.226}$ and $N_{BR}^{1.884}$ between E24 and Ad.

Addition of neurons to these structures is continuous between E24 and Ad, with no significant increase in N_{BR}, N_{OLs} and N_{SG} (Wilcoxon, p=0.2453). Moreover, older specimens have relatively more neurons in their BR, OLs and SG (Spearman ρ=0.809, 0.773 and 0.929, respectively; p=0.0026, 0.0053 and 0.0009). Along development, M_{BR}, M_{OLs} and M_{SG} increase with $N_{BR}^{1.426}$, $N_{OLs}^{1.351}$ and $N_{SG}^{1.430}$, that is, these structures gain mass faster than they gain cells.

We found a significant increase of the $Nurr^{+}$-cells between E24 and Ad only in the BR, from 1,008,356±1,026,108 to 7,989,907±11,074,131 (Wilcoxon, p=0.0453). These cells are localized mainly in the olfactory organs, statocysts, optic lobes and the sensory motor lobes of the BR confirming a precocious set up of the sensory system control.

Disclosures: **S.E. Dos santos:** None. **B. Imarazene:** None. **L. Botelho:** None. **L. Bonnaud-Ponticelli:** None. **S. Herculano-Houzel:** None.

Poster

778. Comparative Anatomy

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 778.20/D13

Topic: A.10. Development and Evolution

Support: German Research Foundation (DFG) Grant SFB 874

Title: The canonical circuit of the avian sensory forebrain

Authors: *M. STACHO, O. GUNTURKUN;
Biopsychology, Ruhr-University Bochum, Bochum, Germany

Abstract: Up to the end of the 20th century, birds were thought to have limited cognitive abilities and their forebrain was mostly thought to be constituted by hypertrophied basal ganglia with only a minimal fraction of the forebrain recognized as pallium. These facts together with the knowledge about the basal ganglia function at that time resulted in the conclusion that birds were only capable of instinctive behavior. Nowadays, scientific evidence about the avian cognition and modern neuroanatomical studies unequivocally disproved this view and shed light on a radically different picture. Although birds do not possess a six-layered neocortex, detailed studies of the visual and auditory system in chicken uncovered columnar-like organization and canonical circuits akin to neocortical columns and canonical circuits in mammals. To confirm and further extend these results, we performed in-vitro tracing on the visual and trigeminal system as well as the somatosensory and visual hyperpallium (H) in pigeons. We found that the thalamo-recipient sensory areas Field L2 (auditory), entopallium (visual), and nucleus basalis (trigeminal) were directly interconnected with dorsal and ventral mesopallium. The intercalated nidopallium was reciprocally connected with both the primary sensory areas and the mesopallium. The nido- and mesopallium were the sources of projections to arcopallium - the output region of the avian forebrain. Interestingly, the H showed a conspicuously different organization. In contrast to nido/mesopallial areas, the H (both visual and somatosensory components) did not display such a strict columnar organization and showed strong within-layer connections. Moreover, the interstitial part of the H apicale (IHA, the thalamo-recipient layer of H) directly projected to the apical part of H (HA), the output layer of the H, and did not project to mesopallium. The intercalated part of the H (HI) was reciprocally connected to IHA, HA and to adjacent densocellular part of the H (HD). HD further projected to HA and IHA, and together with HI and HA also to the mesopallium. In turn, the mesopallium projected to all layers of H. Despite profound differences between the H and the nidopallial circuit, some similarities in the connectivity can be pointed out. The canonical pathway from IHA to HA via HI with feedback connections at each level is similar to the organization centered around the nidopallium. Thus, the avian sensory forebrain seems to be characterized by a single canonical circuit that has some

local variations. Future studies have to show how similar the avian canonical circuit is to its mammalian cortical counterpart.

Disclosures: **M. Stacho:** None. **O. Gunturkun:** None.

Poster

778. Comparative Anatomy

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 778.21/D14

Topic: A.10. Development and Evolution

Support: Deanship of Academic Research, The University of Jordan. Amman, Jordan (grant to Amjad Alshatarat)

Title: Ultrastructure differences in various subregions of the corpus callosum between male and female rats; an electron microscopic study

Authors: *D. J. AL QATTAN[1], L. ALZGHOUL[4], A. I. ABDALLAH[2], A. K. ABD-ELHAFITH[2], A. AL-SHATARAT[3];
[1]Pathology, [2]Fac. of Pharm., [3]Dept. of Anat., The Univ. of Jordan, Amman, Jordan; [4]Physiol. and Biochem., The university of Jordan, Amman, Jordan

Abstract: Sexual dimorphism exists at all levels of the nervous system, from genetic, anatomical, and system levels. These sex differences could underlie gender-related differences in behavior and neuropsychological function, as well as, the sex differences in the prevalence of various mental problems such as autism, attention deficit, and schizophrenia. The corpus callosum (CC) is the largest of the brain commissures, which connects the cerebral cortices of the two hemispheres, and provide interhemispharic connectivity for information transfer and processing between cortical regions. Alteration in the structure of CC will alter interhemispheric connectivity and commonly documented in several psychiatric disorders. The CC consists of myelinated and unmyelinated axons, glial cells, and blood vessels. Several functional studies have reported that CC function is associated with its axon size and density as well as their myelination properties. The sexual dimorphism in the axonal content of the CC has always been controversial, hence, the aim of this study was to analyze he ultra-structural differences of the CC between male and female rats. To assess that, five pairs of adult male and female rats were perfused and the CC was sectioned. Then four sections from different subregions of the corpus callosum that represent the genu, anterior body, posterior body, and splenium of the CC were stained and electron microscopic images were captured using stereological guidelines. Later, the total axon density and the myelinated/unmyelinated ratio was calculated for each subregion and

compared between males and females. Furthermore, the axons characteristics including axon diameter, myelin thickness and G-ratio was calculated for each subregion and compared between males and females. Our preliminary findings of the present study indicate a higher total axon density in female rats compare to males, with region specific differences in the distribution of myelinated and unmyelinated axons and their characteristics in the CC between male and female rats.

Disclosures: D.J. Al Qattan: None. **L. Alzghoul:** None. **A.I. Abdallah:** None. **A.K. Abd-elhafith:** None. **A. Al-Shatarat:** None.

Poster

778. Comparative Anatomy

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 778.22/D15

Topic: A.10. Development and Evolution

Support: MINECO Grant BFU2015-68537-R

Title: Differential gene expression patterns suggest a distinct embryonic origin of the medial and lateral parts of the entorhinal cortex

Authors: *A. ABELLAN, E. DESFILIS, L. MEDINA;
Univ. of Lleida - IRBLLEIDA, Lleida, Spain

Abstract: The entorhinal cortex forms part of a functional network that is essential for navigation and memory. It includes two subdivisions: (1) a medial part related to spatial navigation and memory; and (2) a lateral part that processes non-spatial, contextual information, being critical for novel object-context recognition. While both have ample connections with the hippocampal formation, they show differences regarding their connections with the neocortex and the amygdala. For example, only the lateral entorhinal cortex has strong connections with the basal amygdalar complex. In order to understand the origin of these connectivity and functional differences, we studied in mouse and chicken the expression of a battery of transcription factors and other regulatory proteins during development, including *Lef1*, *Lhx2*, *Lhx9*, *Lmo3*, *Lmo4*, *ER81*, *Dbx1*, *Jagg1* and *Sfrp2*. The combinatorial expression of these genes allowed identification of the major pallial domains, such as medial, dorsal, lateral and ventral pallia. During early development of mouse, the anlage of the medial entorhinal cortex showed a gene expression profile (*Lef1*, *Lhx2*, *Lhx9*, *Lmo4*) very similar to that of the hippocampal primordium. Based on this and their adjacent topological location on the medial side of the telencephalic vesicles, we suggest that both structures originate in the medial pallium. In contrast, the lateral

entorhinal cortex showed a gene expression profile different from that of the medial pallium, but also from the ventral, lateral and dorsal pallium. The distinct embryonic origins of medial and lateral parts of the entorhinal cortex are likely behind their different developmental trajectories and connectivity patterns. Comparison with the expression of the orthologous genes in chicken in combination with other data suggested the existence of an area comparable to the medial entorhinal cortex. However, our data did not allow identification of the lateral entorhinal cortex in chicken. MINECO Grant BFU2015-68537-R.

Disclosures: **A. Abellan:** None. **E. Desfilis:** None. **L. Medina:** None.

Poster

778. Comparative Anatomy

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 778.23/D16

Topic: A.10. Development and Evolution

Support: The Mathers Foundation

Title: Anterior to posterior distribution of neurons across the cerebral cortex of infant macaques

Authors: ***M. GABI**, E. C. TURNER, D. J. MILLER, J. H. KAAS;
Psychology Dept., Vanderbilt Univ., Nashville, TN

Abstract: During brain development, the cerebral cortex is under striking changes including prenatal neurogenesis, sudden death of most of neurons in the first postnatal week, followed by an increase in neuronal number. However, not all brains are built in the same way. For instance, neuronal proportions of rodents and primates brains do not scale universally with structure size and little research has evidenced how these differences arise during development, specifically across the functional areas of the cerebral cortex.
In this study, we initiate a systematic comparison of the anterior-posterior distribution of neurons and other cells along the surface of the cerebral cortex of infant macaque monkeys, aiming to determine the pattern in which the cells are allocated in the different areas of the cortex during early stages of postnatal development. An anterior-posterior gradient of neuron densities has been described in various species of adult primates, but how this will be comparable when most of the cortical neurons are being generated, and considerable cortical growth will yet occur is still a question.
One cortical hemisphere of three infant *Macaca mulatta* of different ages (stillborn, 4 days old and 11 days old) was embedded in agar and sliced into a series of 2mm thick coronal sections. The grey matter of each section was separated from the underlying white matter and weighed. To

determine the total number of neuronal and other cells in the grey matter we applied the isotropic fractionator.
The cerebral cortex of the three macaques exhibits a heterogeneous distribution of neuronal densities, which increased systematically 4-fold along the anterior-posterior axis. This distribution shows a single neuronal gradient across the different areas, with the lowest densities in the frontal regions and the highest towards the posterior area. The distribution of other cells density shows a 5-fold variation along the anterior-posterior axis. In contrast, the glia/neuron (g/n) ratio varies over 2-fold among cortical regions in all ages, but does not show a simple gradient distribution. The g/n ratio varies as a negative power function of neuronal density, decreasing as neuronal density increases, exactly as found in previous data for adult primates. This suggests that the number of glial cells per neuron in each section increases with the increasing average size of neurons.
Overall, the results are similar to those reported for adult macaques, and support that an adult-like pattern of neuron distribution and total number of neurons exists in postnatal macaques from the time of birth. A more detailed analysis could reveal additional features of the pattern of neuronal distribution.

Disclosures: **M. Gabi:** None. **E.C. Turner:** None. **D.J. Miller:** None. **J.H. Kaas:** None.

Poster

778. Comparative Anatomy

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 778.24/D17

Topic: A.10. Development and Evolution

Title: Molecular imaging of multitasking processes in the pigeon (Columba livia)

Authors: *S. LETZNER[1], O. GUNTURKUN[1], C. BESTE[2];
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[2]Universitaetsklinikum, Dresden, Germany

Abstract: Multitasking is a common psychological phenomenon. Every day people switch from one task to another in response to changes in the environment. Thereby an executive goal (GO1) is induced, stopped (STOP) and replaced by a second executive goal (GO2). To what extent the single executive components in this process are processed serial or parallel and which brain areas are activated during the different components is still unknown. A well-established paradigm in humans to analyze multitasking processes is the stop change paradigm, in which the response for a primary GO1 goal had to be stopped and replaced by a response for a secondary GO2 goal. Thus this paradigm allows the analysis of the three cognitive goals involved in the multitasking

process: GO1 goal, STOP goal and GO2 goal. We adopted this paradigm to pigeons to analyze on behavioral level to what extent a serial or parallel information processing is existent. Additionally, different to humans the pigeon model gives us the opportunity to analyze the anatomical correlates which are activated during a stop change paradigm by molecular imaging. In our task each trial was initialized by pecking on a pecking key at the left panel of a conditioning chamber directly followed by the presentation of a green GO1 stimulus on the front panel. Pecking on the GO1 stimulus results in a food reward. On some trials a STOP signal (red house light) is shown. The delay between the GO1 and the STOP signal is adjusted that in 50% the reaction to GO1 can be executed and in the other 50% the reaction to GO1 is inhibited and a white stop change stimulus (GO2) is presented on a further pecking key. To differentiate the essential processes GO1, STOP and GO2 we used three groups of pigeons. The first group only performed the GO1 trials and served as control group for the neuronal activation. For the separation of STOP and GO2 processes a second experimental group performed GO1 and STOP but no GO2 of the paradigm, while a third experimental group performed the whole paradigm. When the pigeons successfully performed the paradigm they were directly decapitated after the session and the brains fixated for immunohistochemical staining of the molecular activity marker ZENK. Like this, we are able to directly compare behavioral results across different species, namely pigeons and humans, and study underlying brain function in a detailed manner that would not be possible in humans.

Disclosures: **S. Letzner:** None. **O. Gunturkun:** None. **C. Beste:** None.

Poster

778. Comparative Anatomy

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 778.25/D18

Topic: A.10. Development and Evolution

Title: Volumes of claustrums are not directly proportional to volumes of forebrains across the mammalian radiation

Authors: *J. I. JOHNSON[1], B. A. FENSKE[2], H. YORK[3];
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Abstract: In the brains of mammals, most of the connections of the claustrum are with the forebrain. To investigate whether the sizes of claustrums reflect a consistent relationship with the sizes of the connected forebrains, we computed volumes of claustrums and volumes of their connected forebrains in representative species from most mammalian orders. We used digital

three-dimensional reconstruction programs to render volumes of claustrums and forebrains from the areas of claustrums and forebrains measured in regular series of sections through these structures observed in tissue sections stained with the Nissl method.
We found no consistent relationship of sizes of claustrums and forebrains, meaning that individual taxa have developed more or less unique size relationships between these brain components. For example, grizzly bears *Ursus arctos)* and domestic pigs *(Sus scrofa)* exhibit extraordinarily large claustrums for their size of forebrain, while colugoes *(Cynocephalus volans)*, and mongoose lemurs *(Eulemur mongoz)* have smaller claustrums than would be predicted from the sizes of their forebrains.
A larger than expected claustrum is often associated with the development of a large "puddle" of claustral tissue. This suggests that regional intraclaustral specializations related to neurobehavioral specializations have arisen in certain species.

Disclosures: J.I. Johnson: None. **B.A. Fenske:** None. **H. York:** None.

Poster

778. Comparative Anatomy

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 778.26/D19

Topic: A.10. Development and Evolution

Title: Semantic categories in the pigeon's nidopallium frontolaterale: a reverse engineering approach

Authors: *R. PUSCH[1], C. KOENEN[2], A. AZIZI[3], J. KELLERMANN[4], F. BROKER[2], S. THIELE[2], S. CHENG[3], O. GUNTURKUN[2];
[2]Biopsychology, [3]Inst. for Neural Computation, [4]Statistics/Econometrics, [1]Ruhr-University Bochum, Bochum, Germany

Abstract: Pigeons are well known for their ability to categorize objects but the neuronal mechanisms guiding this behavior remain poorly understood. So, how do pigeons see the world? And how do they cope with all the varieties of visual objects they are confronted with in their avian environment? In the present study we are interested in the central representation of different objects addressing one key question: Are neuronal mechanisms of visual object representation comparable across different classes of vertebrates ranging from avian species to human and hon-human primates?
Addressing this question we recorded single neurons in the pigeon's nidopallium frontolaterale (NFL), a higher visual area and the putative analog to the inferior temporal (IT) cortex of primates. During our experiments we presented different sets of stimuli to freely moving and

behaving pigeons while recording single cell activity from the NFL. Instead of training pigeons on predefined categories, we simply presented stimuli and analyzed the neural output. Resulting categories were built post-hoc based on computations of the neuronal pattern elicited by each stimulus. We used basic visual stimuli, i.e. simple forms in different colors as well as gratings varying in their spatial frequencies and contrasts. Additionally, we showed pictures of real-world objects representing different categories. Kriegeskorte et al. (2008) presented these pictures of real-world objects to humans and monkeys and revealed an activity pattern in IT in line with semantic categories. Moreover, category clusters where highly similar between man and monkey, recorded with fMRI and single cell recording, respectively. With our approach we investigate the neural basis of perceptual discrimination in the NFL of pigeons. Based on our results we compare to what extend neuronal mechanisms of object categorization are shared by these different classes of vertebrates.

Disclosures: R. Pusch: None. **C. Koenen:** None. **A. Azizi:** None. **J. Kellermann:** None. **F. Broker:** None. **S. Thiele:** None. **S. Cheng:** None. **O. Gunturkun:** None.

Poster

778. Comparative Anatomy

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 778.27/D20

Topic: A.10. Development and Evolution

Support: DFG Grant FOR1581

Title: The neural circuit underlying extinction learning in pigeons - evidence from pharmacological studies

Authors: *M. GAO[1], D. LENGERSDORF[1], M. C. STUTTGEN[2], O. GUNTURKUN[1]; [1]AE Biopsychology, Ruhr-University Bochum, Bochum, Germany; [2]Inst. of Pathophysiology, Univ. Med. Ctr. Mainz, Mainz, Germany

Abstract: Extinction learning is an essential learning mechanism that enables constant adaptation to the ever changing environmental conditions. The underlying neural circuit was mostly studied with rodent models using fear conditioning tasks. In order to uncover the variant and the invariant neural properties of extinction learning, we adopted pigeons as an animal model in an appetitive sign-tracking paradigm. The animals firstly learned to respond to two stimuli in two different contexts (CS-1 in context A and CS-2 in context B) and then extinguished their conditioned responses to the corresponding stimulus in the opposite contexts (CS-1 in context B and CS-2 in context A). Finally, they were tested for both stimuli in both

contexts. Before the extinction training, we locally injected the sodium-channel blocker tetrodotoxin (TTX) or the N-methyl-D-aspartate receptor (NMDAR) antagonist 2-Amino-5-phospho-novalerianacid (APV) in specific areas to investigate their involvement in the extinction learning process. With this within-subject renewal design, we discovered that the extinction learning does not only engage the neural circuit of the nidopallium caudolaterale (NCL; the avian equivalent structure to the mammalian PFC), hippocampus, and amygdala, but also involves arcopallium, the avian motoric area, and the nidopallium frontolaterale (NFL), one of the avian higher visual-processing areas. Importantly, our findings suggested that the encoding of extinction memory requires the activation of NCL, amygdala, and NFL: the learning process during extinction was slowed down after drug injection before the extinction training. While the consolidation process involves NCL, hippocampus and arcopallium which can be observed from an unaffected learning dynamic in extinction training after injection but an elevated spontaneous recovery during testing.

Disclosures: **M. Gao:** None. **D. Lengersdorf:** None. **M.C. Stuttgen:** None. **O. Gunturkun:** None.

Poster

778. Comparative Anatomy

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 778.28/D21

Topic: A.10. Development and Evolution

Title: Metabolic changes in the bilateral visual cortex of monocular blindness macaque monkeys: a multi-voxel proton magnetic resonance spectroscopy study

Authors: ***Z. TANG**, L. WU;
radiology, Eye & ENT Hosp. of Fudan Univ., Shanghai, China

Abstract: PURPOSE
To study adaptive plasticity and reorganization in the visual cortex of the monocular blind macaque using multi-voxel proton magnetic resonance spectroscopy study (^{1}H-MRS).
METHOD AND MATERIALS
Four healthy neonatal macaques were randomly divided into 2 groups. One group served as control group (group A). Optic nerve transecting was performed in the right eye of the other group (group B), to establish the monocular blind model. Sixteen (group B^{16M}) and thirty-two (group B^{32M}) months after monocular optic nerve transecting, multi-voxel 1H-MRS was performed on the bilateral visual cortex of all monkeys, respectively. We compared NAA/Cr, Ins/Cr, Cho/Cr and Glx/Cr in the visual cortex between group A and group B as well as between

the left and right visual cortices of group A and B in each time points, respectively. All of the metabolic changes detecting by multi-voxel ^{1}H-MRS were further compared with the immunofluorescent staining findings.
RESULTS
Compared with group A, in bilateral visual cortex, NAA/Cr in both group B^{16M} and group B^{32M}, as well as Glx/Cr in group B^{32M} were all significant decrease ($p<0.05$), whereas the Cho/Cr and Ins/Cr of group B^{32M} were significant increase ($p<0.05$). Meanwhile, significant difference of NAA/Cr in group B^{32M} was found between the left and right visual cortex, whereas no statistical difference of Ins/Cr, Cho/Cr and Glx/Cr between the left and right visual cortex was found in both group B^{16M} and group B^{32M}. All of these ^{1}H-MRS findings (with the exception of group B^{16M}) were further confirmed by the immunofluorescent staining.
CONCLUSION
Multi-voxel ^{1}H-MRS was able to detect the different metabolic changes in the visual cortex, which was valuable for investigating its adaptive plasticity and reorganization.

Disclosures: **Z. Tang:** None. **L. Wu:** None.

Poster

778. Comparative Anatomy

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 778.29/D22

Topic: A.10. Development and Evolution

Support: NSERC

Title: Domestication affects Purkinje cell size and foliation in the cerebellar cortex in laboratory rats (Rattus norvegicus)

Authors: ***L. WILLIAMS**[1], T. SALIK[1], R. STRYJEK[2], K. MODLINSKA[2], W. PISULA[2], S. M. PELLIS[1], A. N. IWANIUK[1];
[1]Neurosci., Univ. of Lethbridge, Lethbridge, AB, Canada; [2]Inst. of Psychology, Polish Acad. of Sci., Warsaw, Poland

Abstract: Domestication is the process by which wild organisms are adapted for human use. Over time, isolated populations raised in captivity begin to phenotypically diverge from their wild counterparts in both morphology and behaviour. The lab rat, an important model organism in scientific research, is the result of domestication of the wild Norway rat *(Rattus norvegicus)*. Similar to other domesticated animals, lab rats have relatively smaller brains compared to wild rats. In addition, lab rats exhibit less spontaneous motor behaviour and acrobatic play than their

wild counterparts. Such variation in motor behavior likely reflects underlying changes in regions that coordinate and regulate motor activity, such as the cerebellum. Although the "ecological niche" of a domesticated lifestyle produces changes in brain size, the effects of domestication on the cerebellum are not well understood. Here, we compared the cerebella of female wild-caught Norway and Long-Evans rats to assess the effect of domestication on cerebellar folding (foliation), cerebellar volume, the number of Purkinje cells, and Purkinje soma size. Sagittal sections were stained for Nissl substance and quantified with unbiased stereology. Our analyses indicate that lab and wild rats have similar cerebellar volumes, but wild rats had a significantly higher degree of folding in the cerebellar cortex. Wild rats also had significantly larger Purkinje neurons compared to domestic rats, but there was no clear effect on the number of Purkinje neurons. These results suggest that the cerebellum of laboratory rats has indeed undergone anatomical changes in response to domestication. Further, our results suggest that the reduction in cerebellar folding observed in lab rats was driven by a decrease in soma size, but not a decrease in the number of neurons. One implication of having a more foliated cerebellum with larger cells is that wild rats presumably retain a greater capacity to process and modulate muscular activity compared to laboratory rats. Similarly, those motor functions governed by the cerebellum may be less ecologically relevant in a domestic setting than in the wild. This knowledge will help to improve our understanding of how domestication affects brain morphology and the putative role of the cerebellum in modulating play behavior.

Disclosures: **L. Williams:** None. **T. Salik:** None. **R. Stryjek:** None. **K. Modlinska:** None. **W. Pisula:** None. **S.M. Pellis:** None. **A.N. Iwaniuk:** None.

Poster

778. Comparative Anatomy

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 778.30/D23

Topic: D.03. Somatosensation: Touch

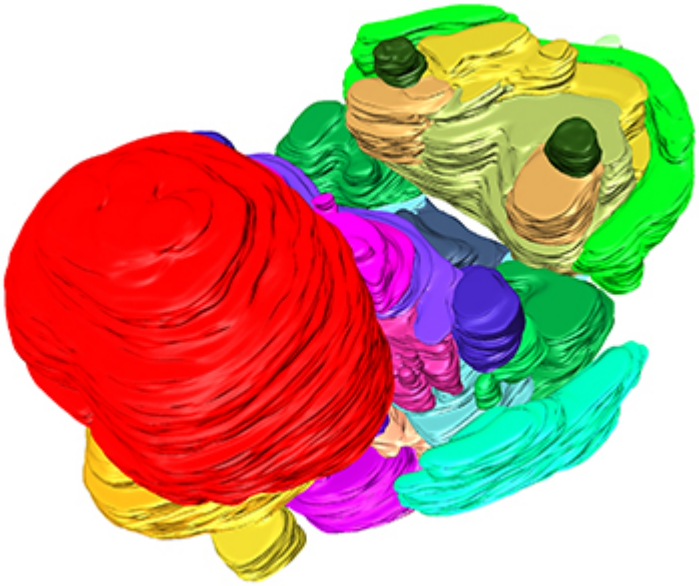
Support: PRESTO, JST

Title: Three-dimensional brain atlas of pygmy squid, Idiosepius paradoxus

Authors: ***N. TANAKA**[1], M. KOIZUMI[1], S. SHIGENO[2];
[1]Hokkaido Univ., Sapporo, Japan; [2]JAMSTEC, Yokosuka, Japan

Abstract: Cephalopods have very unique behaviors, for example camouflage and also show some intelligent behaviors such as observational learning. Although these behaviors have fascinated many biologists, the brain functions underlying these behaviors still remain unclear.

To understand the mechanisms, we have started to analyze the brain circuit of pygmy squids, *Idiosepius paradoxus*, as a model, because it has the small-size brain among cephalopods and because it can be raised easily in still sea water. In addition, this smallest species has similar behaviors such as camouflage as observed in other squids. By immunolabeling the central brain with anti-*Drosophila* SYNAPSIN and anti-*Tetrahymena* TUBULIN antibodies, we three-dimensionally reconstructed the whole brain and analyzed the pathways between lobes. We could identify one new lobe in the brain and also revealed that as has been reported on the other cephalopod species, in *I. paradoxus* the juvenile brain is much (more than 35 times) bigger than the hatchling one and the relative size of the vertical lobe, which is concerned with learning and memory of visual and tactile tasks, is four times bigger in the juvenile than in the hatchling. We are currently developing neurotracing and calcium imaging techniques to visualize the sensory maps in a live squid.



Disclosures: **N. Tanaka:** None. **M. Koizumi:** None. **S. Shigeno:** None.

Poster

778. Comparative Anatomy

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 778.31/D24

Topic: A.01. Neurogenesis and Gliogenesis

Support: 2R15NS060099-02A1

8TL4GM118977-02

Title: Chromophore formation in developing frogs

Authors: ***M. D. PEREZ**[1], M. REYES[2], N. ZUHDI[2], M. E. DE BELLARD[2];
[1]California State University, Northridge, Northridge, CA; [2]biology, CSUN, northridge, CA

Abstract: The purpose of this research it to investigate whether the frogs already have melanocytes and chromophores, if melanocytes become chromophores and to find where the chromophores are coming from. Frog embryos at different stages of development were collected. Some of the embryos were injected with DiI, while others were left as is. The embryos were stained with the antibody HNK1 as a marker to see if the chromophores were present at each stage in development. Different technique are being used to obtain a clear idea of the embryos

anatomy and to be able to see if the cells are present. We have used whole mount of the embryos, vibratome sections and we are currently working on paraffin sections. Upon examination, unique cells were seen, but we have yet to determine that these cells are chromophores. Funding was by NIH/NINDS AREA grant 2R15NS060099-02A1 to MEdB and a BUILD/PODER scholarship to DP.

Disclosures: **M.D. Perez:** None. **M. reyes:** None. **N. Zuhdi:** None. **M.E. de Bellard:** None.

Poster

779. Development and Evolution

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 779.01/D25

Topic: A.10. Development and Evolution

Title: Physid snails respond to light before hatching

Authors: E. M. REMBETSKI[1], T. M. MCCARTHY[2], *A. K. PACK[3];
[1]Neurosci., [2]Biol., [3]Utica Col., Utica, NY

Abstract: Freshwater snails use vision, but it is not clear in all species when their eyes/retinas form. We observed movement in the freshwater snail *Physa acuta* (N=9) before hatching (i.e., still in the egg mass) 2-5 days after the eggs were laid. *P. acuta* moved more while exposed to light in the egg than dark-exposed controls (Chi-square test, $X^2 = 38.025$, $p < 0.001$). This was not a response to temperature, warm water did not increase activity (Wilcoxon, $p = 0.317$). Unhatched snails, therefore, are already sensitive to light. This has implications for behavior and light pollution studies.

Disclosures: **E.M. Rembetski:** None. **T.M. McCarthy:** None. **A.K. Pack:** None.

Poster

779. Development and Evolution

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 779.02/D26

Topic: A.10. Development and Evolution

Support: Medizinische Forschungskommission Universitaet Duesseldorf

Title: Of mice and pigeons-a comparative view of adult neurogenesis in two different animal models

Authors: *J. MEHLHORN[1], I. MASSON[1], K. AMUNTS[2,3], C. HEROLD[2];
[1]Inst. of Anat. I, Univ. of Düsseldorf, Duesseldorf, Germany; [2]C. & O. Vogt Inst. of Brain Research, Univ. of Düsseldorf, Düsseldorf, Germany; [3]Inst. of Neurosci. and Med. INM-1, Res. Ctr. Jülich, Jülich, Germany

Abstract: Adult neurogenesis is a dynamic process that includes the generation and proliferation of neurons in the brain over lifespan and across species. While in mammals particularly the dentate gyrus (DG) and the olfactory bulb (OB) integrate newborn neurons into functional circuits, in birds it is known that adult neurogenesis occurs in several telecenephalic structures. Further, birds seem to have a higher number of immature neurons indicating a wider range in plasticity and possible recovery mechanisms. Here we show differences and similarities of adult neurogenesis in C57BL/6 mice (*Mus musculus*) that were housed in cages with enriched environment and free flying homing pigeons (*Columba livia* f.d.). Both groups were treated with 5-bromo-deoxyuridine (BrdU) to label dividing cells and sacrificed about three months after injection. Brains were dissected and immunohistochemically processed to a) examine cell proliferation with Nestin, SOX2 and doublecortin (DCX), b) show newly generated neurons or glia, visualized by NeuN/BrdU or S100/BrdU double labelling and c) get information about apoptosis, with TUNEL detection. In pigeons, BrdU-positive (BrdU-ir) and DCX-positive (DCX-ir) neurons were widely distributed in the telencephalon, with the highest numbers in the ventricular zone, in the ventrolateral part of the V-complex and the dorsolateral region of the hippocampal formation, along the mesopallial lamina, the superior and supreme frontal lamina, the caudolateral and central nidopallium, the olfactory bulb and the striatum. Thereby, the number of DCX-ir cells was much higher compared to BrdU-ir cells and comparable to markers of early stages of progenitors like Nestin-ir cells. No signs of increased apoptosis were observed. In mice the highest numbers of newborn neurons were detected in the subgranular zone of DG and in the OB. A few BrdU/NeuN-ir cells were also observed all over the cortex. Most DCX-ir neurons were detected in the ventricular zone, the subgranular zone of DG, the OB, and lower numbers in CA3, CA2 and the ventral striatum. A few DCX-ir cells were also counted along the alveus and the corpus callosum. TUNEL-labelling showed no signs of increased apoptosis. Our findings suggest that species-specific or even class-specific differences in anatomy, behaviour, ecological niche etc. may have a larger influence on brain plasticity as assumed and that it would be interesting to investigate the functional consequences of adult neurogenesis into more detail. Besides, our findings may introduce the pigeon as a new model organism in comparison to humans, because both species show newborn neurons during adulthood in the striatum.

Disclosures: **J. Mehlhorn:** None. **I. Masson:** None. **K. Amunts:** None. **C. Herold:** None.

Poster

779. Development and Evolution

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 779.03/D27

Topic: A.10. Development and Evolution

Support: NIMH MH901645

NIMH MH100031

NICHD HD003352

Title: Cerebral white matter development in rhesus macaque during the early postnatal phase as measured via diffusion MRI

Authors: *J. YOUNG[1], Y. SHI[1], C. COE[2], R. KNICKMEYER[1], M. STYNER[1];
[1]Univ. of North Carolina At Chapel Hill, Chapel Hill, NC; [2]Univ. of Wisconsin-Madison, Madison, WI

Abstract: Diffusion tensor imaging provides a unique way for researchers to capture the microstructure of white matter tracts throughout the brain and examine developmental trajectories. Additionally, the rhesus macaque (*Macaca mulatta*) is one of the most commonly used nonhuman primates for translational investigations, and provides a unique opportunity to study normal brain maturation, especially in early infancy, where crucial information about formative developmental trajectories is still missing in young children. Here, we have created a detailed longitudinal diffusion tensor atlas, along with characterizing the corresponding white matter fiber tracts in the rhesus macaque at 0.5 to 36 months of age from the UNC-Wisconsin Neurodevelopment Rhesus Macaque Database. We employed the UNC NA-MIC DTI Analysis Framework: to: 1) build the subject specific longitudinal atlases, 2) combine these atlases into a single population atlas space, 3) propagate prior white matter tracts from a high resolution atlas, and 4) extract fiber bundle profile measurements. Our results show that the macaque white matter tracts continue to change throughout this maturational period at varying rates with a spatially varying pattern from birth to puberty. Examples of this variation include the inter-hemispheric tracts of the corpus callosum, which show a much larger rate of change as compared to other tracts. All data and atlases, both raw and processed, are being disseminated publically to serve as a resource for the neuroimaging and neurodevelopmental communities.

Disclosures: J. Young: None. **Y. Shi:** None. **C. Coe:** None. **R. Knickmeyer:** None. **M. Styner:** None.

Poster

779. Development and Evolution

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 779.04/D28

Topic: A.10. Development and Evolution

Title: The molecular evolution of plasticity and the human hippocampus.

Authors: *B. M. SCHILDER[1], B. J. BRADLEY[2], C. C. SHERWOOD[2];
[2]Ctr. for the Advanced Study of Human Paleobiology, [1]George Washington Univ., Washington, DC

Abstract: The hippocampus is a neuroanatomical structure critical for long-term memory and spatial navigation. The human hippocampus has evolved in terms of both relative volume expansion and changes in gene expression compared to nonhuman primates (NHPs). However, little is known regarding how the constituent subfields of the hippocampus have been modified in the human lineage. We analyzed microarray data from the Allen Brain Atlas to compare the expression of four candidate genes important for plasticity and adult neurogenesis (doublecortin [*DCX*], brain-derived neurotrophic factor [*BDNF*], glial fibrillary acidic protein [*GFAP*], and ephrin-B1 [*EPHB1*]) across the hippocampal subfields of humans and rhesus macaques. While gene expression did not always differ between species at the level of whole-hippocampus (i.e. DCX; $p > 0.05$), analyses of the individual subfields revealed many interspecies gene expression differences for all four candidate genes ($p \leq 0.05$).
Furthermore, we explored whether these gene expression differences could be attributed to evolutionary changes in the protein-coding DNA sequences of these candidate genes. Aligned orthologous sequences of 12 primates and 3 non-primates were downloaded from the UCSC Table Browser, filtered to exclude regions of questionable homology using Block Mapping & Gathering with Entropy (BMGE), and tested five different substitution models of positive selection detection using the HyPhy packages on the Datamonkey server (i.e. *Mixed Effects Model of Evolution*, *Fixed Effects Likelihood*, *Genetic Algorithm with branching*, *Branch-site Real Estimated Likelihood*, and *Adaptive Branch-Site Random Effects Likelihood)*. The only genes that showed any evidence of positive selection ($p \leq 0.05$) were *DCX* (S36N in the *Pan troglodytes* branch) and *GFAP* (G149A in the branch leading to the *Homo-Pan-Gorilla* clade, and G149T in the *Tupaia chinensis* branch). However, when the effects of these substitutions were modeled using PolyPhen2 and SNAP2 they were predicted to have no functional effect on the protein. In sum, while the pattern of gene expression of these key plasticity-regulating genes across the hippocampal subfields has evolved since the divergence of humans and macaques, this does not appear to be related to changes in protein-coding sequences of those genes. Future work should explore the evolution of regulatory-region sequence evolution as a potential source of these differences.

Disclosures: **B.M. Schilder:** None. **B.J. Bradley:** None. **C.C. Sherwood:** None.

Poster

779. Development and Evolution

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 779.05/D29

Topic: A.10. Development and Evolution

Support: NIDA R01.DA037924

NSF HRD.1137725

MBRS-RISE R25.GM061838

NIH-RCMI G12.RR03051

Title: Roles of cannabinoid 2 receptor (CB2) in the development of zebrafish nervous system

Authors: *A. ACEVEDO-CANABAL[1], L. COLÓN-CRUZ[1], M. BEHRA[1], G. A. YUDOWSKI[2];
[1]Univ. of Puerto Rico - RCM, San Juan, PR; [2]Univ. of Puerto Rico - Inst. of Neurobio., San Juan, PR

Abstract: The importance of the endocannabinoid signaling during vertebrate development of the central nervous system (CNS) has been extensively hypothesized but scarce studies have been published. The endocannabinoid signaling is mediated through the cannabinoid receptors 1 and 2 (CB1 and CB2). Knockout (KO) mice have been generated for the *cnr1* and *cnr2* genes that encode for the CB1 and CB2, respectively. Homozygote cnr1-/- and cnr2-/- animals are viable, arguing against a critical role for either of the genes in the overall nervous system development. However, more subtle thalamocortical axon misrouting and aberrant fasciculation have been found in CB1 KO mice but nothing has been documented in CB2 with regards of brain development. We hypothesize that CB2 plays a role in modulating the endocannabinoid signaling and therefore, plays important roles during early brain development.
We used CRISPR-Cas9 target-genome editing to generate *cnr2* KO zebrafish. We raised homozygotes carrying 2nucleotide deletion ($cnr2^{\Delta 2-/-}$) which is generating a frame-shift and an early stop codon. We will assess how the levels of the cnr2 gene products are affected. The predictions are that only non-functional truncated CB2 probably unstable will be made. We are currently testing an anti-CB2 specific antibody in whole-mount and in westernblot to validate the loss of function allele. Next, we will monitor neuronal wiring and axonal fasciculation formation through immunohistochemistry with a numbers of axonal markers in different developmental

stages of zebrafish embryos and larvae. In particular, we will focus in the diencephalon, telencephalon, hindbrain, and midbrain since CB2 has been reported to be expressed in those regions during embryonic stages of mice. This will allow us to highlight possible morphological changes caused by the absence of a functional CB2 receptor.

Disclosures: A. Acevedo-Canabal: None. **L. Colón-Cruz:** None. **M. Behra:** None. **G.A. Yudowski:** None.

Poster

779. Development and Evolution

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 779.06/D30

Topic: A.10. Development and Evolution

Support: ARC DP160103958

ARC DE160101394

Ian Potter Foundation

Title: Ancient origin and conservation of a bilateral map in the mammalian cortex

Authors: *R. SUAREZ[1], A. PAOLINO[1], L. MORCOM[1], P. KOZULIN[1], L. R. FENLON[1], N. KURNIAWAN[2], L. J. RICHARDS[1,3];
[1]Queensland Brain Inst., [2]Ctr. for Advanced Imaging, [3]Sch. of Biomed. Sci., The Univ. of Queensland, Brisbane, Australia

Abstract: Bilateral integration between the cerebral cortices is crucial for sensorimotor, associative and cognitive functions. In placental mammals this is achieved by axons forming the corpus callosum. Development of callosal circuits involves a *Satb2*$^{+}$*/Ctip2*$^{-}$ genetic program, an axonal arrangement based on the position of cell bodies within the cortex, and co-existence of mirror-image, homotopic connections with heterotopic and hyper-connected bilateral circuits. Whether these features are mechanistically related to the development and evolution of the corpus callosum in early placentals, or instead represent traces of an older bilateral map in the common mammalian ancestors remains unknown. Here we show that the main molecular, developmental and connectivity features of bilateral cortical circuits were already present in mammals before the evolution of the corpus callosum. We found that cortical connections through the anterior commissure of monotremes and marsupials share a callosal-like topography, whereby axons connecting main cortical regions cross the midline through spatially segregated subdomains. These axons arise from *Satb2*$^{+}$*/Ctip2*$^{-}$ cortical neurons in marsupial pouch-young,

and establish a bilateral map that includes homotopic and heterotopic connections, as well as hyperconnected hubs at the medial (cingulate) and temporal (claustro-insula) margins of the neocortex. Thus, our results suggest an ancient origin and conservation of a bilateral cortical map in the mammalian brain, predating the origin of the corpus callosum by at least 40 million years. The conservation of a connectivity map despite significant alterations in the route taken by axons suggest that evolution of the corpus callosum likely involved key but subtle innovations, possibly including exaptation of pre-existing mechanisms not primarily involved in circuit formation.

Disclosures: **R. Suarez:** None. **A. Paolino:** None. **L. Morcom:** None. **P. Kozulin:** None. **L.R. Fenlon:** None. **N. Kurniawan:** None. **L.J. Richards:** None.

Poster

779. Development and Evolution

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 779.07/D31

Topic: A.10. Development and Evolution

Support: UIC Provost Award 2014

LAS Award for Faculty of Science 2015/2016

Title: The unusual structure and function of the African naked mole rat endocannabinoid system

Authors: ***B. M. BROWE**[1], E. KEIMPEMA[2], T. HARKANY[2], J. LARSON[1], T. J. PARK[1]; [1]Biol. Sciences- Neurobio., Univ. of Illinois At Chicago, Chicago, IL; [2]Med. Univ. of Vienna, Vienna, Austria

Abstract: The endocannabinoid system is a major regulator of synaptic transmission in many brain areas and cannabinoid receptors are the most highly expressed GPCRs in the mammalian brain. Pharmacological manipulation of the endocannabinoid system has shown promise in medical treatments of many diseases including epilepsy, cancer, Alzheimer's, and hypoxic injury. However, there are still many mechanisms of the endocannabinoid system that are yet unknown, in part because the widespread, subtle nature of this regulatory system makes parsing out individual aspects difficult. We examined the endocannabinoid system of the African Naked Mole-Rat (NMR), a long-living mammal (lifespans reaching >30 years) with high resistance to many of these previously stated diseases including: cancer, dementia, and hypoxia. Here, we show that the developmental regulation of endogenous cannabinoid ligands (endocannabinoids) and cannabinoid receptors is very different in NMRs compared to typical laboratory rodents (mice). In mice, cannabinoid receptor expression decreases in early postnatal development and

endocannabinoid levels increase with maturation while in NMRs the pattern of change is opposite to this. Furthermore, this change in expression is correlated with a profound age-dependent change in the behavioral response to synthetic cannabinoids (WIN55) in NMRs. Up to 9 months old, NMRs show a dose-dependent decrease in locomotion, as seen in other laboratory mammals. However, after 1 year of age, NMRs no longer respond to WIN55. The NMR's age-related differential expression of endocannabinoids and cannabinoid receptors and changes in behavioral sensitivity to exogenous ligands has potential to clarify the mechanisms by which cannabinoids affect behavior by providing alternative phenotypes to manipulate. In addition, species-specific alterations in the endocannabinoid system may participate in the resilience of NMRs to hypoxic brain damage and cancer, and help to explain their extraordinary longevity. These results encourage further exploration of the endocannabinoid system's link to neuroprotection and longevity.

Disclosures: **B.M. Browe:** None. **E. Keimpema:** None. **T. Harkany:** None. **J. Larson:** None. **T.J. Park:** None.

Poster

779. Development and Evolution

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 779.08/D32

Topic: A.10. Development and Evolution

Support: Spanish Ministry of Economy and Competitivenes Grant BFU2015-66041-P

Title: Prosomeric interpretation of the developing hypothalamus in Xenopus laevis

Authors: *A. GONZALEZ[1], R. MORONA[2], J. M. LÓPEZ[2], N. MORENO[2];
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Abstract: Most studies in mammals and birds have demonstrated common patterns of hypothalamic development highlighted by the combination of developmental regulatory genes (genoarchitecture), supporting the notion of the hypothalamus as a component of the secondary prosencephalon, topologically rostral to the diencephalon, and consisting of alar and basal parts. In our comparative analysis we have summarized the data on the expression patterns of different transcription factors and neuroactive substances, used as anatomical markers, in the developing hypothalamus of the amphibian *Xenopus laevis*. This analysis served to highlight the organization of the hypothalamus in the of anamniote/amniotic transition. We have identified paraventricular (Pa; dorsal) and the subparaventricular (SPa; ventral) regions in the alar part of the hypothalamus, and tuberal (Tu; dorsorostral) and mamillary (M; ventrocaudal) regions in the

basal hypothalamus. Main distinct features are: 1) The Pa region is defined by the expression of Otp and the lack of Nkx2.1/Isl1. It is subdivided into rostral, rich in Otp and Nkx2.2, and caudal, only Otp-positive, portions. 2) The SPa area contains catecholaminergic cell groups and lacks Otp, and can be further divided into rostral (rich in Nkx2.1 and Nkx2.2) and a caudal (rich in Isl1 and devoid of Nkx2.1) portions. 3) Expression of Nkx2.1 and Isl1 define the Tu hypothalamus and only the rostral portion expresses Otp. 4) Its caudal boundary is evident by the lack of Isl1 in the adjacent M region, which expresses Nkx2.1 and Otp. In summary, the genoarchitecture of the hypothalamus observed in *Xenopus* shows major common features with amniotes.

Disclosures: A. Gonzalez: None. **R. Morona:** None. **J.M. López:** None. **N. Moreno:** None.

Poster

779. Development and Evolution

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 779.09/D33

Topic: A.10. Development and Evolution

Support: NHMRC Discovery Project 1068140

Ruhr University Research School PLUS, funded by Germany's Excellence Initiative [DFG GSC 98/3]

Title: Claustrum connections of posterior cingulate regions in the marmoset cerebral cortex

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Abstract: The posterior cingulate cortex is characterized by widespread functional connectivity and early activation in the emergence of conscious states. Similar widespread connectivity is also a feature of the claustrum, which has been hypothesized to play a role in modulation of consciousness. Here we examine the topography of claustrum connections to the posterior cingulate region of the common marmoset (*Callithrix jacchus*) using microinjections of neuroanatomical tracers. Nine injections in four animals were performed under general anaesthesia in accordance with a protocol approved by the Monash Animal Research Ethics Committee. Cell counts, topographic organization, and 3-D reconstructions of the claustrum

were obtained following fluorescent tracer injections into A23b, A23V, PGM, and 19M. All areas received strong claustrum input, especially from the dorsal claustrum. Topographic organization was evident in the A23b connections, with more caudal injections yielding denser label in the caudal-most claustrum sections. Posterior cingulate areas obtain negligible input from the insular cortex, which may interpretation of activation patterns in imaging studies. The pattern of claustrum connections partially overlapped the portion of the claustrum that we have previously demonstrated to project to medial prefrontal areas. The location and connectional strength of claustrum projections to the posterior cingulate cortex is consistent with a role for the claustrum in modulation of resting state functional networks.

Disclosures: **D.H. Reser:** None. **B. Knauer:** None. **P. Majka:** None. **J.M.H. Chan:** None. **K.J. Watkins:** None. **K. Worthy:** None. **M.D.M. Quiroga:** None. **M.G.P. Rosa:** None.

Poster

779. Development and Evolution

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 779.10/D34

Topic: A.10. Development and Evolution

Support: KAKENHI 25293254

KAKENHI 15K08707

KAKENHI 15K12779

KAKENHI 26118517

Brain Mapping by Integrated Neurotechnologies for Disease Studies (Brain/MINDS) from AMED

Title: A grayordinate pipeline for magnetic resonance imaging of marmoset brain

Authors: ***T. HAYASHI**[1], M. GLASSER[2], C. YOKOYAMA[1], T. OSE[1], C. TAKEDA[1], A. KAWASAKI[1], J. AUTIO[1], D. VAN ESSEN[2];
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Abstract: There is increasing interest in using marmosets for animal studies in neuroscience. Several technologies such as neural tracing and genetic manipulation are recently available for this species, however, non-invasive imaging technique is not well established, nor are analyses

standardized across species. Here, we introduce a preprocessing pipeline for marmoset MRI data adapted from that for the Human Connectome Project (HCP). In six anesthetized marmosets, we obtained T1 weighted and T2 weighted MRI images (spatial resolution of 0.35 x 0.35 x 0.35 mm^3) of the brain using a 3T MRI scanner (MAGNETOME PRISMA, Siemens Healthcare, Erlangen, Germany) and a custom-made 16-channel array coil (Takashima Seisakusho KK, Hino, Japan). The images were corrected for bias field, brain extracted, non-linearly registered to a standard atlas space, segmented into gray (cortical and subcortical) and white matter areas based on supervised classification, and then estimated for cortical surface boundaries. Cortical surface was co-registered across subjects based on the folding pattern. Estimated surface was minimally inflated to allow the visualization of sulcal area of cortical folding. The data was embedded in the standardized grayordinates of 164k or 32k, where metric data can be evaluated either at vertices of cortical surface or at voxels of subcortical structures (basal ganglia, thalamus, brainstem and cerebellum). Of note, some of the animals showed variant cortical folding pattern in the lateral fissure (corresponding to the Sylvian fissure in human) despite scarce gyral formation in this species. The cortical surface myelin contrast, as assessed by T1w/T2w, was high in the visual, sensorimotor, auditory, and MT areas, similar to that in human, chimpanzee and macaque using the HCP pipeline (Glasser et al. 2013). The current findings support the idea that cross-species homology exits at least in the cortical myelin distribution of marmoset brain. Future work should extend this technique to analyze other modalities such as resting-state functional and diffusion MRI, potentially useful for investigating marmoset connectome and its association with genetic, molecular, or histological aspects.

Disclosures: **T. Hayashi:** None. **M. Glasser:** None. **C. Yokoyama:** None. **T. Ose:** None. **C. Takeda:** None. **A. Kawasaki:** None. **J. Autio:** None. **D. Van Essen:** None.

Poster

779. Development and Evolution

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 779.11/E1

Topic: A.10. Development and Evolution

Support: KAKENHI 25293254

KAKENHI 26118517

KAKENHI 15K12779

KAKENHI 15K08707

Brain/MINDS from AMED

Title: *In vivo* cortical dopamine D2 receptor binding in human, macaques and marmosets

Authors: *C. YOKOYAMA, J. AUTIO, T. OSE, A. KAWASAKI, C. TAKEDA, K. TAKAHASHI, A. IGESAKA, H. DOI, T. HAYASHI;
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Abstract: Cortical dopamine function is of particular interest for investigating higher cognitive processing in humans and non-human primates. Dopamine D2 receptor has been widely measured in vivo by positron emission tomography (PET) with ^{11}C-raclopride, however, assessment of the cortical binding has been limited by insufficient accuracy largely caused by partial volume (PV) effect and low spatial resolution of the detector. Here, we visualize PV-corrected, cortical binding potential (BP) of ^{11}C-raclopride in three primate species, enabled by high-resolution magnetic resonance (MR) images. A PET scan with ^{11}C-raclopride as well as T1- and T2-weighted MR images were obtained in humans (n=4), rhesus macaques (n=4) and common marmosets (n=6). Animals were scanned under generalized isoflurane anesthesia, and humans under consciousness. We used a PET scanner for human (Biograph-16, Siemens, Germany) and that for animals (microPET220, Siemens, Germany), and a 3T MR scanner for all species (MAGNETOM Prisma, Siemens, Germany). MR and PET images were processed using the Human Connectome Project (HCP) pipeline, and PV-correction of radioactivity was performed with a region-based voxel-wise method (Thomas et al., 2011) using Freesurfer. The BP of ^{11}C-raclopride was calculated with a simplified reference tissue model (Gunn et al., 1997), and mapped onto the inflated cortical surface. Cross-species cortical mapping of ^{11}C-raclopride BP revealed a similar pattern of distribution, i.e., high in the insular, middle temporal and anterior cingulate cortices and low in the visual cortex. The distribution was consistent with previous postmortem studies in humans and macaques. Humans tend to have highly variable binding around the perisylvian areas as compared with monkeys, potentially associated with evolution of language abilities. Our findings suggest that cortical ^{11}C-raclopride binding can be assessed quantitatively and used for investigation of cognitive function in primates despite limited availability of cortical D2 receptors.

Disclosures: C. Yokoyama: None. **J. Autio:** None. **T. Ose:** None. **A. Kawasaki:** None. **C. Takeda:** None. **K. Takahashi:** None. **A. Igesaka:** None. **H. Doi:** None. **T. Hayashi:** None.

Poster

779. Development and Evolution

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 779.12/E2

Topic: A.10. Development and Evolution

Support: 2R15NS060099-02A1

8TL4GM118977-02

Title: Neural Crest Derived Chromatophores in Red-Eyed Tree Frogs

Authors: *P. SANGUANVICHAIKUL[1], M. E. DE BELLARD[2], M. LUEVANOS[2], M. REYES[2];
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Abstract: The Red-eye Tree Frog has striking skin colors that allow it to select mates. Skin coloration comes from neural crest stem cells that give rise to melanocytes and chromatophores. Although chromatophores had been studied in other organisms like chameleons and fish, their location and phenotype has not been studied in these green tree frogs. The purpose of this study is to develop skin histology methods and identify neural crest derived cells in the Red-eye Tree Frog. For this, we used immunofluorescence and standard hematoxylin to label different skin cells. Thus, we were able to identify poison and mucous glans as well as chromatophores in the skin of adult frogs. We are beginning to collect similar samples from pre-metamorphosized tadpoles. We plan to continue mapping the histology during the different stages of development. By doing so, we can follow the development of melanocytes and chromatophores to determine which of these cells are derived from neural crest cells like those of other organisms. Funding was by NIH/NINDS AREA grant 1R15-NS060099-02 to MEdB and a BUILD/PODER scholarship to PS.

Disclosures: P. Sanguanvichaikul: None. **M.E. de Bellard:** None. **M. Luevanos:** None. **M. reyes:** None.

Poster

779. Development and Evolution

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 779.13/E3

Topic: A.10. Development and Evolution

Support: The John Templeton Foundation Award 40463

NIH Office of Research Infrastructure Programs/OD P51OD11132

Title: Oxytocin (OT) and arginine-vasopressin (AVP) cell bodies and fibers in the social behavior neural network in rhesus macaque, chimpanzee, and human brains

Authors: *C. ROGERS[1,4,6], A. P. ROSS[7,6], J. DOOYEMA[5,6], M. A. CREE[5,6], S. P. SAHU[4,6], E. SIEGEL[4,6], E. G. STOPA[8,6], J. K. RILLING[1,2,3,6,4], H. E. ALBERS[7,6], T. M. PREUSS[5,9,6,3]; [1]Anthrop., [2]Psychiatry and Behavioral Sci., [3]Ctr. for Translational Social Neurosci., Emory Univ., Atlanta, GA; [5]Div. of Neuropharm. and Neurodegenerative Dis., [4]Yerkes Natl. Primate Res. Ctr., Atlanta, GA; [6]Ctr. for Behavioral Neurosci., [7]Neurosci. Inst., Georgia State Univ., Atlanta, GA; [8]Pathology (Neuropathology) and Neurosurg., The Warren Alpert Med. School, Brown Univ., Providence, RI; [9]Pathology and Lab. Med., Emory Univ. Sch. of Med., Atlanta, GA

Abstract: The neuropeptides OT and AVP are strongly implicated in the regulation of social behavior in mammalian species. While oxytocin- and vasopressin-producing cells are consistently located in the hypothalamus across species, less is known about variation in the distribution of extra-hypothalamic cell bodies and processes. Moreover, the anatomical distribution of these neuropeptides in great apes, such as chimpanzees, the animals most closely related to humans, has not been studied to date. We used immunohistochemistry to identify cell bodies and fibers containing OT and AVP within the social behavioral neural network in fixed, postmortem tissue from humans (n= 3), chimpanzees (n=3), and rhesus macaques (n=3). All three species showed labeling for OT and AVP cell bodies in the hypothalamus. Rhesus macaques showed a wider distribution of labeling for AVP than chimpanzees or humans, with cell bodies distributed throughout the caudate and putamen as well as fibers in the lateral septum and periaqueductal gray of the midbrain. Across the three species, labeling for OT cell bodies was more restricted, being mainly localized to the hypothalamus. Our results suggest that primates differ from many rodent species (e.g., mice, rats, and voles), which have prominent AVP-containing cell bodies in the medial amygdala and bed nucleus of the stria terminalis that send dense fiber projections to several forebrain areas. Our results also suggest that the distribution of AVP cell bodies and fibers may have been reduced over the course of evolution in great apes and humans.

Disclosures: C. Rogers: None. **A.P. Ross:** None. **J. Dooyema:** None. **M.A. Cree:** None. **S.P. Sahu:** None. **E. Siegel:** None. **E.G. Stopa:** None. **J.K. Rilling:** None. **H.E. Albers:** None. **T.M. Preuss:** None.

Poster

779. Development and Evolution

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 779.14/E4

Topic: A.10. Development and Evolution

Support: NSF Grant BCS-0549117

NSF Grant BCS-0824531

NSF Grant BCS-0827546

NSF Grant DGE-0801634

NIH Grant NS042867

NIH Grant RR000165

NIH Grant HHSN268201100065C

Title: Intracellular distributions of Lactate Dehydrogenase isoenzymes in primate forebrain

Authors: *T. I. DUKA[1], S. ANDERSON[1], Z. COLLINS[1], M. RAGHANTI[2], J. J. ELY[3,4], P. R. HOF[5], D. E. WILDMAN[6], L. I. GROSSMAN[7], C. C. SHERWOOD[1];
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Abstract: The compartmentalization and association of lactate dehydrogenase (LDH) with specific cellular structures (e.g., synaptosomal, sarcoplasmic, or mitochondrial) may play an important role in brain energy metabolism. Our previous research revealed that LDH in the synaptosomal fraction shifted towards the aerobic isoforms, LDH-B, among the large-brained haplorhine primates compared to strepsirrhines. Here, we further analyzed the subcellular localization of LDH in primate forebrain structures using quantitative Western blotting and ELISA. We show that in cytosolic and mitochondrial subfractions from haplorhines**,** LDH-B expression level was elevated and LDH-A declined compared to strepsirrhines. LDH-B expression in mitochondrial fractions of the neocortex was preferentially increased, showing a particularly significant rise in the ratio of LDH-B to LDH-A in apes. We also found a significant correlation between the protein levels of LDH-B in mitochondrial fractions from haplorhine neocortex and the synaptosomal-associated LDH-B that suggests LDH isoforms shift from a predominance of A-subunits toward B-subunits as part of a system that spatially buffers dynamic energy requirements of brain cells. Our results indicate that there is differential subcellular compartmentalization of LDH isoenzymes that evolved among different primate lineages to meet the energy requirements in neocortical and striatal cells.

Disclosures: T.I. Duka: None. **S. Anderson:** None. **Z. Collins:** None. **M. Raghanti:** None. **J.J. Ely:** None. **P.R. Hof:** None. **D.E. Wildman:** None. **L.I. Grossman:** None. **C.C. Sherwood:** None.

Poster

779. Development and Evolution

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 779.15/E5

Topic: A.10. Development and Evolution

Title: Cerebrovascular beta-dystroglycan in vertebrates: its immunonegativity in anurans and advanced teleostei

Authors: D. LORINCZ[1], V. JANCSIK[2], E. OSZWALD[1], O. SEBőK[1], *M. KALMAN[3]; [1]Semmelweis University, Dept. of Anatomy, Histology and Embryology, Budapest, Hungary; [2]Szent István University, Fac. of Vet. Sci., Budapest, Hungary; [3]Semmelweis Univ., Budapest, Hungary

Abstract: Dystroglycan has pivotal function in the gliovascular connections. Its transmembrane beta subunit forms a complex of receptors and ion channels and connects them to the cytoskeleton. It's alpha subunit anchors this complex to the basal lamina. In the mammalian and avian brains the beta-dystroglycan immunopositivity (bDG+) delineates the vessels, although dystroglycan is localized in the vascular astroglial end-feet. Our former investigations proved the cerebrovascular bDG+ in Chondrichthyes (Kálmán and Ari, 2010, 6th European Congress of Comparative Neuroanatomy, Valencia, Spain). Further studies failed to detect bDG+ along the cerebral vessels in teleost fishes (less advanced ones: e.g. catfish, *Ameiurus nebulosus*, goldfish, *Carassius auratus*; and most advanced ones: e.g. cichlid perch *Amatitlania nigrofasciata*) as well as in frogs, e.g *Pelophylax ridibundusxlessonae* (formerly *R. esculenta*) (Sebők and Kálmán, 2010, 7th Europ. Congr. of Comp. Neuroanatomy, Budapest). Our recent investigations has extended on urodeles: *Ambystoma mexicanum, Pleruodeles waltly* and reptiles (turtle, *Trachemys scripta,* lizards, e.g. *Eublepharis macularis* and snakes*,* e.g. *Python regius).* some ancient-type fishes were also examined: a lungfish (*Protopterus annectens,* Dipnoi), an early representative of the tetrapoda clad; bicirrh (*Polypterus senegalensis,* Cladistia)*,* one of the closest extant relatives of the stock-actinopterygians; sterlet (*Acipenser ruthenus*, Chondrostei) and butterfly fish (*Pantodon buchholzi* Osteoglossiformes), one of the most ancient types of Teleostei. Animals were obtained from breeders, anaesthetized, then transcardially perfused with buffered 4% paraformaldehyde. Serial transversal sections were cut by vibratome from agarose embedded brains, and immunohistochemical reactions were performed with anti-bDG (monoclonal, Novocastra), according to both immunoperoxidase and immunofluorescent protocols. As positive and negative controls rat and primer-serum free medium were applied. Results obtained until now refers to that in each species bDG+ delineates the vessels. Pre-embedding immunoelectronmicroscopy on *Heterodontus japonicus* shark brains demonstrated that bDG is localized in the perivascular glial end-feet in Elasmobranchii despite the divergent construction of their blood-brain barrier. It refers to that bDG- is an apomorphic, secondary phenomenon

emerged separately in anurans and in teleosts. Western blot probes however, demonstrated the bDG even in the brains of frogs and teleosts. It may be due to the non-perivascular dystroglycan dissipated throughout the brain.

Disclosures: D. Lorincz: None. **V. Jancsik:** None. **E. Oszwald:** None. **O. Sebők:** None. **M. Kalman:** None.

Poster

779. Development and Evolution

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 779.16/E6

Topic: A.10. Development and Evolution

Support: NIH Grant NS042867

NIH Grant NS073134

James S. McDonnell Foundation Grant 220020293

Title: Analysis of expression patterns of neurotrophin genes in humans and chimpanzees.

Authors: *A. VERENDEEV[1,2], W. D. HOPKINS[3,4], C. C. SHERWOOD[1,2];
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Abstract: Evolution of the human brain shows pronounced changes in gene expression patterns, which may underlie some of the differences in behavior and cognition with our closest living relatives, the chimpanzees. To further characterize the interspecific differences in gene expression, we examined expression patterns of neurotrophin genes in human and chimpanzee brains. Neurotrophins are growth factors that promote survival, differentiation, and myelination of neurons during development. Using qPCR, we assessed differences in expression of *NGF* (nerve growth factor) and *BDNF* (brain-derived neurotrophic factor) in frontal, temporal, and cerebellar cortices of humans and chimpanzees. *NGF* expression was elevated in temporal lobe compared to frontal lobe in humans, but showed decreased expression in temporal lobe relative to frontal lobe in chimpanzees. *BDNF* expression showed similar patterns in all cortices in both species.

Disclosures: A. Verendeev: None. **W.D. Hopkins:** None. **C.C. Sherwood:** None.

Poster

779. Development and Evolution

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 779.17/E7

Topic: A.10. Development and Evolution

Support: JSPS KAKENHI Grant Number 26115508

JSPS KAKENHI Grant Number 26290003

JSPS KAKENHI Grant Number 23300115

Grant-in-Aid for JSPS

Title: Analysis of construction mechanism of medaka telencephalon by post-hatch neurogenesis.

Authors: *Y. ISOE[1], T. OKUYAMA[1], Y. SUEHIRO[1], K. NARUSE[2], M. KINOSHITA[3], Y. KAMEI[2], S. NONAKA[2], A. SHIMIZU[4], T. KUBO[1], H. TAKEUCHI[5];
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Abstract: In vertebrates, the basic brain neural networks are defined during embryonic development. The brain growth spurt occurs postnatally, accompanied by the rapid increases in cell number and brain volume. It remains unknown, however, how postnatal (post-hatch) neurogenesis contributes to the organization of neural network required for social behaviors. To address this subject, I focused on medaka fish (*Oryzias latipes*), which is a model animal for molecular genetics and show prominent post-hatch brain growth and behavioral development. First, I examined transgenic medaka fish in which post-hatch neurogenesis can be genetically modified and used the transgenic line (*HuC*:loxP-*DsRed*-loxP-*GFP*) that *HuC* promoter drives specifically in newborn neural progenitors in the adult brain. Further when stochastic recombination was induced by micro-injection of Cre mRNA into the Tg embryos at the 1 cell stage, it resulted that visualization of clonally-related cells in compartmented regions in the telencephalon in the adult medaka brain. Also, heat induction of transgenic embryo (*HSP*:*Cre*) led to Cre-recombination in the nervous system. Interestingly, by using this both lines (*HSP:Cre* and *HuC*:loxP-*DsRed*-loxP-*GFP*), heat induction can induce different Cre-recombination pattern depending on the developmental stages when heat induction was performed. As a result of systematic analysis of stochastic recombinated samples, I identified that the telencephalon of adult brain was constituted by almost 40 clonal units and that the traditional anatomical regions were constituted by a few clonal units. In addition, the morphological pattern of clonal units was different between dorsal and ventral anatomical regions. In order to investigate the molecular

mechanism of the structural difference, I performed ATAC-seq and RNA-seq and examined the gene expression regulation specific to dorsal or ventral telencephalon.

Disclosures: **Y. Isoe:** None. **T. Okuyama:** None. **Y. Suehiro:** None. **K. Naruse:** None. **M. Kinoshita:** None. **Y. Kamei:** None. **S. Nonaka:** None. **A. Shimizu:** None. **T. Kubo:** None. **H. Takeuchi:** None.

Poster

779. Development and Evolution

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 779.18/E8

Topic: A.10. Development and Evolution

Support: MH101188

Title: A new model of brain development: BATS

Authors: V. MARTINEZ-CERDENO[1], J. CAMACHO[1], R. BEHRINGER[3], J. ARIZA[1], H. ROGERS[1], R. IKEDA[1], *S. C. NOCTOR[2];
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Abstract: While the laminar (radial) organization of the cortex is similar across mammalian species, increased cell production during development and an enormous tangential expansion of cortical surface area accompanied the transformation of smooth cerebral cortex to the highly folded primate cortex. Based on our previous studies of cortical development in non-mammalian species (reptiles, birds), mammalian species with lissencephalic cortex (rodents), and mammalian species with gyrencephalic cortex (ferret, macaque, human), we hypothesized that a two-step pattern of neurogenesis played an important role in the expansion of the cerebral cortex. However, we still lack an appropriate comparative animal model of species that are closely related - evolved within the same family. For this reason many questions on cortical development and evolution remain unanswered, and our hypotheses lack sufficient predictive power. To address this problem we are introducing a new animal model for studies of brain evolution. We are using, for the first time, the developing bat brain as a tool to understand the evolution of developmental programs that guide formation of the cerebral cortex in mammals. Our novel data regarding the developing cerebral cortex of bats allowed us to identify mechanisms that contribute to gyri formation and drive tangential expansion of the cerebral cortex.

Disclosures: **V. Martinez-Cerdeno:** None. **J. Camacho:** None. **R. Behringer:** None. **J. Ariza:** None. **H. Rogers:** None. **R. Ikeda:** None. **S.C. Noctor:** None.

Poster

779. Development and Evolution

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 779.19/E9

Topic: A.10. Development and Evolution

Support: James S. McDonnell Foundation Grant 22002078

James S. McDonnell Foundation Grant 220020293

South African National Research Foundation

Title: Neocortical neuronal morphology in the Siberian tiger (Panthera tigris altaica) and the clouded leopard (Neofelis nebulosa)

Authors: C. B. JOHNSON[1], M. SCHALL[1], M. E. TENNISON[1], M. E. GARCIA[1], N. B. SHEA-SHUMSKY[1], M. RAGHANTI[2], A. H. LEWANDOWSKI[3], M. F. BERTELSEN[4], L. WALLER[1], T. WALSH[5], J. F. ROBERTS[6], P. R. HOF[7], C. C. SHERWOOD[8], P. R. MANGER[9], *B. G. JACOBS[1];
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Abstract: Despite extensive investigations of the neocortex in the domestic cat, little is known about neuronal morphology in larger felids. To this end, the present study characterized and quantified the somatodendritic morphology of neocortical neurons in prefrontal, motor, and visual cortices of the Siberian tiger (*Panthera tigris altaica*) and clouded leopard (*Neofelis nebulosa*). After neurons were stained with a modified Golgi technique ($N = 194$), dendritic branching and spine distributions were analyzed using computer-assisted morphometry. Qualitatively, aspiny and spiny neurons in both species appeared morphologically similar to those observed in the domestic cat. Although the morphology of spiny neurons was diverse, with the presence of extraverted, inverted, horizontal, and multi-apical pyramidal neurons, the most common variant was the typical pyramidal neuron. Gigantopyramidal neurons in the motor

cortex were extremely large, confirming Brodmann's (1909) observation of large somata for these neurons in carnivores in general, and felids in particular. Quantitatively, a MARSplines analysis of dendritic measures differentiated typical pyramidal neurons between the Siberian tiger and the clouded leopard with 93% accuracy. In general, the dendrites of typical pyramidal neurons were more complex in the tiger than in the leopards. Moreover, dendritic measures in tiger pyramidal neurons were disproportionally large relative to body/brain size insofar as they were nearly as extensive as those observed in much larger mammals (e.g., African elephant). Comparison of neuronal morphology in a more diverse collection of larger felids may elucidate the comparative context for the relatively large size of the pyramidal neurons observed in the present study.

Disclosures: C.B. Johnson: None. **M. Schall:** None. **M.E. Tennison:** None. **M.E. Garcia:** None. **N.B. Shea-Shumsky:** None. **M. Raghanti:** None. **A.H. Lewandowski:** None. **M.F. Bertelsen:** None. **L. Waller:** None. **T. Walsh:** None. **J.F. Roberts:** None. **P.R. Hof:** None. **C.C. Sherwood:** None. **P.R. Manger:** None. **B.G. Jacobs:** None.

Poster

779. Development and Evolution

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 779.20/E10

Topic: A.10. Development and Evolution

Support: SFB 936/A1,Z3; TRR169/A2 to CCH

Alexander von Humboldt scholarship to AG

Title: The connectional architecture of the mouse, cat, rat and macaque cortex in the light of the theory of the dual origin of the cortex.

Authors: *A. GOULAS[1], G. BEZGIN[2], C. C. HILGETAG[1,3];
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Abstract: Understanding the organization of the cortex requires uncovering the fundamental principles pertaining to its different levels of architecture including the macroscale connectional architecture. One such principle postulates that the cortex of reptiles and mammals has a dual origin with cortical areas originating from two different primordial formations: the piriform cortex (paleocortex) and the hippocampus (archicortex). The dual origin of cortical areas has

been inferred from the observation that cortical areas constitute streams of stepwise myelo- and/or cytoarchitectonic changes from these primordial formations. Such studies on brains of monotremata, marsupials, reptiles, human and non-human primates can be traced back at least to the first decades of the last century (Shellshear, 1929; Dart, 1934; Abbie, 1940; Abbie, 1942; Sanides, 1962). Importantly, the duality of the cortex is also reflected in the organization of the cortico-cortical connections of the macaque monkey (Pandya and Yeterian, 1985). The dual connectional architecture of the cortex was conceptualized and quantified as the presence of topologically symmetric structures (Bezgin et al, 2014). Here, we applied this definition and approach to all available mammalian connectomes: the macaque monkey (Markov et al, 2014), cat (Scannel et al, 1995), mouse (Oh et al, 2014; Zingg et al, 2014) and rat (Bota and Swanson, 2007). First, we investigated the presence of a dual connectional architecture in the aforementioned species. Second, we exploited the detailed transcriptional data for the mouse cortex (Lein et al, 2007) and investigated if the dual architecture defined on a connectional basis is also reflected on its transcriptional architecture. Our results demonstrate the presence of the dual connectional structure in all examined mammalian species, setting apart areas presumably derived from the piriform cortex (insula, gustatory cortex) and the hippocampus (retrosplenial, cingulate cortex). We also show that the connectivity-based dual structure in the mouse constitutes a major axis of organization of its transcriptome reflecting 12% of its variance. We conclude that the dual structure of the adult cortex constitutes a fundamental principle of its organization, possibly reflecting histogenetic gradients and patterning centers during telencephalic development.

Disclosures: **A. Goulas:** None. **G. Bezgin:** None. **C.C. Hilgetag:** None.

Poster

779. Development and Evolution

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 779.21/E11

Topic: A.10. Development and Evolution

Support: FAPERJ Grant E-26/111.541/2010

FAPERJ Grant E-26/110.372/2012

FAPERJ Grant E-26/111.517/2013

CNPq Grant 477130/2010-0

CNPq Grant 477959/2012-1

Title: Functional test of PCDHB11, the most human-specific neuronal surface protein

Authors: *G. B. DE FREITAS, R. A. GONCALVES, M. D. GRALLE;
Federal Univ. of Rio De Janeiro, Rio DE Janeiro, Brazil

Abstract: Background
Brain-expressed proteins that have undergone functional change during human evolution may contribute to human cognitive capacities, and may also leave us vulnerable to specifically human diseases, such as schizophrenia, autism or Alzheimer's disease. In order to search systematically for those proteins that have changed the most during human evolution and that might contribute to brain function and pathology, all proteins with orthologs in chimpanzee, orangutan and rhesus macaque and annotated as being expressed on the surface of cells in the human central nervous system were ordered by the number of human-specific amino acid differences that are fixed in modern populations.
Results
PCDHB11, a beta-protocadherin homologous to murine cell adhesion proteins, stood out with 12 substitutions and maintained its lead after normalizing for protein size and applying weights for amino acid exchange probabilities. Human PCDHB11 was found to cause homophilic cell adhesion, but at lower levels than shown for other clustered protocadherins. Homophilic adhesion caused by a PCDHB11 with reversion of human-specific changes was as low as for modern human PCDHB11; while neither human nor reverted PCDHB11 adhered to controls, they did adhere to each other. A loss of function in PCDHB11 is unlikely because intra-human variability did not increase relative to the other human beta-protocadherins.
Conclusions
The brain-expressed protein with the highest number of human-specific substitutions is PCDHB11. In spite of its fast evolution and low intra-human variability, cell-based tests on the only proposed function for PCDHB11 did not indicate a functional change.

Disclosures: G.B. De Freitas: None. **R.A. Goncalves:** None. **M.D. Gralle:** None.

Poster

779. Development and Evolution

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 779.22/DP01 (Dynamic Poster)

Topic: A.10. Development and Evolution

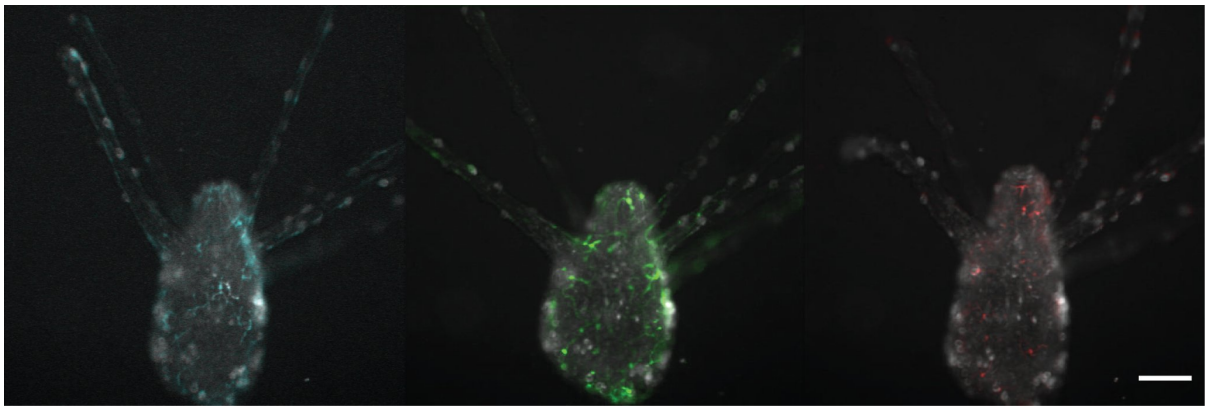
Support: NIH Grant DP1EY024503

Army Grant ARO W911NF-12-1-0594 (MURI)

Title: Calcium imaging in Hydra

Authors: ***C. DUPRE**, S. SALWI, S. LEONG, R. YUSTE;
Columbia Univ., New York, NY

Abstract: To tackle the function of neural circuits it would be ideal to record the activity of every neuron in a behaving animal and understand how it relates to behavior. We have achieved this with the cnidarian Hydra vulgaris. Yet using genetically engineered animals and calcium imaging to measure the activity of essentially all of its neurons in behaving animals. While the nervous system of Hydra is traditionally described as a simple nerve net, we surprisingly find instead a series of independent neural networks that are anatomically non-overlapping and are associated with specific behaviors. Three major functional networks extend through the entire animal and are activated selectively during contractions, elongations in response to light and egestion. These results demonstrate the functional sophistication of apparently simple nerve nets, and the potential of Hydra and other basal metazoans as a model system for neural circuit studies.



Disclosures: **C. Dupre:** None. **S. Salwi:** None. **S. Leong:** None. **R. Yuste:** None.

Poster

779. Development and Evolution

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 779.23/E12

Topic: A.10. Development and Evolution

Title: Evidence for generative homology of cerebellum and cerebellum-like structures in a basal vertebrate

Authors: *C. SURIANO, D. BODZNICK;
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Abstract: Most of the neurons located in the mammalian brain reside within the cerebellum. Yet, the evolutionary origins of the cerebellum are not well understood. There are several different sensory nuclei present across vertebrates collectively termed cerebellum-like structures due to a shared anatomy and physiology with the cerebellum. Common structure and function may arise due to a shared genetic toolkit used during development to create a common geno-architecture. We have studied three critical genes from the proposed toolkit; *Pax6*, *Clbn1*, and *Grid2* to link these areas in a generatively homologous relationship. Within the mammalian cerebellum *Pax6* is critical for polarizing granule cell axons to form the molecular layer. *Clbn1* is used to form granule cell-principal cell synapses. *Grid2* is used to form synapses via the extra-cellular N-terminus and used in AMPAR endocytosis creating cerebellar LTD via the intra-cellular C-terminus. In order to determine if cerebellum and cerebellum-like structures are generatively homologous we tested whether these three critical proteins are expressed in the cerebellum and cerebellum-like structures of a basal vertebrate, *Leucoraja erinacea*. We found that granule cells of the cerebellum and granule cells of the dorsal granular ridge that supply the cerebellum-like structures both express *Pax6* and *Clbn1*. If *Pax6* and *Clbn1* perform the same function in the skate cerebellum and cerebellum-like structures as they do in the mammalian cerebellum, then these structures may develop using a shared genetic toolkit. We also found dendrites in the cerebellar molecular layer as well as dendrites in the molecular layer of cerebellum-like structures expressing *Grid2*. In addition to measuring protein expression in the skate cerebellum and cerebellum-like structures, protein sequence data from several vertebrates was used to compare the evolution of these genes to their prescribed function during the genesis of the cerebellum from the rhombic lip early in vertebrate phylogeny. While *Pax6* and *Clbn1* are well conserved throughout the species tested, *Grid2* has undergone major changes correlated with two whole rounds of genome duplication and the advent of the cerebellum in the gnathostomes. Within the gnathostomes there appears to be a stable elongation of the *Grid2* N terminus and C terminus allowing for more extra-cellular and intra-cellular protein-protein interactions thus allowing increased synaptic complexity in these regions. Before the genesis of the cerebellum, in the lamprey lineage, *Grid2* appears truncated, missing several key protein domains.

Disclosures: C. Suriano: None. **D. Bodznick:** None.

Poster

779. Development and Evolution

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 779.24/E13

Topic: A.10. Development and Evolution

Support: NSF grant SBE-131719

NIH grant 1R01MH103517-01A1

Strategic Priority Research Program of the Chinese Academy of Sciences XDB13010000

National Natural Science Foundation of China 31130051

West-light Doctoral Program and Youth Innovation Promotion Association of the Chinese Academy of Sciences

post-doctoral grant from the Basque Government

Title: Comparative methylome analyses of human, chimpanzee, macaque brains

Authors: *S. YI[1], I. MENDIZABAL[1], L. SHI[2], T. KELLER[1], G. KONOPKA[3], T. PREUSS[4], T.-F. HSIEH[5], E. HU[2], Z. ZHANG[2], B. SU[2];
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Abstract: The regulatory significance of epigenetic modifications is increasingly appreciated. However, the ways in which epigenetic modifications change and impact phenotypes in evolution remain as a fundamental yet unresolved question in biology. In particular, previous studies suggested that epigenetic evolution of human brains has deeply impacted human cognition and neuropsychiatric diseases. However, to fully understand the role of epigenetic divergence on human brain evolution, it is critical to examine epigenetic variation in a large panel of individuals, and to employ unbiased epigenome-wide methods and include outgroup species. Here we report comprehensive identification and analyses of differentially methylated regions (DMRs) in human brains. We used comparative whole genome bisulfite sequencing (WGBS) of human, chimpanzee and rhesus macaque prefrontal cortices (n=8), unbiased non-parametric tests, as well as targeted deep genomic and bisulfite sequencing in an independent panel of 37 individuals across six primate species. Our comparative approach identified hundreds of DMRs. We demonstrate, using a subset of DMRs, that the unique epigenetic profiles of the human brain are indeed supported in a large number of samples across multiple species. Intriguingly, evolutionary epigenetic modifications preferentially occur at genomic regions related to transcriptional regulation, as evidenced by chromatin features and transcription factor binding profiles. In particular, we identify many loci annotated as intergenic yet exhibiting conspicuous chromatin signatures of active transcription in brains, indicating that they represent currently unannotated loci of human brain-specific transcription. Remarkably, a large number of DMRs are found in a spatially clustered manner and tend to participate in active chromatin loops, indicating evolutionary remodeling at the higher-order chromatin structure. Analyses of previously generated gene expression and epigenetic data also support a role of DMRs in

regulation of transcription. Substantial reprogramming of the epigenomic landscape at regulatory regions appears to contribute to the evolutionary specializations in our brains.

Disclosures: **S. Yi:** None. **I. Mendizabal:** None. **L. Shi:** None. **T. Keller:** None. **G. Konopka:** None. **T. Preuss:** None. **T. Hsieh:** None. **E. Hu:** None. **Z. Zhang:** None. **B. Su:** None.

Poster

780. Neurotransmitters and Signaling Molecules

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 780.01/E14

Topic: B.01. Neurotransmitters and Signaling Molecules

Support: NIH Grants DA035217

NIH Grants MH101146

Title: Neuronal and astrocytic monoacylglycerol lipase limit the spread of endocannabinoid signaling in the cerebellum

Authors: ***Y. CHEN**[1,2], X. LIU[1], C. R. VICKSTROM[1], M. J. LIU[1], L. ZHAO[2], A. VIADER[3], B. F. CRAVATT[3], Q.-S. LIU[1];
[1]Med. Col. of Wisconsin, Milwaukee, WI; [2]Beijing Sport Univ., Beijing, China; [3]The Scripps Res. Inst., La Jolla, CA

Abstract: Endocannabinoids are diffusible lipophilic molecules that may spread to neighboring synapses. Monoacylglycerol lipase (MAGL) is the principal enzyme that degrades the endocannabinoid 2-arachidonoylglycerol (2-AG). Using knockout mice in which MAGL is deleted globally or selectively in neurons and astrocytes, we investigated the extent to which neuronal and astrocytic MAGL limit the spread of 2-AG-mediated retrograde synaptic depression in cerebellar slices. A brief tetanic stimulation of parallel fibers in the molecular layer induced synaptically evoked suppression of excitation (SSE) in Purkinje cells, and both neuronal and astrocytic MAGL contribute to the termination of this form of endocannabinoid-mediated synaptic depression. The spread of SSE among Purkinje cells occurred only after global knockout of MAGL or pharmacological blockade of either MAGL or glutamate uptake, but no spread was detected following neuron- or astrocyte-specific deletion of MAGL. The spread of endocannabinoid signaling was also influenced by the spatial pattern of synaptic stimulation as it did not occur at spatially dispersed parallel fiber synapses induced by stimulating the granular layer. The tetanic stimulation of parallel fibers did not induce endocannabinoid-mediated synaptic suppression in Golgi cells even after disruption of MAGL and glutamate uptake,

suggesting that heightened release of 2-AG by Purkinje cells does not spread the retrograde signal to parallel fibers that innervate Golgi cells. These results suggest that both neuronal and astrocytic MAGL limit the spatial diffusion of 2-AG and confer synapse-specificity of endocannabinoid signaling.

Disclosures: Y. Chen: None. **X. Liu:** None. **C.R. Vickstrom:** None. **M.J. Liu:** None. **L. Zhao:** None. **A. Viader:** None. **B.F. Cravatt:** None. **Q. Liu:** None.

Poster

780. Neurotransmitters and Signaling Molecules

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 780.02/E15

Topic: B.01. Neurotransmitters and Signaling Molecules

Support: German Research Foundation (DFG: CRC1080, TPA7)

Chinese scholarship council (Grand NO.201406140131)

NEUROWIND e.V.

Title: NO/cGMP signaling via Guanylyl Cyclase isoform 1 (NO-GC1) modulates presynaptic transmitter release in somatosensory cortex of mice.

Authors: Q. WANG[1], *S. C. THAL[1], E. MERGIA[2], D. KOESLING[2], T. MITTMANN[1]; [1]Johannes Gutenberg-University, Mainz, Germany; [2]Inst. für Pharmakologie und Toxikologie, Medizinische Fakultät MA N1, Ruhr-Universität Bochum, Bochum, Germany

Abstract: Synapse function is critical for sensory perception, cognition and memory in mammalian brains and these functions can be modulated by several factors. In this context, it is well known that NO can generate cGMP via two isoforms of the NO-sensitive guanylyl cyclases (NO-GCs) (NO-GC1 and NO-GC2) to regulate downstream proteins, thereby altering synaptic transmission and long-term synaptic plasticity. For example, NO is well known to act as a retrograde messenger in hippocampus. However, the role of NO-GC1 for pre- and postsynaptic functions in other brain regions like the somatosensory cortex is not fully understood. By using knockout (KO) mice lacking the NO-GC1 isoform, the present study analyzed glutamatergic and GABAergic synaptic transmission between pyramidal neurons in layers II/III of somatosensory cortex. We observed a reduced frequency of miniature excitatory and inhibitory postsynaptic currents (mEPSCs and mIPSCs) together with an increased paired-pulse ratio (PPR) and a decreased input-output curve of electrically evoked EPSCs and IPSCs, which strongly suggest a functional impairment of presynaptic release of glutamate and GABA in NO-GC 1 KO mice.

The altered neurotransmission in KO mice was rescued to WT-like levels by bath application of the cGMP analog 8-Br-cGMP. Accordingly, an inhibitor of NO-GCs, ODQ, reduced the glutamate and GABA release in wild-type mice to the level of KO-mice. Moreover, we have evidence that NO is mainly produced postsynaptically in response to NMDA receptor activation and acts as a retrograde messenger to modulate GABA release. In conclusion, NO-GC1-cGMP signaling modulates glutamatergic and GABAergic synaptic neurotransmission, which could alter information processing in the somatosensory cortex.

Disclosures: **Q. Wang:** C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); scholarship council (Grand NO.201406140131 to Qi Wang), NEUROWIND e.V. **S.C. Thal:** B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution; German Research Foundation (DFG: CRC1080, TPA7 to Thomas Mittmann). C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); scholarship council (Grand NO.201406140131 to Qi Wang), NEUROWIND e.V.. **E. Mergia:** None. **D. Koesling:** None. **T. Mittmann:** B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution; German Research Foundation (DFG: CRC1080, TPA7 to Thomas Mittmann).

Poster

780. Neurotransmitters and Signaling Molecules

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 780.03/E16

Topic: B.01. Neurotransmitters and Signaling Molecules

Title: Identification of enzymes involved in endocannabinoid synthesis and metabolism in Hirudo verbana

Authors: *B. D. BURRELL[1,2], E. KABEISEMAN[1], R. MISKIMINS[1];
[1]Basic Biomed Sci., Univ. of South Dakota, Vermillion, SD; [2]Ctr. for Brain & Behavior Res., Vermillion, SD

Abstract: Endocannabinoids are lipid neurotransmitters found throughout the animal kingdom, but there has been relatively little in the way of comparative studies in how these signaling molecules function in the nervous system. *Hirudo verbana* (the medicinal leech) provides an excellent model system for such studies. It has a well-described central nervous system (CNS) in which it is possible to record from single, identifiable neurons and link changes in individual

neurons and synapses to changes at the behavioral level. Pharmacological studies have demonstrated endocannabinoid-based modulation of synapses and behavior in *Hirudo* (e.g., Yuan & Burrell, 2013, *J. Neurophysiol.* 110:2607). In this study, we provide the first report of the genes in *Hirudo* that encode proteins responsible for the synthesis and metabolism of 2-arachidonoylglycerol (2-AG), an endocannabinoid transmitter known to be present in the *Hirudo* CNS. A sequence corresponding to the 2-AG synthesizing enzyme, diacylglycerol lipase (DAGL; accession #KU500007), was found to have 34 and 39% amino acid sequence identity when compared to mouse and human DAGL-beta genes, respectively. A sequence corresponding to the 2-AG metabolizing enzyme, monoacylglycerol lipase (MAGL), was found to have 40 and 41% amino acid sequence identity when compared to mouse and human MAGL. The regions corresponding to the predicted active site serine for both *Hirudo* DAGL (hirDAGL; S431) and hirMAGL (S118) were conserved between the *Hirudo* and mammalian versions of these proteins. When expressed in HEK cells both hirDAGL and hirMAGL are localized in the membrane, similar to their mammalian orthologues. Experiments using a natural fluorescent substrate assay (Van der Wal *et al.*, *J Lipid Res* 56: 927) indicate that hirMAGL converts 2-AG into arachidonic acid. Similar assays are currently being conducted to test whether hirDAGL can convert 1-stearoyl-2-arachidonol-*sn*-glycerol (SAG) into 2-AG. Future experiments will focus on examining how hirDAGL and hirMAGL activity is modulated (e.g. by phosphorylation), validating pharmacological agents that act on these enzymes, and their functional contribution to synaptic and behavioral plasticity.

Disclosures: B.D. Burrell: None. **E. Kabeiseman:** None. **R. Miskimins:** None.

Poster

780. Neurotransmitters and Signaling Molecules

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 780.04/E17

Topic: B.01. Neurotransmitters and Signaling Molecules

Support: CNPq-Brazil

CAPES-Brazil

FAPITEC-SE-Brazil

Title: Characterization of NADPH-diaphorase- and doublecortin-positive neurons in the lizard hippocampal formation

Authors: *M. M. LIMA[1], H. C. PIMENTEL[2], L. C. R. F. LINS[3], G. G. VIOLA[3], M. A. M. FREIRE[4], M. MARCHIORO[3];
[1]Psychological and Brain Sci., Univ. of Massachusetts Amherst, Amherst, MA; [2]Faculdade Estácio de Sergipe, Aracaju, SE, Brazil; [3]Dept. de Fisiologia, Univ. Federal de Sergipe, São Cristóvão, SE, Brazil; [4]Programa de Pós-Graduação em Saúde e Sociedade, Univ. do Estado do Rio Grande do Norte, Mossoró, RN, Brazil

Abstract: The lizard cortex has remarkable similarities with the mammalian hippocampus. Both process memories, have similar cytoarchitectural properties, and are important neurogenic foci in adults. Lizards show striking levels of widespread neurogenesis in adulthood and can regenerate entire cortical areas after injury. Nitric oxide (NO) is an important regulatory factor of mammalian neurogenesis and hippocampal function. However, little is known about the role of NO in non-mammalian neurogenesis. Here, we analyzed the distribution, morphology and complexity (Neurolucida reconstructions) of NO-producing neurons through NADPH-diaphorase (NADPHd) activity, and their relationship with doublecortin (DCX)-expressing neurons in the hippocampal formation of the neotropical lizard *Tropidurus hispidus*. NADPHd-positive neurons were present in two clusters: one with small somata and low intensity of staining; and one with inversely correlated soma size and intensity. Moreover, NADPHd-positive neurons in the dorsomedial cortex (DMC; homologous to CA3) were more numerous and complex than the ones in the medial cortex (MC; homologous do the dentate gyrus). We found NADPHd-positive DMC neurons send long projections into the MC. Interestingly, NADPHd-positive neurons were absent in the MC's granular cell layer. In contrast, DCX-positive neurons were scarce in the DMC, but highly numerous in the MC, particularly in the granular cell layer. We hypothesize that NO-producing neurons in the DMC provide important input to proliferating/migrating neurons in the highly neurogenic MC.

Disclosures: M.M. Lima: None. **H.C. Pimentel:** None. **L.C.R.F. Lins:** None. **G.G. Viola:** None. **M.A.M. Freire:** None. **M. Marchioro:** None.

Poster

780. Neurotransmitters and Signaling Molecules

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 780.05/E18

Topic: B.01. Neurotransmitters and Signaling Molecules

Support: Momentum Grant LP2013-54/2015

Wellcome Trust 090946/Z/09/Z

NIH Grant NS089575

Title: Differential contribution of diacylglycerol lipase-alpha to phasic and tonic endocannabinoid signaling at hippocampal GABAergic synapses

Authors: *K. KENESEI[1], M. LEDRI[1], B. TÓTH[2], B. DUDOK[1,3], G. HORVAI[2], I. KATONA[1]; [1]Momentum Lab. of Mol. Neurobio., Inst. of Exptl. Medicine, HAS, Budapest, Hungary; [2]Dept. of Inorganic and Analytical Chem., Budapest Univ. of Technol. and Econ., Budapest, Hungary; [3]Sch. of Ph.D. Studies, Semmelweis Univ., Budapest, Hungary

Abstract: Retrograde endocannabinoid signaling via presynaptic CB1 cannabinoid receptors (CB1R) play an essential role in the activity-dependent calibration of neurotransmitter release probability at various synapses throughout the brain. Recent investigations have also unfolded multiple different molecular mechanisms of how cannabinoid signaling can control synaptic transmission in a phasic or tonic manner. In addition, several serine hydrolase enzymes are known to regulate synaptic levels of the most common endocannabinoid messenger 2-arachidonoyl-glycerol (2-AG) raising the possibility of a molecular division of labor in different forms of endocannabinoid signaling. To mechanistically explore the contribution of diacylglycerol lipase-alpha (DGL-alpha), the predominant 2-AG synthesizing enzyme to phasic and tonic endocannabinoid signaling at perisomatic GABAergic synapses in the mouse hippocampus, we performed paired whole-cell patch-clamp recordings between presynaptic perisomatic interneurons and postsynaptic CA1 pyramidal cells. These physiological investigations have also been complemented by the detailed nanoscale analysis of cell-type-specific CB1R numbers and hippocampal endocannabinoid levels using stochastic optical reconstruction microscopy (STORM) super-resolution imaging and liquid chromatography/tandem mass spectrometry (LC-MS/MS), respectively. In agreement with prior studies, a significant decrease to 23% of wild-type 2-AG levels was observed in DGLα knockout mice. In addition, depolarization-induced suppression of inhibition (DSI), a widespread form of phasic endocannabinoid signaling was absent in DGLα knockout mice, whereas DSI was robust and could be blocked with the CB1 receptor antagonist/inverse agonist AM251 in wild-type animals. Despite the reduced basal tissue 2-AG levels, CB1 receptor numbers on presynaptic interneuron terminals as well as the baseline amplitude of unitary inhibitory postsynaptic currents (uIPSCs) and success rates of unitary synaptic events remained identical between littermate wild-type and DGLα knockout mice suggesting that tonic 2-AG signaling may still be functional in the absence of DGLα. Indeed, AM251 could significantly increase GABAergic synaptic transmission between perisomatic interneurons and CA1 pyramidal cells in DGLα KO mice. Together, these findings are consistent with the prevailing view that DGLα produces synaptic 2-AG for phasic endocannabinoid signaling, but also raise the intriguing possibility that tonic endocannabinoid signaling operates via a DGLα-independent molecular mechanism.

Disclosures: **K. Kenesei:** None. **M. Ledri:** None. **B. Tóth:** None. **B. Dudok:** None. **G. Horvai:** None. **I. Katona:** None.

Poster

780. Neurotransmitters and Signaling Molecules

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 780.06/E19

Topic: B.01. Neurotransmitters and Signaling Molecules

Support: R21MH103515-02

T32MH064913

Title: Endocannabinoid regulation of glutamatergic input onto corticotropin releasing neurons in the central nucleus of the amygdala

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Abstract: The central amygdala (CeA) is a limbic brain structure largely responsible for the generation of threat adaptive behaviors. Corticotropin releasing factor (CRF) signaling within the CeA has been shown to positively regulate fear and anxiety phenotypes, and the use of knock in and transgenic reporter lines has allowed for reliable identification of CRF expressing (CRF+) neurons in this region. Recently, we have demonstrated that endocannabinoid (eCB)-mediated retrograde synaptic suppression is prevalent at excitatory synapses in the CeA. However, how the excitability of CRF+ neurons and the eCB system interact in the CeA remains largely unexplored. Here, we use optogenetic circuit mapping to assess eCB-signaling at ascending and descending glutamatergic inputs onto CRF+ neurons in CeA. We report that CRF+ neurons receive the greatest input from descending cortical-like structures, over ascending inputs from the parabrachial nucleus, and that cannabinoid signaling capacity is greatest at these descending inputs. Furthermore, we identify forms of short-term and long-term eCB-mediated plasticity at specific inputs, suggesting that eCBs regulate CeA function via suppression of glutamate release onto CRF+ neurons.

Disclosures: **N. Hartley:** None. **A. Jameson:** None. **S. Patel:** None.

Poster

780. Neurotransmitters and Signaling Molecules

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 780.07/E20

Topic: B.01. Neurotransmitters and Signaling Molecules

Support: Wellcome Trust 090946/Z/09/Z

Momentum Program LP2013-54/2015

NIH Grant NS089575

Title: Molecular, morphological and physiological properties of different CB_1 cannabinoid receptor-expressing interneuron types of the hippocampus

Authors: *B. DUDOK[1,2], V. MICZÁN[1,3], K. KENESEI[1], M. LEDRI[1], K. KELEMEN[1], B. BARTI[1], M. KISFALI[1], M. WATANABE[4], I. KATONA[1];
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Abstract: Specific GABAergic interneuron types play fundamentally different roles in the regulation of network activity in cortical circuits. Prior studies have classified specific interneuron types based on the characteristic differences in their neurochemical markers, morphological features, cell physiological properties and firing activity patterns during distinct brain and behavioral states. However, the comprehensive classification of cortical interneurons has not been completed yet, and novel methods, such as single-cell transcriptomics suggest a greater variability of cortical cell types than previously expected. A major population of cortical GABAergic interneurons expresses high levels of CB_1 cannabinoid receptors and can usually be divided into two morphological subpopulations of perisomatically- and dendritically-targeting interneurons. In accordance, previous studies have shown that the vesicular glutamate transporter VGluT3 is also present only in a selected subpopulation of CB_1-positive interneurons. In order to establish how these molecular and morphological differences are associated with specific physiological properties of distinct CB_1-positive interneuron populations, we used a combination of paired whole-cell patch-clamp recordings together with correlated confocal and STORM super-resolution imaging. The data showed that vGluT3 is expressed by selected subtypes of perisomatically- and dendritically-targeting interneurons defined by their non-overlapping bouton distribution index (see Dudok et al., 2015, Nature Neuroscience, 18:75-86) in the mouse CA1 hippocampus. The gross axonal and dendritic morphology, and the intrinsic physiological properties of VGluT3-positive or VGluT3-negative interneurons were indistinguishable. In contrast, VGluT3-expressing cells had larger boutons, which contained significantly more CB_1

receptors. Surprisingly, VGluT3-positive perisomatic interneuron synapses onto CA1 pyramidal neurons exhibited lower baseline synaptic efficacy and release probability compared to VGluT3-negative perisomatic connections. The remarkably smaller amplitude of unitary inhibitory synaptic currents and the lower success rate of synaptic events are likely due to high constitutive CB_1 receptor activity present at VGluT3-containing perisomatic synapses, but not at VGluT3-negative perisomatic or dendritic interneuron synapses. These distinct molecular, morphological and synaptic properties suggest that CB_1-positive interneuron types may contribute to hippocampal network activity and behavior in a more complex manner than anticipated before.

Disclosures: **B. Dudok:** None. **V. Miczán:** None. **K. Kenesei:** None. **M. Ledri:** None. **K. Kelemen:** None. **B. Barti:** None. **M. Kisfali:** None. **M. Watanabe:** None. **I. Katona:** None.

Poster

780. Neurotransmitters and Signaling Molecules

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 780.08/E21

Topic: B.01. Neurotransmitters and Signaling Molecules

Support: NIH-NIDA DA15014

NIH-NIDA DA32444

Title: μ-opioid mediated changes of neuronal iron levels may upregulate Ferritin Heavy Chain protein in specific cortical neurons

Authors: *B. S. NASH[1], R. A. NOLAN[2], K. TARN[2], O. MEUCCI[2];
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Abstract: HIV associated neurocognitive disorder is a common complication of HIV infection, and can be exacerbated by mu-opioid drug abuse. A potential mechanism of mu-opioid induced cognitive impairment examines negative regulation of the homeostatic chemokine receptor CXCR4 by mu-opioids. Morphine and DAMGO induce upregulation of Ferritin Heavy Chain protein in cortical neurons in vitro and in vivo, which is colocalized with CXCR4 and correlated with reduced activation of the receptor and its homeostatic downstream signals. The work presented here further characterizes mu-opioid induced FHC expression in cortical neurons. Morphine induced FHC from a dose range of 0.1 to 1 μM in vitro, and fractionation studies revealed that cytoplasmic FHC levels increase, while nuclear FHC levels remained constant. Rats sacrificed 24 hours after a single 20mg/kg morphine s.c. injection had elevated neuronal FHC levels in cortical neurons, with notable variability between individual cells, suggesting a

subpopulation of neurons is more susceptible to this effect. In vitro calcein imaging studies show that intracellular free labile iron concentrations are increased as early as 30 minutes after 1 μM morphine treatment, and sustained over 24 hours. Changes in neuronal iron levels may be a driver of mu-opioid mediated FHC protein expression, since they both regulate FHC expression post-transcriptionally. Additionally, we show that FHC expression is dependent on intracellular iron, and cannot be induced by morphine in the presence of the iron chelator Deferroxamine. Morphine can upregulate FHC if only extracellular iron is chelated, highlighting the importance of intracellular iron in this process. Subsequently, we show neurons that are iron loaded with 50 μM Ferric Ammonium Citrate, but not treated with morphine, both upregulate FHC and partially inhibit downstream mediators of CXCR4 signals. These experiments suggest a novel mechanism of regulation between the opioid and iron regulatory systems that coordinate to modulate downstream homeostatic signals from CXCR4. This has potential implications for HIV+ patients who are prescribed opioid medications or abuse opioid drugs, and may describe a novel avenue of cognitive impairment in this patient group. Future studies will examine and characterize neuronal subtypes susceptible to FHC upregulation in order to identify circuit specific elements that may be impaired among opioid abusers.

Disclosures: **B.S. Nash:** None. **R.A. Nolan:** None. **K. Tarn:** None. **O. Meucci:** None.

Poster

780. Neurotransmitters and Signaling Molecules

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 780.09/E22

Topic: B.01. Neurotransmitters and Signaling Molecules

Support: Financial support has been provided by Department of Biotechnology (Grant no-BT/PR14279/MED/30/452/2010), Government of India

Title: Expression of cannabinoid type 1 receptors in the rat spinal cord following surgical incision

Authors: *P. PRASOON[1], R. KUMAR[2], M. GAUTAM, 110029[2], S. RAY[2];
[2]Anat., [1]AIIMS, New Delhi, India

Abstract: Background: The active principal of cannabis known as $^{9}{}_{\alpha}$ -Tetrahydrocannabinol (THC) binds to cannabinoid (CB) receptors, which are classified into CB1 and CB2 subtypes. These belong to the G-protein coupled receptor family. Cannabis has a prominent analgesic action in humans and has been recommended for the treatment of cancer pain. Recently, activation of CB1 receptors has also been observed to produce relief in neuropathic pain.

However, little is known about the role of CB1 receptors in postoperative pain. Hence, the expression of these receptors was studied in the rat spinal cord following surgical incision on the hind paw. **Materials and Methods:** Sprague-Dawley rats were subjected to incision on the plantar surface of the right hind paw. Behavioural assessment of nociception was done. Spinal cords (L4-5 segments) were processed for immunohistochemical localization of CB1 receptors. Western blotting was also done. Expression of CB1 receptors in Rexed's lamina I-II of dorsal horn was quantified by NIS-Element software. **Results:** Both allodynia and hyperalgesia were highest, immediately after incision. Expression of CB1 receptor in laminae I-II increased at all post incision time points though significant increase was observed at 2 h and day 3. Result of Immunoblot confirmed these finding. **Conclusions:** Up-regulation immediately after incision suggests that these receptors could be important in the initial part of postoperative pain. Previous studies indicate that these receptors inhibit the release of excitatory neurotransmitters from presynaptic terminals, which decrease the transmission of pain. Further studies are in progress for evaluation of the precise role of CB1 receptors. **Key words**: CB1 receptor, hindpaw incision, Postoperative pain, CB2 receptor, Neuropathic Pain. **Acknowledgment:** Financial support has been provided by Department of Biotechnology (Grant no-BT/PR14279/MED/30/452/2010), Government of India

Disclosures: P. Prasoon: A. Employment/Salary (full or part-time): Senior Research Fellowship from University Grants Commission,India. B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution; Financial support has been provided by Department of Biotechnology (Grant no-BT/PR14279/MED/30/452/2010), Government of India. **R. Kumar:** None. **M. Gautam:** None. **S. Ray:** None.

Poster

780. Neurotransmitters and Signaling Molecules

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 780.10/E23

Topic: B.01. Neurotransmitters and Signaling Molecules

Title: Hippocalcin promotes neuronal differentiation and inhibits astrocytic differentiation in neural stem cells

Authors: *S.-Y. PARK[1], M.-J. KANG[1], S. JUNG[2], J.-S. HAN[3];
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Abstract: Hippocalcin is a calcium-binding protein that is restricted to nervous tissue and contributes to neuronal activity. However, the mechanisms by which hippocalcin regulates neuronal differentiation in neural stem cells (NSCs) are poorly studied. We report that, in addition to inducing neurogenesis, hippocalcin inhibits astrocytic differentiation of NSCs. It promotes neurogenesis by regulating protein kinase Cα (PKCα) activation by translocating to the membrane and binding to phosphoinositide-dependent protein kinase-1 (PDK1), which induces PKCα phosphorylation. We also found that phospholipase D1 (PLD1) is implicated in the hippocalcin-mediated neurogenesis pathway; this enzyme promotes dephosphorylation of STAT3 (Y705), which is necessary for astrocytic differentiation. Moreover, we found that the tyrosine phosphatase SHP-1 acts upstream of STAT3. SHP-1 acts as a negative regulator of STAT3, which is required for neurogenesis. Importantly, this SHP-1-dependent STAT3 inhibitory mechanism is closely involved in neurogenesis and suppression of gliogenesis by hippocalcin. Taken together, these observations suggest that hippocalcin promotes neuronal differentiation through activation of the PKCα/PLD1 cascade followed by activation of SHP-1, which dephosphorylates STAT3 (Y705), leading to inhibition of astrocytic differentiation.

Disclosures: **S. Park:** None. **M. Kang:** None. **S. Jung:** None. **J. Han:** None.

Poster

780. Neurotransmitters and Signaling Molecules

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 780.11/E24

Topic: B.01. Neurotransmitters and Signaling Molecules

Support: National Science Foundation Graduate Fellowship DGE 1106400

NIDA grant R01DA016782

Title: Circuit specific modulation of corticotrophin releasing factor in ventral tegmental neurons

Authors: ***J. R. DRISCOLL**[1,2], H. L. FIELDS[3,2], E. B. MARGOLIS[3];
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Abstract: A major hypothesis in the pathology of addiction is that maladaptive behaviors result from a disruption in the homeostatic balance between stress and reward circuitry. Several rodent models of stress (i.e. footshock, foot pinch, restraint stress, and social defeat stress) increase the activity of VTA neurons and result in an increase in dopamine in terminal regions of VTA neurons. Corticotrophin releasing factor (CRF) is released in the VTA during stress and is

reported to increase the firing rate of dopamine neurons, yet decrease dopamine release in the Nucleus Accumbens (NAc). These results suggest that CRF differentially modulates VTA neurons with different projection targets. However, the synaptic action of CRF on specific subsets of VTA neurons and their role in influencing behavior has yet to be characterized. We made *ex vivo* whole cell current clamp recordings to examine the synaptic actions of CRF. We measured responses to (100 nM to 1 mM) CRF in both TH(+) and TH(-) neurons from throughout the VTA. CRF consistently increased the firing rate of spontaneously active neurons (n=22/25). However in quiescent neurons we observed either depolarizations (40%) or hyperpolarizations (35%). Firing rate increases were not dependent on HCN channel function, as blocking them using 10nM ZD7288 did not prevent this increase (n=5/6). To analyze circuit specificity of CRF, recordings were made in labeled neurons 7 days after the retrograde fluorescent marker DiI was injected into VTA terminal regions including medial prefrontal cortex (mPFC), NAc, and amygdala (AMY). AMY-projecting VTA neurons were consistently excited by CRF, whether firing spontaneously or quiescent (n=5/5). We also observed an increase in the amplitude of evoked glutamatergic EPSCs in response to CRF in this projection (n=4/5, 240% increase amplitude). In contrast, mPFC and NAc projecting neurons did not show a consistent response pattern in quiescent neurons (n=14 for mPFC, n=17 for NAc). Spontaneously active neurons in all projections were consistently excited by CRF (n=7). These findings demonstrate that the effect of CRF on VTA neurons is heterogeneous and depends on both the state of the neuron and its projection. Cells that are firing spontaneously fire more, strengthening ongoing activity. In neurons that are not firing, CRF is biasing a subset of VTA neurons that will respond to an excitatory input. Both dopaminergic and non-dopaminergic neurons are modulated. To understand how these effects modulate behavior, further work must be done to probe the contribution of AMY-projecting VTA neurons by activation of this projection in tasks that explore the role of stress in modulating aversion and reward.

Disclosures: **J.R. Driscoll:** None. **H.L. Fields:** None. **E.B. Margolis:** None.

Poster

780. Neurotransmitters and Signaling Molecules

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 780.12/E25

Topic: B.01. Neurotransmitters and Signaling Molecules

Support: NIH grant HL98589

Title: NPY receptor characterization in guinea pig intracardiac neurons: Evidence for multiple receptor subtypes.

Authors: *J. C. HARDWICK[1], K. A. LUCKETT[2], M. GERUNTHO[1], S. A. ROSEN[1];
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Abstract: Chronic heart disease leads to imbalances within the autonomic nervous system, often resulting in an upregulation of sympathetic output with a concomitant decrease in central parasympathetic preganglionic activity. In addition to the increased release of norepinephrine from sympathetic fibers, there is also an elevation in the release of the neuropeptide, NPY. This study examined the function and responses of intrinsic parasympathetic postganglionic cardiac neurons to local application of NPY. Previous studies have shown that these neurons respond to NPY, but the receptors and mechanism underlying these responses are unknown. We used a multidisciplinary approach to determine which NPY receptors are present in the guinea pig intracardiac neurons and what functional responses they induce. Biochemical analysis of mRNA levels with RT-qPCR shows evidence for Y1 and Y5 receptors, and possibly Y2 receptors. Western blot analysis of protein expression from dissected guinea pig cardiac ganglia and atrial muscle show evidence for Y4 and Y5 receptors. Intracellular voltage recordings from individual neurons supported previous results, where NPY induces a hyperpolarization of the membrane potential and reduces the time course of the afterhyperpolarization (AHP) phase in single action potentials. Using specific Y1, Y2 and Y5 antagonists, we determined that the Y5 receptor appears to mediate the change in AHP time course. The hyperpolarization of the membrane potential appears to have heterogeneous receptor mediation, since some cells showed significant inhibition with Y5 antagonists and others showed no significant inhibition to any antagonist tested. In separate experiments examining ganglia from animals with a surgical model of chronic myocardial infarction (MI), we found significant (~2.5 fold) upregulation of NPY mRNA in the ganglion. We also saw an increase in NPY-induced neuronal excitability with depolarizing current pulses in these MI animals. These results indicate that NPY expression in neurons is altered with chronic heart disease. Additionally, the neurons of the cardiac ganglion express multiple NPY receptors and these receptors may also show differential expression levels following the induction of a chronic MI.

Disclosures: J.C. Hardwick: None. **K.A. Luckett:** None. **M. Geruntho:** None. **S.A. Rosen:** None.

Poster

780. Neurotransmitters and Signaling Molecules

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 780.13/E26

Topic: B.01. Neurotransmitters and Signaling Molecules

Support: NIH Grant R01 MH048153

NIH Grant R01 MH098554

Title: Increased Toll-like receptors in the prefrontal cortex of depressed suicide

Authors: *X. REN, H. S. RIZAVI, H. ZHANG, G. N. PANDEY;
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Abstract: Abnormalities of the immune function in depression and suicide are based in part on the observation of increased levels of proinflammatory cytokines in the serum and in the postmortem brain of depressed and suicidal patients. Several studies suggest dysregulation of the immune system in suicide as increased microgliosis has been reported in postmortem brain of suicide subjects and increased levels of proinflammatory cytokines in the cerebrospinal fluid (CSF) of suicidal patients. The observed abnormality of cytokines in suicide may be related to altered innate immune receptors known as Toll-like receptors (TLRs). We have earlier reported a significant increase in the protein and mRNA levels of TLR3 and TLR4 in depressed and suicide brain. To further examine the role of TLRs in suicide we have now studied the expression of TLR1, TLR2, TLR6, TLR7, TLR8, TLR9 and TLR10 in depressed suicide subjects. We determined the protein expression of TLR1, TLR2, TLR5, TLR6, TLR7, TLR8, TLR9, and TLR10 in the prefrontal cortex (PFC) of 24 depressed suicide victim and 24 normal control subjects. The postmortem brain tissues were obtained from the Maryland Brain Collection and the psychological autopsies were performed for the diagnosis of the subjects using DSM-IV-SCID. Protein expression was determined using Western blot technique. When we compared the protein expression of different TLRs, we found that the protein expression of TLR2, TLR6, TLR7 and TLR10 was significantly increased in the PFC of depressed suicide victims compared with normal control subjects, while there was no difference in protein expression of TLR1, TLR5, TLR8 and TLR9 in depressed suicide victims compared with normal control subjects. These results suggest that protein overexpression of TLR2, TLR6, TLR7 and TLR10 may be in part related to the abnormalities of proinflammatory cytokines in the brain of suicide victims and that abnormalities of innate immunity are associated with suicide.

Disclosures: X. Ren: None. **H.S. Rizavi:** None. **H. Zhang:** None. **G.N. Pandey:** None.

Poster

780. Neurotransmitters and Signaling Molecules

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 780.14/E27

Topic: B.01. Neurotransmitters and Signaling Molecules

Support: NIH Grant AR059397

Title: Potentiation of ASIC channel currents by high affinity endogenous opioids, independent of mu opioid receptor stimulation, in rat sensory neurons

Authors: M. FARRAG[1], H. L. PUHL[2], *V. RUIZ-VELASCO[1];
[1]Anesthesiol., Penn State Col. of Med., Hershey, PA; [2]Lab. of Mol. Physiol., Natl. Inst. of Health, Natl. Inst. on Alcohol Abuse and Alcoholism, Bethesda, MD

Abstract: The naturally occurring endomorphins 1 and 2 (E-1 and E-2) exhibit high affinity and selectivity for mu opioid receptors (MOR) over kappa and delta receptors. Both of these tetrapeptides have been shown to exert analgesic properties in some animal models of pain. E-1 and E-2 release is enhanced under ischemic and inflammatory conditions. Additionally, a pH drop in ischemic tissue activates the H^+-gated acid sensing ion channels (ASIC). ASIC are expressed primarily in peripheral and central nervous system. Some reports have shown that DRG neurons express primarily ASIC1 and ASIC3 isoforms. ASIC3 channel currents are characterized by two components: fast component that rapidly desensitizes and a slow, sustained current that lasts as long as the external pH remains acidic. The purpose of the present study was to examine the effect of E-1 and E-2 peptides on ASIC channel currents employing the whole-cell variant of the patch-clamp technique. In acutely isolated rat DRG neurons, exposure to either 10 μM E1 or E2 (pH 6.0) enhanced the sustained ASIC currents 76±29% (n=11) and 113±35% (n=17), respectively, when compared to activation by pH 6.0 alone. The sustained ASIC currents also were potentiated (115±39%, n=5) by E-2 (10 μM) in DRG neurons pretreated overnight with pertussis toxin—suggesting that MOR were not involved in this signaling event. To better understand the effect of endomorphins on ASIC3 homotrimers, mouse ASIC3 (mASIC3) channels were heterologously expressed in the mouse fibroblast L cell line that does not natively express MOR or ASIC channels. Either 10 μM E-1 or E-2 greatly potentiated ASIC3 currents (1700±252%, n=9; 2033±456%, n=5) when compared to pH 6.0 alone. The pH-dependent activation was shifted to more alkaline pH while the pH-dependent inactivation was shifted to a more acidic pH, resulting in an amplification of the window current. Given that endomorphins are released under ischemic conditions, we next ligated the femoral artery in rats to produce muscle ischemia. Following a 72 hr ligation period, the rat DRG neurons were isolated and the effect of endomorphins on ASIC currents was examined. When compared to control DRG neurons exposed to either 10 μM E-1 or E-2 (pH 6.0), E-1 or E-2 application (pH 6.0) resulted in a significantly ($p<0.05$) greater ASIC current potentiation of 194±68% (n=10) and 244±60% (n=9), respectively. Overall, these results suggest that endogenous endomorphins potentiate sustained ASIC3 currents—an effect that is enhanced under ischemic conditions.

Disclosures: **M. Farrag:** None. **H.L. Puhl:** None. **V. Ruiz-Velasco:** None.

Poster

780. Neurotransmitters and Signaling Molecules

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 780.15/E28

Topic: B.01. Neurotransmitters and Signaling Molecules

Support: NIH Grant RO1 MH106565

Title: Glucocorticoid receptor exon 1F and dynamics of DNA methylation in teenage suicide

Authors: *H. S. RIZAVI, D. R. GRAYSON, H. ZHANG, X. REN, G. N. PANDEY;
Univ. Illinois Chicago, Chicago, IL

Abstract: Impaired hypothalamic-pituitary-adrenal (HPA) axis function is linked to depression and increased susceptibility to suicide. Dysregulation of HPA axis function observed in depression and suicide may be due partially to a disturbed feedback inhibition by endogenous corticoids. Glucocorticoid receptors (GR) play an important role in the regulation of stress response when endogenous levels of glucocorticoids are high. In this study, our goal was to understand the regulation of GR exon 1_F expression and the dynamic epigenetic mechanisms that may alter the expression of this promoter. Gene expression and methylation levels were measured in the postmortem prefrontal cortex (PFC) of 22 teenage suicide victims and 22 teenage normal control subjects. Our results show that GR exon 1_F expression was decreased while methylation levels were increased and hydroxyl-methylation levels were decreased in teenage suicide victims as compared to normal controls. Expression of TET1 and TET2 was decreased with no change in TET3 in teenage suicide victims as compared to normal controls. In addition, DNMT1 and DNMT3a expression was increased with no change in DNMT3b in teenage suicide victims as compared to normal controls. Our data supports the hypothesis that epigenetic variations caused by aberrant regulation of DNMT and TET lead to higher methylation levels in $GR1_F$ and affect $GR1_F$ mRNA levels. Our data indicate that dynamic epigenetic mechanisms are involved in gene regulation and contribute significantly to understanding the neurobiology of teenage suicide.

Disclosures: H.S. Rizavi: None. **D.R. Grayson:** None. **H. Zhang:** None. **X. Ren:** None. **G.N. Pandey:** None.

Poster

780. Neurotransmitters and Signaling Molecules

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 780.16/E29

Topic: B.01. Neurotransmitters and Signaling Molecules

Support: R01MH101178

R00AA021782

Title: Galanin receptor expression and origins of galanin input from noradrenergic nuclei to the bed nucleus of the stria terminalis

Authors: *A. GARGIULO[1], J. R. BARSON[1], B. D. WATERHOUSE[2];
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Abstract: Reinstatement of drug-seeking is one of the greatest challenges in treating addiction, and roughly half of individuals treated for it relapse within a year of cessation. Medical approaches for treating relapse are lacking because the mechanisms underlying relapse are multifactorial and poorly understood. Stress is a common cause of relapse with devastating consequences for recovering addicts. Brief exposure to various stressors have been shown to induce relapse experimentally, and our laboratory is interested in characterizing the role of galanin that originates from noradrenergic nuclei in this behavior. The bed nucleus of the stria terminalis (BNST), a brain region involved in integrating hypothalamus-pituitary-adrenal (HPA) axis signaling as well as fear- and reward-neurocircuitry, is heavily involved in stress-induced relapse behavior. This region is important in that it receives extensive noradrenergic innervation and is responsive to infusion of galanin and norepinephrine (NE) agonists and antagonists, yet much about its cytoarchitecture, especially with respect to patterns of galanin receptor distribution and galanin innervation remains to be thoroughly examined. Galanin has been shown to be an important anxiolytic neuropeptide, and increased galanin expression in locus coeruleus, the major source of NE to the forebrain, has been shown to promote resilience to stress. Therefore, we used immunohistochemical procedures to explore galanin receptor expression throughout BNST subregions, with particular focus on the ventral and lateral portions of the nucleus which receive a prominent noradrenergic innervation. Male, Sprague-Dawley rats were sacrificed, perfused, and brain slices processed with primary antibodies against galanin receptors 1 (GalR1) or 2 (GalR2) to detect galanin receptor expression, as well as co-stains for glutamic acid decarboxylase (GAD67) and Ca^{2+}/Calmodulin-dependent protein kinase II (CaMKII) to identify expression of galanin receptors on GABA-ergic and glutamatergic BNST cells, respectively. In line with *in situ* hybridization and genetic cell targeting studies of other laboratories, we noted galanin receptor expression in subregions and subsets of cells in the

BNST. These findings suggest that regional expression of galanin receptors in BNST underlie the neuromodulatory effects of galanin on stress-induced reinstatement of drug-seeking behavior. Additional retrograde tract tracing studies are focused on identifying of the source of galanin projections to these sub-regions.

Disclosures: **A. Gargiulo:** None. **J.R. Barson:** None. **B.D. Waterhouse:** None.

Poster

780. Neurotransmitters and Signaling Molecules

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 780.17/E30

Topic: B.01. Neurotransmitters and Signaling Molecules

Support: NIH

Title: Neuropeptide and protease systems in stress-responsive dense core secretory vesicles analyzed by mass spectrometry-based peptidomics, proteomics, and protease activity profiling

Authors: ***C. B. LIETZ**[1], D. J. GONZALEZ[1,2], A. J. O'DONOGHUE[1], Z. JIANG[1,3], T. TONEFF[1], N. BANDEIRA[1,4], V. HOOK[1,2,5];
[1]Skaggs Sch. of Pharm. and Pharmaceut. Sci., [2]Pharmacology, Sch. of Med., [3]Chem. and Biochem., [4]Computer Sci. and Engin., [5]Neurosciences, Sch. of Med., Univ. of California San Diego, La Jolla, CA

Abstract: Stress induces the release of bioactive neuropeptides and catecholamines from sympathetic adrenal medullary chromaffin cells for intercellular signaling regulation of physiological responses in ‘fight or flight’ stress reactions to environmental changes. Dense core secretory vesicles secrete stress-regulating neuropeptides which include, among others, enkephalins, Neuropeptide Y (NPY), and chromogranin-derived peptides such as catestatin. Neuropeptides are co-released with the catecholamines dopamine, norepinephrine, and epinephrine. This study applied an integrated “omics” strategy combining high-resolution liquid chromatography-mass spectrometry (LC-MS) peptidomics, proteomics, and protease activity profiling of DCSVs isolated from primary bovine chromaffin cells. Analysis of these DCSVs will help provide a greater understanding of the vital functions performed by proteases and other DCSV proteins related to neuropeptide biosynthesis, storage, and release.
LC-MS data was subjected to bioinformatics analysis by PEAKS and MSGFDB. Results identified endogenous peptides derived from chromagranins, proenkephalin, pro-NPY, and Kininogen (bradykinins), among others. Preliminary bottom-up proteomic experiments of isolated DCSVs identified 2328 unique proteins. These proteins include 78 putative proteases

from the cysteine, aspartyl, metallo, and serine protease subclasses. Several of these proteases are known to participate in pro-neuropeptide processing, however many new proteases not previously identified in these DCSVs were also found. Activity profiling using a diverse set of fluorescent peptide substrates and class-specific protease inhibitors, determined that multiple proteases are active at pH 5.0 - 5.5, which corresponds to the internal pH of DSCVs. Systems biology analyses of these multi-omics DCSV data illustrate the complex network of protein functions involved DCSV stress responses.

Disclosures: **C.B. Lietz:** None. **D.J. Gonzalez:** None. **A.J. O'Donoghue:** None. **Z. Jiang:** None. **T. Toneff:** None. **N. Bandeira:** None. **V. Hook:** None.

Poster

780. Neurotransmitters and Signaling Molecules

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 780.18/E31

Topic: B.01. Neurotransmitters and Signaling Molecules

Support: CONACYT 253631

CONACYT 252756

Fronteras 374

PAPIIT IN200512

PAPIIT IN203615

Title: Naloxone blocks the neurogenesis, evaluated by double labelled cells, induced by paced mating in the olfactory bulb of the female rat.

Authors: *M. SANTOYO ZEDILLO[1], R. G. PAREDES G.[2], W. PORTILLO MARTINEZ[2]; [1]Inst. de Neurobiologia, UNAM, Queretaro, Mexico; [2]Dept. de Neurobiologia Conductual y Cognitiva, Inst. de Neurobiologia,UNAM, Queretaro, Mexico

Abstract: Neurogenesis is a process that occurs continuously in the adult mammalian brain. But environmental conditions or internal states can modify different stages of this process.
Our group has demonstrated that when female rats are allowed to pace the sexual interaction, there is an increase in the number of newborn cells BrdU inmunoreactive (BrdU-IR), in the accessory olfactory bulb (AOB). Some of this cells are also positive for NeuN IR (nuclear neuronal marker), suggesting that they differentiate into neurons. Moreover, females that pace

their sexual interaction develop a positive affective (reward) state, which has been evaluated by the conditioned place preference paradigm (CPP). This reward state is mediated by opioids because we showed that the intraperitoneal injection of naloxone (NX, opioid receptor antagonist) blocks CPP induced by paced mating.
In the present study we evaluated if blocking the opioid receptors with naloxone could reduce the number of new cells that incorporate to the AOB, that are generated during the first paced mating sexual interaction. Sexually-naïve female rats, bilaterally ovariectomized and hormonally supplemented were randomly assigned to one of five groups: 1) without sexual contact injected with saline, 2) without sexual contact injected with NX, 3) females that mated without pacing the sexual interaction injected with saline, 4) females injected with saline before paced mating and 5) females injected with NX before paced mating.
Females treated with saline that paced the sexual interaction, showed an increase in newborn cells and an increase in double labeled cells BrdU IR and NeuN IR in the AOB when compared to the other groups. NX administration before paced mating blocked the increase in the number of BrdU-IR cells and of double labelled cells BrdU-NeuN IR.
These data support that opioid peptides, have a fundamental role in the neurogenesis in the AOB induced by paced mating in the female rat. Further research will evaluate if these newborn cells are involved in the physiology of reproduction.
Acknowledgments: Technical assistance Francisco Camacho. Supported by CONACYT 253631, 252756 Fronteras 374 and PAPIIT IN210215 and IN203615.

Disclosures: **M. Santoyo Zedillo:** None. **R.G. Paredes G.:** None. **W. Portillo Martinez:** None.

Poster

780. Neurotransmitters and Signaling Molecules

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 780.19/E32

Topic: B.01. Neurotransmitters and Signaling Molecules

Support: NIH Grant NS031609

NIH Grant P30DA018310

Title: Characterization of L-to-D peptide isomerase activity in *Aplysia* californica

Authors: ***H.-C. TAI**, I. LIVNAT, J. W. CHECCO, E. V. ROMANOVA, P. M. YAU, J. V. SWEEDLER;
Univ. of Illinois At Urbana-Champaign, Urbana, IL

Abstract: Neuropeptides are cell-to-cell signaling molecules that mediate the activity of most neuronal circuits. Neuropeptides are derived from larger protein precursors, and undergo a range of post-translational modifications to form the bioactive peptides. Importantly, post-translational conversion of an L-amino acid residue into a D-amino acid residue in a neuropeptide can substantially alter the three dimensional structure and modify the bioactivity and metabolism of the resulting D-amino acid-containing peptide (DAACP). Current research into peptide isomerization is limited because this PTM is not easily detected in mass spectrometry-based peptidomics experiments due to the lack of an associated mass shift. Therefore, we have established protocols to screen for and characterize DAACPs in a non-targeted manner. Three novel DAACPs were identified in *Aplysia californica* using this approach. Our results suggest that the peptide isomerase responsible for the L-to-D modification in *A. californica* works only on the second amino acid residue from the N-terminus but is promiscuous in terms of peptide length as well as specific residue to isomerize. To advance our understanding of this fascinating enzyme, an assay for characterizing peptide isomerase activity was developed. Initial efforts focused on dissecting known DAACP expressing regions in specific neural ganglia and incubating the homogenate with all-L-peptide substrates. Peptide samples post incubation were analyzed with liquid chromatography coupled to multiple-reaction-monitoring mass spectrometry, and the L- or D- peptide isomer assigned based on matching retention times to synthetic standards. Since the peptides NdWFa, GdFFD and GdYFD are known to exist as DAACPs in *A. californica,* the all-L-forms of these peptides were used as substrates to evaluate peptide isomerase activity. The corresponding DAACPs were detected post incubation, suggesting that isomerase activity is indeed active in the homogenates. Importantly, formation of DAACPs was not observed when the homogenate was heated in boiling water prior to incubation, which strongly suggests that the isomerization was the result of an enzymatic process rather than spontaneous isomerization. Isomerase activity was observed in the presence of ethylenediaminetetraacetic acid (EDTA), which implies that the isomerase is not metal-dependent. Additional cofactors are being evaluated for their impact on isomerase activity, and enzyme purification for sequencing and further characterization is currently underway.

Disclosures: H. Tai: None. **I. Livnat:** None. **J.W. Checco:** None. **E.V. Romanova:** None. **P.M. Yau:** None. **J.V. Sweedler:** None.

Poster

780. Neurotransmitters and Signaling Molecules

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 780.20/E33

Topic: B.06. Neurotransmitter Release

Support: NIH Grant 1K01AG049055-01A1

NIH Grant 1P20GM103653-01A1

Title: Role of central acetylcholine release in the regulation of locomotion circuits

Authors: A. C. BLAKE, Jr[1], M. HEREDIA[1], *H. O. LAWAL[2];
[1]Biol. Sci., [2]Biol., Delaware State Univ., Dover, DE

Abstract: Impairment in cholinergic neurotransmission is associated with normal and pathological aging, making cholinergic release a subject of high interest to human biology. However, the precise role of changes in central acetylcholine release in mediating behaviors, such as locomotion, has not been fully elucidated. The vesicular acetylcholine transporter (VAChT) is present in many species, including worms, flies, and humans, and is responsible for the packaging of acetylcholine for exocytotic release. A complete loss of VAChT function is lethal, while severe mutations can cause decreased locomotive performance in *Drosophila*. Here, we hypothesize that deficits in VAChT function can be rescued by a pharmacological or genetic increase in VAChT function, which can be identified by a shift in the rate of locomotion towards normal. The overall purpose of this study was to determine an effective method of rescuing mutations in *Drosophila Vacht*. In order to rescue the locomotion deficit seen in *Vacht* mutants, cholinergic drugs in different concentrations were administered to the *Vacht* mutant larvae for a 2 hour time period; dimethyl sulfoxide or water were used as vehicle. Drug or vehicle-only fed larvae were then tested in two locomotion assays, using the automated MultiWorm Tracker, and the touch response assay. For a genetic rescue, a wildtype copy of the VAChT gene was expressed in the *Vacht* mutant background. Here we report that the expression of a wildtype copy of VAChT rescues one locomotion assay phenotype but not the other. Furthermore, our results indicate a differential effect of cholinergic agonist on the rescue of locomotion deficits in *Vacht* mutants. These results show that both genetic and pharmacological interventions are capable of ameliorating deficits caused by a loss of VAChT function. Together, these studies could pave way for future strategies to treat behavioral deficits associated altered cholinergic signaling.

Disclosures: A.C. Blake: None. **M. Heredia:** None. **H.O. Lawal:** None.

Poster

780. Neurotransmitters and Signaling Molecules

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 780.21/E34

Topic: B.01. Neurotransmitters and Signaling Molecules

Support: NIH Grant NS046579

Title: Cortical disinhibition by ChAT expressing interneurons

Authors: *A. J. GRANGER[1], B. L. SABATINI[2];
[2]Neurobio., [1]Harvard Med. Sch., Boston, MA

Abstract: Acetylcholine is a major neurotransmitter and neuromodulator in the mammalian forebrain, important for maintaining alertness, directing attention, promoting learning, and mediating detection of salient sensory cues. In the cortex, acetylcholine can provide phasic depolarization of postsynaptic neurons through excitatory ionotropic receptors or tonic metabotropic modulation of cellular excitability and synaptic plasticity. However, we have recently shown that many cholinergic neurons also have the potential to transmit the inhibitory neurotransmitter GABA, fundamentally altering our view of how cholinergic neurons influence cortical circuits. To study the function of GABA/ACh cotransmission, we have focused on local ChAT-expressing cortical interneurons. In addition to ChAT, these neurons also express vasoactive intestinal peptide (VIP), and share a similar morphology and laminar distribution as previously described VIP interneurons. Activation of cortical ChAT interneurons results in GABA release onto all other classes of cortical interneurons, most prominently onto somatostatin-expressing interneurons, without inhibiting nearby pyramidal neurons. This suggests that ChAT neurons provide a GABAergic disinhibitory signal that acts in concert with acetylcholine release to promote cortical activity and plasticity.

Disclosures: A.J. Granger: None. **B.L. Sabatini:** None.

Poster

780. Neurotransmitters and Signaling Molecules

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 780.22/E35

Topic: B.01. Neurotransmitters and Signaling Molecules

Support: Gulbenkian Cambridge International Scholarship

Title: Effects of cholinergic activation on hippocampal local field potentials and a long-term spatial memory task

Authors: C. S. TANG, *O. PAULSEN;
Univ. of Cambridge, Cambridge, United Kingdom

Abstract: A variety of experiments have implicated the cholinergic system in attention, learning and memory. The hippocampus, which is important for spatial memory in rodents, receives a major cholinergic input from the medial septum. Here, we used transgenic mice expressing channelrhodopsin (ChR2) selectively in cholinergic neurons to investigate the effects of activation of medial septal cholinergic neurons on local field potentials (LFP) recorded in the hippocampus *in vivo* and how the activation of these neurons at various phases of a long-term spatial memory task impacted learning. This study used offspring of the ChAT-Cre line (mice expressing the Cre recombinase under the control of the choline acetyl-transferase promoter) crossed with the Cre-reporter Ai32 line bearing a Cre-dependent, enhanced YFP-tagged ChR2-containing expression cassette. For LFP recordings, mice were anaesthetised with urethane (1.2 gkg^{-1} i.p.) and their head fixed in a stereotaxic frame. An extracellular tungsten microelectrode (127 μm diameter, 2 MΩ) was lowered into the CA3 of the hippocampus for electrical recording and a stripped optical fibre (200 μm diameter, 0.22 NA) coupled to a 470 nm laser was lowered into the medial septum for optical activation. The appetitive Y-maze task was used to test spatial long-term memory. Mice were implanted with a 4 mm-long fibre optic cannula (200 μm, 0.22 NA) lowered into the medial septum and secured to the skull using dental cement. Activation of cholinergic neurons in urethane-anesthetized mice increased the power in the theta band (2–6 Hz) by 325 ± 85% (n = 10) and slow gamma band (20–40 Hz) by 225 ± 48% (n = 10), while slow oscillations (0.5–2 Hz) were suppressed to 58 ± 10% (n = 10). In the Y-maze task, in which the mice learned which arm of a 3-arm maze contains a food reward, cholinergic activation throughout the task significantly impaired learning. By day 3 of the testing period, the control group (n = 6) chose the rewarded arm in 92 ± 4% of trials while the group with cholinergic activation throughout the task (n = 6) chose the rewarded arm in only 60 ± 10% of trials (p = 0.02). Cholinergic activation only in the reward area also significantly impaired learning; these mice (n = 6) chose the correct arm in 55 ± 6% of trials on day 3 (p = 0.005), while mice receiving cholinergic activation during exploration only (n = 5) were largely unaffected, choosing the correct arm in 88 ± 6% of trials (p = 0.982). These results show that 1) cholinergic activation increases the power in the theta and slow gamma band while suppressing slow oscillations; and 2) tonic cholinergic activation, especially during reward consumption can impair learning of a long-term spatial memory task.

Disclosures: **C.S. Tang:** None. **O. Paulsen:** None.

Poster

780. Neurotransmitters and Signaling Molecules

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 780.23/E36

Topic: B.01. Neurotransmitters and Signaling Molecules

Support: NIH R01MH096946

NIH U01MH105971

NARSAD Young Investigator Grant

NIH R01NS075531

Title: Brain wide projectome of cholinergic neurons of the mouse basal forebrain

Authors: *Y. KIM[1,2], H. PI[2], S. RANADE[2], A. NARASIMHAN[2], P. OSTEN[2], A. KEPECS[2]; [1]Col. of Medicine, Penn State Univ., Hershey, PA; [2]Cold Spring Harbor Lab., Cold Spring Harbor, NY

Abstract: Cholinergic neurons in the basal forebrain play important roles in numerous brain functions, such as arousal and learning, while their degeneration has been implicated in brain disorders, including Alzheimer's disease. Previous studies have revealed the broad projection patterns of the cholinergic neurons across the brain, but quantiative knowledge on their projection patterns across the entire brain is limited. Here, we utilized serial two-photon tomography (STPT) based whole-brain imaging at cellular resolution to obtain complete brain-wide projection maps of basal forebrain cholinergic neurons. First we determined the distribution of all cholinergic neurons by crossing cholinergic neuron specific Cre driver (Chat-cre) with cre-dependent reporter labeling nucleus of the cells (LoxP-Stop-LoxP-H2B-GFP). STPT imaging with automated cell counting revealed the number and density of cholinergic neurons in the basal forebrain area; about 5,000 cell/mm3 in Magnocellular nucleus and diagonal band nucleus, and about 2,000 cell/mm3 in substantia innominata and medial septal nucleus. Second, we constructed brain wide projectome of the basal forebrain cholinergic neurons. To label axonal projections from cholinergic neurons, Cre-dependent adeno-associated virus expressing GFP was injected in Chat-cre mice systematically throughout the entire region of the basal forebrain. We quantified the GFP labeled axonal projections and determined their patterns of projection density across different regions ("projectome") across the entire brain. We found that cholinergic neurons along the anterior to postural basal forebrain axis (DB-SI-NB) provide topographic cortical projections in a diagonal pattern along a anterior-medial to posterior-lateral axis. Moreover, distinct subregions of cholinergic basal forebrain project to distinct sets of anatomical regions throughout the entire brain. In summary, the current results provide a comprehensive map of anatomical organization of cholinergic neurons in the basal forebrain.

Disclosures: Y. Kim: None. **H. Pi:** None. **S. Ranade:** None. **A. Narasimhan:** None. **P. Osten:** None. **A. Kepecs:** None.

Poster

780. Neurotransmitters and Signaling Molecules

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 780.24/E37

Topic: B.01. Neurotransmitters and Signaling Molecules

Support: Ribble Mini Grant

Title: Pharmacological identification of cholinergic receptor subtypes in modulation of a sensory-motor circuit in *Drosophila melanogaster*

Authors: *C. MALLOY[1], A. OMAR[2], E. SOMASUNDARAM[2], R. COOPER[2];
[1]Biol., [2]Univ. of Kentucky, Lexington, KY

Abstract: Acetylcholine (ACh) is an abundant neurotransmitter found in many species across various taxa. In mammals, it is known to be integral in modulating neural circuits underlying important processes such as learning, memory, and reward processing. In *Drosophila melanogaster*, ACh and the components mediating cholinergic signaling, exhibit comparable importance. It is the neurotransmitter used in peripheral sensory neurons and is the primary excitatory neurotransmitter within the CNS. The receptors that facilitate synaptic transmission at cholinergic synapses are divided into two broad subtypes: the ionotropic nicotinic acetylcholine receptors (nAChRs) and the metabotropic muscarinic acetylcholine receptors (mAChRs). This receptor classification is shared in both mammals and insects; however, both the pharmacological and functional characterization of these receptors within the *Drosophila* nervous system has lagged behind its mammalian model counterparts. In order to further classification of these receptors in the nervous system of a model organism that has become vital to neuroscientists across the globe, we have used a combined behavioral and electrophysiological approach to identify important cholinergic receptor subtypes within the *Drosophila* CNS that may be crucial in modulating defined neural circuits. We have exposed intact *Drosophila* 3rd instar larvae to various concentrations of ACh agonists and antagonists by way of feeding to observe modulation of locomotion. In addition, we have utilized a well-characterized electrophysiological approach to assess the efficacy of a defined sensory-CNS-motor circuit in the presence of cholinergic agonists and antagonists exposed directly to the CNS of a semi-intact larval preparation. Preliminary results suggest that exposing the CNS directly to ACh and agonists, nicotine and muscarine, enhances electrical activity of a sensory-CNS-motor circuit. Conversely, acute feeding of nicotine and acetylcholine suppresses locomotion. These results suggest both nAChRs and mAChRs within the CNS may act to modulate a motor circuit which mediates general locomotion in larval *Drosophila*.

Disclosures: **C. Malloy:** None. **A. Omar:** None. **E. Somasundaram:** None. **R. Cooper:** None.

Poster

780. Neurotransmitters and Signaling Molecules

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 780.25/E38

Topic: B.01. Neurotransmitters and Signaling Molecules

Support: NIH Grant NS077989

Title: Overexpression of vesicular acetylcholine transporter in ChAT-ChR2-EYFP transgenic mice alters short-term synaptic plasticity at cholinergic synapses

Authors: *J. O'MALLEY, R. DASGUPTA, F. SEIBT, M. BEIERLEIN;
Neurobio. and Anat., McGovern Med. Sch. At Uthealth, Houston, TX

Abstract: Release of acetylcholine from cholinergic afferents controls diverse cognitive functions, including learning and memory, sensory processing, and attention. Our understanding of cholinergic signaling and its role in controlling distinct cell types, neuronal circuits, and behavior has greatly benefited from genetic strategies aimed to express channelrhodopsin-2 (ChR2) specifically in choline acetyltransferase (ChAT) positive neurons. One such strategy has been the development of bacterial artificial chromosome (BAC) transgenic mouse models that express ChR2 under the control of the ChAT promoter (ChAT-ChR2-EYFP). However, ChAT-ChR2-EYFP mice also carry several additional copies of the vesicular acetylcholine transporter gene (VAChT), resulting in overexpression of functional VAChT. Behaviorally, ChAT-ChR2-EYFP mice display enhanced motor endurance and a number of cognitive defects, including impaired attention and memory. It remains unknown how VAChT overexpression influences cholinergic synaptic signaling. We have addressed this question by characterizing electrical stimulation-evoked cholinergic synaptic responses in neurons of the thalamic reticular nucleus (TRN), in slices of wild-type (WT) and ChAT-ChR2-EYFP transgenic mice. For both mouse lines, single stimuli led to biphasic E-I responses mediated by nicotinic ACh receptors (nAChRs) and muscarinic ACh receptors (mAChRs), respectively. However, isolated nAChR-mediated EPSCs (nEPSCs) displayed faster decay kinetics in transgenic animals as compared to WT. Furthermore, we found that for transgenic animals nEPSCs evoked by stimulus trains displayed reduced short-term synaptic depression, suggesting more efficient synaptic vesicle refilling during ongoing synaptic activity. Our findings suggest that overexpression of VAChT leads to distinct alterations in cholinergic synaptic transmission and short-term plasticity.

Disclosures: **J. O'Malley:** None. **R. Dasgupta:** None. **F. Seibt:** None. **M. Beierlein:** None.

Poster

780. Neurotransmitters and Signaling Molecules

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 780.26/DP02 (Dynamic Poster)

Topic: B.01. Neurotransmitters and Signaling Molecules

Support: NIH RO1 GM098578

Department of Anesthesiology

Title: Modulation of cholinergic, but not noradrenergic, signaling in rat prefrontal cortex reverses traits of sevoflurane anesthesia

Authors: *D. PAL, B. H. SILVERSTEIN, D. LI, S. WISIDAGAMAGE, G. A. MASHOUR; Dept. of Anesthesiol., Univ. of Michigan, Ann Arbor, MI

Abstract: Systemic infusion of cholinergic and aminergic agents - as well as direct manipulation of subcortical sites in forebrain, thalamus, and brainstem - produce signs of behavioral arousal during general anesthesia.[1-6] However, the role of top-down or cortical processes in the states of arousal is not clear. In this study, we investigated the effect of increase in cholinergic and noradrenergic tone in rat prefrontal cortex (PFC) during sevoflurane anesthesia (2.0-2.2 %) on behavioral states. Male Sprague-Dawley rats (300-350g) were surgically implanted with 1) screw electrodes to record monopolar electroencephalogram (EEG) across the cortex, and 2) a guide tube in PFC for dialysis delivery of either carbachol (N=9, 5mM) or noradrenaline (N=9, 20mM), and simultaneous measurement of changes in local acetylcholine (ACh) levels. Carbachol-induced changes in local ACh levels were quantified using high performance liquid chromatography while noradrenaline-induced changes will be analyzed using mass spectrometry. We demonstrate that carbachol in rat PFC during sevoflurane anesthesia caused a significant increase in local ACh levels ($p<0.001$) and produced signs of behavioral arousal (limb and torso movements, increased respiratory rate) and EEG activation in all rats. In addition, 4/9 rats were able to regain righting reflex and showed complete mobility while still inhaling clinically-relevant concentrations of sevoflurane anesthesia. By contrast, infusion of noradrenaline into PFC did not produce any effect on behavioral state but did cause a transient desynchronization of EEG. These results suggest that cholinergic signaling in rat PFC contributes to top-down control of arousal state. **References:** 1. Meuret et al. (2000) Anesthesiology 93:708-717. 2. Hudetz et al. (2003) Anesthesiology 99:1125-1131. 3. Solt et al. (2011) Anesthesiology 115:791-803. 4. Pillay et al. (2011) Anesthesiology 115:733-442. 5. Alkire et al (2007) Anesthesiology 107:264-272. 6. Solt et al. 2014, Anesthesiology 121:311-319.

Disclosures: D. Pal: None. **B.H. Silverstein:** None. **D. Li:** None. **S. Wisidagamage:** None. **G.A. Mashour:** None.

Poster

780. Neurotransmitters and Signaling Molecules

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 780.27/F1

Topic: B.01. Neurotransmitters and Signaling Molecules

Support: NIH Grant R44 DA031578-02

NIH grant HL70029

Title: Inhalation of cigarette smoking-relevant nicotine aerosol induces cardiac arrhythmia leading to systemic and uterine hemodynamic disruption in pregnant rats

Authors: *X. M. SHAO[1], H. E. LÓPEZ-VALDÉS[3], J. LIANG[2], J. L. FELDMAN[1];
[1]Neurobio., [2]Mol. and Med. Pharmacol., David Geffen Sch. Med. at UCLA, Los Angeles, CA;
[3]Res. Division,, Fac. of Medicine, Univ. Nacional Autónoma de México, Mexico City, Mexico

Abstract: Maternal smoking is associated with preterm delivery, low birth weight, sudden infant death syndrome and developmental defects of neonates. We tested the hypothesis that cigarette smoking-relevant nicotine exposure in pregnancy induces disruption of systemic and local uterine hemodynamics that decreases blood flow to the uterus and placenta leading to fetal ischemia. Blood pressure (BP) was continuously recorded via a femoral artery catheter and ECG was simultaneously recorded with subcutaneous needle electrodes from awake, constrained pregnant rats. A perivascular ultrasound flowprobe was chronically implanted on the uterine artery for continuous blood flow measurement. With a newly developed non-invasive, alveolar region-targeted aerosol method to deliver nicotine to pregnant rats, controllable amounts of nicotine got into the systemic circulation and the brain quickly producing nicotine pharmacokinetics in both arterial and venous blood resembling that of smoking a cigarette in humans. Nicotine aerosol inhalation induced cardiac arrhythmia and high magnitude irregular fluctuation of systemic BP. The arrhythmia included sinus bradycardia, sinus arrhythmia, atrioventricular (A-V) block 1^{o} and 2^{o} (Wenckebach), atrial premature beats, atrial tachycardia, ventricular premature beats, ventricular tachycardia. Nicotine aerosol inhalation also induced a reduction and high magnitude irregular fluctuation of uterine artery blood flow. These effects were transient, starting 3 to 10 seconds from the start of nicotine aerosol exposure with hemodynamics recovering within 1-2 min in the presence of nicotine. These effects could be blocked by i.p. injection of the nicotinic acetylcholine receptor (nAChR) antagonist mecamylamine. Our data suggest that nicotine aerosol exposure resulting in a rapid rise of arterial blood nicotine concentration with pharmacokinetics similar to cigarette smoking stimulates and then desensitizes nAChRs in the autonomic nervous system that induces cardiac arrhythmia leading to systemic and uterine hemodynamic disruption, as well as constriction of the uterine artery resulting in a reduction in uterine artery blood flow. Transient hemodynamic

disruption result from smoking can lead to placental and fetal ischemia that could potentiate the risk of pregnancy complications and developmental disorders known to associate with maternal smoking. In addition, arrhythmia and hemodynamic disruption can put adult life at risk by inducing cardiac ischemia, heart failure and stroke. These findings challenge the safety of inhalation of pure nicotine as an alternative for cigarette smoking, such as E-cigarettes.

Disclosures: X.M. Shao: None. **H.E. López-Valdés:** None. **J. Liang:** None. **J.L. Feldman:** None.

Poster

780. Neurotransmitters and Signaling Molecules

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 780.28/F2

Topic: B.01. Neurotransmitters and Signaling Molecules

Support: Long Term Organization Development Plan – 1011

Czech Science Foundation No. GA15-16701S

Title: 7-Methoxytacrine - 4-pyridinealdoxime hybrid as novel prophylactic agent with reactivation properties in organophosphate intoxications

Authors: *O. SOUKUP[1], J. KORABECNY[2], E. NEPOVIMOVA[2], D. JUN[3], K. KUCA[4]; [1]Univ. of Defence, Hradec Kralove, Czech Republic; [2]Univ. of Def., Hradec Kralove, Czech Republic; [3]Univ. of Defese, Hradec Kralove, Czech Republic; [4]Univ. Hosp. Hradec Kralove, Hradec Kralove, Czech Republic

Abstract: Chemical warfare agents constitute an increasing threat to both military and civilian population. Therefore, effective prophylactic approach is urgently needed. Herein, we present novel hybrid compound able not only to keep acetylcholinesterase resistant to organophosphate (OP) inhibitors, but also to serve as enzyme reactivator in case of OP intoxication. We describe novel promising prophylactic approach exploitable in case of OP intoxications. Encouraging in vitro results should, however, be approved by in vivo tests prior to determination of its real therapeutic value.

Disclosures: O. Soukup: None. **J. Korabecny:** None. **E. Nepovimova:** None. **D. Jun:** None. **K. Kuca:** None.

Poster

781. G-Protein-Coupled Receptors

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 781.01/F3

Topic: B.03. G-Protein Coupled Receptors

Support: MH105482

Title: Role of membrane anchoring of RGS7 in regulating $GABA_B$-GIRK in hippocampus

Authors: *O. I. OSTROVSKAYA, C. ORLANDI, K. A. MARTEMYANOV;
Dept. Neurosci., The Scripps Res. Inst., Jupiter, FL

Abstract: Disruption of G protein Coupled Receptor (GPCR) signaling substantially contributes to the etiology of mental disorders. Agonist-bound GPCRs initiate multiple signaling reactions by switching G proteins from inactive GDP-bound to active GTP-bound state. Regulators of G-protein signaling (RGS) proteins speed up GTP hydrolysis on an activated Gα subunit, thus ensuring sharp cessation of the signal. Recently, we discovered that a member of RGS family RGS7 is involved in hippocampal learning and memory by negatively regulating signaling from $GABA_B$ receptors to G protein gated Inwardly Rectifying K+ (GIRK) channels. It is thought that effective regulation of GPCR signaling requires targeting of RGS proteins to the plasma membrane. RGS7 has been shown to directly interact with two membrane proteins: R7BP and GPR158, which anchor RGS7 to the plasma membrane and impact its stability and activity. However, the relevance of these anchoring mechanisms to regulation of $GABA_B$-GIRK signaling in the endogenous setting is unknown. In this work we elucidated the role of GPR158 and R7BP in the ability of RGS7 to regulate hippocampal $GABA_B$-GIRK signaling. First, using in-situ hybridization we established that all hippocampal neurons coexpress R7BP and GPR158 together with RGS7. Knockout (KO) of R7BP or GPR158 alone had modest effects on membrane localization of RGS7, however concurrent elimination of both R7BP and GPR158 (DKO) resulted in almost complete loss of RGS7 from the membrane fraction. Next, using patch clamp whole-cell electrophysiology we studied the impact of GPR158 and R7BP ablation on GIRK channel kinetics in response to its activation by $GABA_B$ receptors in hippocampal primary cultures. While we detected impact of R7BP ablation on deactivation of GIRK currents, no such effect was present in GPR158 KO neurons. Furthermore, DKO pyramidal neurons were indistinguishable from R7BP KO, suggesting that GPR158 does not further contribute to GIRK regulation in neonatal neurons. Interestingly, we found that GPR158 expression undergoes induction late in brain development. Therefore, we next studied the impact of R7BP and GPR158 on $GABA_B$-GIRK signaling in slices from adult animals. Ablation of RGS7 significantly delayed the decay of slow Inhibitory Postsynaptic Currents (sIPSCs) in CA1 pyramidal neurons known to be mediated by $GABA_B$-GIRK. KO of either GPR158 or R7BP alone was similar to wild-type

neurons. However, DKO sIPSCs showed significantly delayed deactivation. Thus we conclude that R7BP and GPR158 play a redundant role in regulation of GABAB-GIRK signaling in hippocampal neurons by controlling membrane targeting of RGS7 complexes.

Disclosures: O.I. Ostrovskaya: None. **C. Orlandi:** None. **K.A. Martemyanov:** None.

Poster

781. G-Protein-Coupled Receptors

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 781.02/F4

Topic: B.03. G-Protein Coupled Receptors

Support: NIH Grant MH105482

Title: The orphan receptor GPR158 is a novel stress-induced modulator of signaling in depression

Authors: *C. ORLANDI, L. P. SUTTON, C. SONG, B. S. MUNTEAN, K. A. MARTEMYANOV;
Neurosci., The Scripps Res. Inst. (TSRI), Jupiter, FL

Abstract: Mood disorders are among the most common and debilitating neurological disorders, but their molecular basis are not fully understood. The inability of dealing with enduring stressful events leads to depression in almost 7% of the U.S. population. Current antidepressant treatments potentiate serotonin (5HT) and norepinephrine (NE) neurotransmission by blocking their synaptic reuptake or degradation. Unfortunately these drugs require weeks to be effective and fail in 50% of the cases. The search for new potential targets is therefore a priority to generate more effective drugs. Most of the post-synaptic receptors of 5HT and NE are G protein coupled receptors (GPCR) hence understanding the G protein signaling regulation in critical brain regions such as the medial prefrontal cortex is fundamental to gain insight in the processes that lead to depression. We found that the expression of the orphan receptor GPR158 in the medial prefrontal cortex is induced by chronic stress. At the molecular level, GPR158 forms complexes with the Regulator of G protein Signaling 7 (RGS7) protein and serves as a positive modulator of its activity. Our working model suggests that GPR158-RGS7 complex negatively regulates the signaling of several GPCRs instead of activating G proteins as classical neurotransmitter receptors do. We found that stress up-regulates GPR158 levels resulting in increased recruitment of RGS7 to the plasma membrane. To investigate the physiological relevance of GPR158-RGS7 complex we generated GPR158 and RGS7 knockout (KO) mice and measured their performance in a battery of behavioral tasks. We found that both GPR158 KO

and RGS7 KO mice show a robust antidepressant- and anxiolytic-like phenotype compared to their wild type littermates. When exposed to chronic mild stress the KO mice showed resilience and these data were supported by a reduced stress-induced hyperthermia. To examine which GPCR signaling are modulated by GPR158-RGS7 we treated mice with antagonists of several GPCRs known to have a role in mood control. We found that treatments with α2A-adrenergic receptor antagonists reversed the antidepressant-like phenotype in GPR158 KO mice without affecting the performance of WT in the tail suspension test. We conclude that the GPR158-RGS7 complex regulates NE signaling in the brain. Our evidence suggests that the GPR158-RGS7 complex is a novel player with a unique role in mood regulation in response to chronic stress. We hope that these findings may lead to a better knowledge of the pathophysiology of depression while uncovering a new pharmacological target for preventing detrimental effects of chronic stress and improving treatments for mood disorders.

Disclosures: **C. Orlandi:** None. **L.P. Sutton:** None. **C. Song:** None. **B.S. Muntean:** None. **K.A. Martemyanov:** None.

Poster

781. G-Protein-Coupled Receptors

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 781.03/F5

Topic: B.03. G-Protein Coupled Receptors

Support: MH105482

Title: Orphan receptor GPR158 modulates intrinsic excitability and synaptic transmission of layer 2/3 neurons in prelimbic cortex

Authors: *C. SONG, C. ORLANDI, L. P. SUTTON, K. A. MARTEMYANOV;
Dept. of Neurosci., The Scripps Res. Inst., Jupiter, FL

Abstract: G protein coupled receptors (GPCRs) are a large and diverse family of receptors that have become the most important targets in modern pharmacology. Growing evidence suggests that GPCRs play critical roles in mood disorders and their treatments. We have recently found that the orphan receptor GPR158 plays a role in emotional control and is highly expressed in the prefrontal cortex. The current study aimed at determining the cellular mechanisms of GPR158 action underlying behavioral effects. We utilized whole-cell patch-clamp recordings to examine the effect of GPR158 deletion (KO) on electrophysiological properties of pyramidal neurons in prelimbic (PL) area. We focused on these neurons because this area is critical for emotional control. First, we determined that GPR158 KO does not significantly change

electrophysiological properties of layer 5 PL neurons. In contrast, layer 2/3 neurons were significantly affected. Analysis of the data (48 neurons from 20 mice) revealed that the intrinsic excitability was significantly increased in GPR158 KO neurons compared to wild type (WT) neurons ($p < 0.01$), as evidenced by KO neurons firing more spikes in response to depolarizing current injection (all neurons were held at -70 mV). In addition, GPR158 KO neurons displayed larger input resistance and lower rheobase current ($p < 0.05$ for both measurements). Interestingly, increase intracellular cAMP levels by adding Sp-cAMPs into the internal solutions for WT but not KO neurons mimicked the effect of GPR158 KO, suggesting GPR158 suppresses intrinsic excitability through modulating intracellular cAMP level. Furthermore, the frequency but not amplitude of spontaneous excitatory postsynaptic currents (sEPSC) was increased in GPR158 KO neurons ($p < 0.05$), suggesting that GPR158 also modulates synaptic transmission. Consistent with this, the AMPA/NMDA current ratio was significantly increased in GPR158 KO neurons compared with WT neurons ($p < 0.05$). Analysis of confocal images from biocytin-labled neurons indicates that GPR158 KO significantly increases the spine density of apical dendrites. Taken together, these data suggest that GPR158 modulates both intrinsic excitability and synaptic transmission of L2/3 pyramidal neurons in prelimbic area, and may be a potential target for novel anti-depressants.

Disclosures: **C. Song:** None. **C. Orlandi:** None. **L.P. Sutton:** None. **K.A. Martemyanov:** None.

Poster

781. G-Protein-Coupled Receptors

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 781.04/F6

Topic: B.03. G-Protein Coupled Receptors

Support: NARSAD Young Investigator (DJF)

F32MH095285 (DJF)

Tourette Association of America (ZX)

R01MH086601 (CKJ)

R01MH073676 (PJC)

DMRF Foundation (PJC)

Title: M_4 activation reduces striatal dopamine release and has antipsychotic-like effects via a CB_2 cannabinoid receptor-dependent mechanism

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[1]Vanderbilt Ctr. For Neurosci. Drug Discovery, Nashville, TN; [2]Mol. Signaling Section, Lab. of Bioorganic Chem., Natl. Inst. of Diabetes and Digestive and Kidney Dis., Bethesda, MD; [3]Chem., [4]Mol. Physiol. and Biophysics, Vanderbilt Univ., Nashville, TN

Abstract: Muscarinic receptors represent a promising therapeutic target for schizophrenia, but the mechanisms underlying the antipsychotic efficacy of muscarinic modulators are not well understood. Two seminal clinical studies have demonstrated that the M_1/M_4 preferring agonist xanomeline can provide significant therapeutic efficacy in treating psychosis in patients with Alzheimer's disease or schizophrenia. Unfortunately gastrointestinal side-effects, likely mediated by M_2/M_3 receptors, have removed xanomeline from consideration for clinical use. However, these studies suggest that compounds that selectively modulate M_1 and/or M_4 could be therapeutically beneficial in treating psychosis. Recent reports utilizing novel subtype-selective M_4 positive allosteric modulators (PAMs) have demonstrated efficacy in several preclinical models of psychosis. However, the mechanism whereby M_4 can mediate these antipsychotic-like effects is unclear. Here we report that activation of M_4 receptors on medium spiny neurons results in a novel form of dopaminergic regulation resulting in sustained depression of striatal dopamine release that is observed more than 30 minutes after removal of mAChR agonist. This suppression of dopamine release was not dependent on intracellular Ca^{2+} signaling but was completely blocked by pretreatment with the DAG-Lipase inhibitor DO34. Furthermore, both the M_4-mediated sustained inhibition of dopamine release and the antipsychotic-like efficacy in reversing disrupted pre-pulse inhibition were found to require intact signaling through CB_2 cannabinoid receptors. These findings highlight a novel mechanism by which striatal cholinergic and cannabinoid signaling leads to sustained reductions in dopaminergic transmission and concurrent behavioral effects predictive of antipsychotic efficacy.

Disclosures: **D.J. Foster:** None. **J.M. Wilson:** None. **M.S. Mahmood:** None. **D.H. Remke:** None. **J. Wess:** None. **L.J. Marnett:** None. **S. Patel:** None. **C.M. Niswender:** C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); AstraZeneca. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Is an inventor on patents protecting M4 PAMs. **C.K. Jones:** C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); AstraZeneca. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Is an inventor on patents protecting M4 PAMs. **Z. Xiang:** None. **C.W. Lindsley:** C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); AstraZeneca. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Is an inventor on patents protecting M4 PAMs. **J.M. Rook:** None. **P.J. Conn:** C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); AstraZeneca. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property

rights/patent holder, excluding diversified mutual funds); Is an inventor on patents protecting M4 PAMs.

Poster

781. G-Protein-Coupled Receptors

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 781.05/F7

Topic: B.03. G-Protein Coupled Receptors

Support: American Heart Association (AHA) 16POST127770113

Title: Tubulin acetylation translocates $G\alpha_s$ from lipid-rafts: a novel mechanism for antidepressant effects of HDAC-6 inhibitors

Authors: *H. SINGH[1], J. SCHAPPI[2], A. PRADHAN[3], M. RASENICK[4,5];
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Abstract: Histone deacetylase-6 (HDAC-6) enzymes deacetylate α-tubulin and have been shown to be upregulated during depression. HDAC6 knockout or HDAC6 inhibitors displayed an antidepressant profile in animal models. Thus, while, a possible role for HDAC6 inhibitors in treatment of depression exists, the potential mechanism for this remains elusive. Previously, our group has shown that treatment of rats or C6 glioma cells with several classes of antidepressant drugs results in facilitation of the activity of the G-protein, $G\alpha_s$, by translocating it from membrane microdomains (lipid-rafts) inducing a sustained elevation in cAMP production. Studies have also demonstrated interplay between tubulin and $G\alpha_s$ in lipid-rafts. Once out of lipid-raft domains, $G\alpha_s$, couples with adenylyl cyclase 6 (AC6). Although $G\alpha_s$ interacts directly with tubulin to modify microtubule dynamics, tubulin also acts as an anchor for $G\alpha_s$ in lipid rafts. Based on established HDAC-6 roles in modifying tubulin acetylation and our data showing $G\alpha_s$ interactions with tubulin in lipid-raft domains, we hypothesized that acetylation of α-tubulin disrupts tubulin-$G\alpha_s$ anchoring, rendering $G\alpha_s$ free to activate AC. To test this, C6 glial cells were treated with the HDAC-6 inhibitor, tubastatin-A. Acetylation status of α-tubulin and localization of $G\alpha_s$ subunit in/out of lipid-raft membrane domains was studied. Chronic treatment with tubastatin-A not only increased acetylation of α-tubulin but also translocated $G\alpha_s$ from lipid-rafts, without changing total $G\alpha_s$. Fluorescence Recovery After Photobleaching (FRAP) on C6 cells stably expressing GFP-$G\alpha_s$, was conducted and cells treated for three days with tubastatin-A showed an "antidepressant signature". Finally, sustained elevation of cAMP was revealed by increased cAMP response element binding protein (CREB) phosphorylation and

increased expression of brain derived neurotrophic factor (BDNF). An increase in acetylated α-tubulin accompanied tubastatin-A treatment and acetylated α-tubulin prevented the formation of tubulin-$G\alpha_s$-complexes in lipid rafts. This did not appear to be a mechanism shared with other classes of antidepressants These findings suggest HDAC6 inhibition shows some commonality with traditional antidepressants. Therefore, compounds that decrease tubulin-$G\alpha_s$ interactions by increasing acetylation of a α-tubulin may show promise for antidepressant therapy.

Disclosures: H. Singh: None. **J. Schappi:** None. **A. Pradhan:** None. **M. Rasenick:** A. Employment/Salary (full or part-time): University of Illinois at Chicago. B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution; NIMH T32 MH0667631, VA Merit Award BX001149-01, NCCIH RO1AT009169, NIAAA P50 AA022538. C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Eli Lilly, Lundbeck. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); PAX Neuroscience. F. Consulting Fees (e.g., advisory boards); Pfizer, Takeda.

Poster

781. G-Protein-Coupled Receptors

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 781.06/F8

Topic: B.03. G-Protein Coupled Receptors

Support: NIMH T32 MH0667631

VA Merit Award BX001149-01

NCCIH R01AT009169

NIAAA P50 AA022538

Title: Sustained antidepressant treatment increases cAMP signaling by translocating $G\alpha_s$ from lipid rafts and increasing association with type 6 adenylyl cyclase (AC6): a process independent of monoamine transporters.

Authors: *J. SCHAPPI[1], M. RASENICK[2];
[1]Physiol. & Biophysics, Univ. of Illinois At Chicago, Chicago, IL; [2]Physiol. and Biophysics, Psychiatry, Univ. of Illinois at Chicago, Chicago, IL

Abstract: Antidepressants of different chemical classes promote a sustained increase in cAMP, due, at least in part to the redistribution of $G_{\alpha}s$ from lipid rafts into non-raft membrane fractions. The net result of this redistribution is increased $G\alpha_s$ coupling with, and activation of, adenylyl cyclase (AC). This has been demonstrated, in both rats and cultured neural and glial cells by a number of techniques, including cell fractionation, functional assays, and imaging studies such as FRAP (Fluorescence Recovery After Photobleaching). Unlike animal models, C6 glioma lack monoamine reuptake transporters, suggesting that mechanisms of antidepressant response entails more than inhibition of neurotransmitter reuptake transporters or inhibition of monoamine breakdown. This is noteworthy, since inhibition of 5HT or NE uptake is quite rapid even though clinical effects of antidepressants require several weeks (and several days in the cellular models). Furthermore, while these neural and glial cells showed an "antidepressant response", $G\alpha_s$ localization and cAMP production in kidney epithelial cells like COS1 and HEK293 were unchanged by antidepressant treatment. Similarly, membranes from liver and kidney of rats treated chronically with antidepressant did not show the same response as brain from those same animals. In this study we sought to determine whether cellular antidepressant response, with respect to increased cAMP signaling and $G\alpha_s$ localization, is dependent on the type of AC isoform expression. Cell lines "insensitive" to antidepressant treatment, such as HEK293, become responsive after transfection with AC6, showing translocation of $G\alpha_s$ from lipid rafts, both by cell fractionation and by FRAP. Likewise, knockdown of AC6 but not other adenylyl cyclase isoforms abolishes the antidepressant response in responsive cell lines such as C6 glioma. Thus, it is suggested that AC6 performs an anchoring function for $G\alpha_s$ outside of rafts, affixing the translocated $G\alpha_s$ into the non-raft domain and facilitating an antidepressant-induced increase in adenylyl cyclase activity.

Disclosures: J. Schappi: None. **M. Rasenick:** C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Eli Lilly, Lundbeck. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Pax Neuroscience. F. Consulting Fees (e.g., advisory boards); Pfizer, Takeda.

Poster

781. G-Protein-Coupled Receptors

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 781.07/F9

Topic: B.03. G-Protein Coupled Receptors

Support: NIMH T32 MH0667631

VA Merit Award BX001149-01

NCCIH R01AT009169

Title: A cellular model for ketamine antidepressant action reveals an NMDA-receptor independent mechanism: roles for $G\alpha_s$ lipid rafts and cyclic AMP

Authors: *N. WRAY[1], J. SCHAPPI[2], M. RASENICK[3];
[1]physiology and biophysics, Univ. of Illinois at Chicago Dept. of Physiol. and Biophysics, Chicago, IL; [2]Physiol. and Biophysics, [3]Physiol. and Biophysics, Psychiatry, Univ. of Illinois at Chicago, Chicago, IL

Abstract: Previous studies have demonstrated that all extant classes of antidepressants increase coupling between the G protein, $G\alpha_s$ and adenylyl cyclase, resulting in persistent cAMP elevation. This effect requires sustained drug treatment and is observed after 3 days in cultured neural or glial cells or 3 weeks in rats. This is apparently due to $G\alpha_s$ being released from constraints of a lipid raft environment to cholesterol-poor regions of the plasma membrane. Consistent with this, both peripheral tissue and postmortem brain from depressed human subjects show a greater proportion of $G\alpha_s$ in lipid rafts. While most antidepressants require several weeks for a clinical effect, ketamine appears to alleviate depression within hours, only to relapse after several days. In an effort to determine whether ketamine showed an antidepressant biosignature similar to other antidepressants, studies in cultured cells were initiated. It was hypothesized that ketamine would have an effect similar to antidepressants but along a shorter time course. C6 cells were treated with 1uM ketamine, harvested and lipid raft fractions prepared and the amount of $G\alpha_s$ was assessed by Western blot. C6 cells with a stable fluorescent $G\alpha_s$ fusion protein (GFP-$G\alpha_s$) was treated similarly with ketamine and the mobility of GFP-$G\alpha_s$ was determined by Fluorescence Recovery after Photobleaching (FRAP). Brief ketamine treatment evokes a biochemical hallmark (translocation of $G\alpha_s$) seen after prolonged treatment with several species of drugs with established antidepressant activity. This is not mimicked by other NMDA antagonists, suggesting an additional site for ketamine action. The ketamine induced $G\alpha_s$ translocation allows increased functional coupling of $G\alpha_s$ and adenylyl cyclase to increase intracellular cyclic adenosine monophosphate (cAMP). Furthermore, increased intracellular cAMP mediates phosphorylation of cAMP response element-binding protein (CREB), which increases BDNF levels. BDNF production was indeed dependent on cAMP as the cAMP antagonist Rp-cAMPS attenuated BDNF expression levels. Furthermore, BDNF expression was also seen in primary astrocytes after ketamine treatment and attenuated by Rp-cAMPs. These results reveal a novel antidepressant mechanism mediated by acute ketamine treatment in glial cells that may contribute to ketamine's antidepressant effect. Furthermore, the translocation of GFP-$G\alpha_s$ produced by ketamine and all tested compounds with antidepressant activity (but not mood-stabilizers, antipsychotics or anxiolytics) might serve as a useful platform for identifying compounds with potential antidepressant activity and for predicting clinical response.

Disclosures: **N. Wray:** None. **J. Schappi:** None. **M. Rasenick:** C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Eli Lilly, Lundbeck. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Pax Neuroscience. F. Consulting Fees (e.g., advisory boards); Pfizer, Takeda.

Poster

781. G-Protein-Coupled Receptors

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 781.08/F10

Topic: B.03. G-Protein Coupled Receptors

Support: MOST 104-2811-B-006-065

Title: TIAM2S-mediated hippocampal neural circuitry shapes affective behaviors via non-canonical, GEF-independent signaling

Authors: *C.-H. CHU[1], J.-S. CHEN[2], H. S. SUN[1,2];
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Abstract: Human T-cell lymphoma invasion and metastasis 2 (TIAM2), a member of the guanine nucleotide exchange factor (GEF) family, physiologically exists either in a long or short transcripts. The protein translated from short-TIAM2 mRNA (TIAM2S) has been noted for its ability to control the proliferation and metastasis of human cancer cells. However, it is unclear if this molecule plays a non-oncogenic role in regulating the function of normal physiology such as nervous systems. Our findings revealed that TIAM2S protein is abundant in normal brain, especially concentrating in neuronal cells of the limbic system such as hippocampus, where the long form of TIAM2 (TAIM2L) protein is undetectable. Up-regulation of TIAM2S protein induction was located in the nuclear during the period of NT2/N cells. Suppression of TIAM2S impacted on neurite outgrowth of NT2/N cells, but not its differentiation. By contrast, overexpressed TIAM2S prompted neurite outgrowth in SH-SY5Y neuroblastoma cells via a GEP-independent signals. To determine if dysregulation of TIAM2S can alter brain structural plasticity in order to cause any abnormal behaviors, transgenic mice for overexpressed human TIAM2S were created and examined by multiple animal behavioral tests plus magnetic resonance imaging (MRI) analysis with T2 and DTI pulse sequences. TIAM2S transgenic mice displayed increases of both locomotion activity and social interaction, along with depression-like behaviors. Furthermore, MRI analysis revealed that overexpressed human TIAM2S remodeled the axonal organization in the hippocampus. Taken together, our results indicated that the brain-enriched TIAM2S protein plays an important role in shaping affective behaviors via modulating formation of neuronal connections and plasticity in hippocampus regardless of GEF activity.

Disclosures: **C. Chu:** None. **J. Chen:** None. **H.S. Sun:** None.

Poster

781. G-Protein-Coupled Receptors

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 781.09/F11

Topic: B.03. G-Protein Coupled Receptors

Support: NIH grant NS084398

A research grant from Ono Pharmaceutical Co.

Title: A new class of lipid mediator: Phosphorylated N-acylethanolamines and their receptors

Authors: *Y. KIHARA[1], H. MIZUNO[2], D. SHEFFLER[3], R. RIVERA[2], J. CHUN[2];
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Abstract: Lysophospholipids, such as lysophosphatidic acid (LPA) and sphingosine 1-phospate (S1P), are known as lipid mediators that regulate neural development, proliferation and differentiation. LPA and S1P bind to their specific G protein-coupled receptors (GPCRs), LPA1-6 and S1P1-5, respectively (Br J Pharmacol., 171:3575-94, 2014). We recently reported a crystal structure of LPA1, which identified phosphorylated-anandamide (pAEA) - a cannabinoid metabolite - as a signaling molecules acting through LPA1 (Cell, 161:1633-1643, 2015). Importantly, pAEA induced neurite retraction on rat B103 neural cell lines heterologously expressing LPA1, implying that pAEA is a new class of lipid neuromodulator. Found in mouse brain, pAEA is produced from N-arachidonoyl phosphatidylethanolamine through cleavage by phospholipase D. pAEA is subsequently dephosphorylated by phosphatases, resulting in anandamide (AEA), which acts on cannabinoid receptors, CB1 and CB2 (PNAS 103:13345-13350, 2006). Here, we evaluate the effects of phosphorylated N-acylethanolamines (pNEA) on additional LPA receptor subtypes. pNEA species transduce calcium signaling through LPA1 and LPA5 at concentrations equivalent to LPA, indicating crosstalk between LPA and endo-cannabinoid systems. Furthermore, we conducted a GPCR screen to identify novel pAEA receptors that successfully identified up LPA1 and LPA5, as well additional receptors hits, which are currently being validated. We propose that pNEA is a novel lipid mediator acting through GPCRs in the CNS, and provide biochemical linkage between the lysophospholipid and cannabinoid pathways.

Disclosures: **Y. Kihara:** None. **H. Mizuno:** A. Employment/Salary (full or part-time): Ono Pharmaceutical Co., Ltd.. **D. Sheffler:** None. **R. Rivera:** None. **J. Chun:** B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution; Ono Pharmaceutical Co, NIH (NS084398).

Poster

781. G-Protein-Coupled Receptors

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 781.10/F12

Topic: B.03. G-Protein Coupled Receptors

Support: Kiban-Kennkyu (B): 18390392, 22390273 from Japanese Ministry of Education, Culture, Sports, Science and Technology

grant from Indian Council of Agricultural Research (ICAR), New Delhi, India under ICAR International Fellowship 2010-11, No: 29-1/2009-EQR/Edn

Title: Role of gpr40 for pufa-mediated bdnf synthesis

Authors: *T. YAMASHIMA, A. MATHIVANAN;
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Abstract: Background: Polyunsaturated fatty acids (PUFA) are known to be crucial for learning and memory. However, the detailed mechanism of PUFA effects upon neuronal functions remains almost unknown except for the possible facilitation of membrane fluidity. G-protein coupled receptor 40 (GPR40) was found to induce Ca^{2+} mobilization in response to diverse PUFA. Thereafter, the authors found GPR40 expression in the newborn neurons of the monkey hippocampus after ischemia. This suggested implications of PUFA-mediated GPR40 signaling for adult neurogenesis underlying learning and memory.
Objective: This study aims at evaluating whether PUFA-mediated GPR40 activation can affect synthesis of brain-derived neurotrophic factor (BDNF) with the aid of its proteolytic enzyme furin.
Methods: Monkeys underwent 20 min transient whole brain ischemia by clamping both the innominate and left subclavian arteries. On days 7 and 15 after ischemia/reperfusion, when adult neurogenesis was shown to be maximal previously by the authors, the brain samples were resected. By the Western blotting analysis of mature-BDNF (m-BDNF), pro-BDNF and furin, syntheses of BDNF in response to two GPR40 agonists as well as selective GPR40 antagonist GW1100, were studied using normal and post-ischemic monkey dentate gyrus (DG) tissue extracts.
Results: Both up-regulation of m-BDNF synthesis in response to two GPR40 agonists; fish oil PUFA and docosahexaenoic acid (DHA) and its down-regulation in response to GW1100, were observed. GPR40 antagonist inhibited m-BDNF synthesis, whereas two GPR40 agonists stimulated m-BDNF synthesis conceivably via furin activation. Cleavage of p-BDNF to m-BDNF by furin as well as syntheses of m-BDNF and furin in the DG tissues, occurred immediately after incubation with fish oil PUFA or DHA. Dynamic changes of GPR40, m-BDNF synthesis, and furin occurred simultaneously.

Conclusion: These data, although correlative, suggested that m-BDNF may be synthesized by the cleavage of pre-stocked pro-BDNF and/or released from the cell store in response to PUFA. By activating GPR40 and furin, PUFA may be related to adult neurogenesis and the concomitant synaptic plasticity for learning and memory.

Disclosures: T. Yamashima: None. **A. Mathivanan:** None.

Poster

781. G-Protein-Coupled Receptors

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 781.11/F13

Topic: B.03. G-Protein Coupled Receptors

Support: Bioprojet

Title: Exploring occupancy of the histamine H3 receptor by BF2.649 (pitolisant) in humans using PET

Authors: *P. SABIONI[1,2], P. RUSJAN[1,2], P. DI CIANO[1,2], E. MANSOURI[1,2], S. HOULE[1,2], A. WILSON[1,2], I. BOILEAU[1,2], A. LAVEILLE[3], M. CAPET[3], T. DUVAUCHELLE[3], J. C. SCHWARTZ[3], B. LE FOLL[1,2];
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Abstract: Rationale: The histamine H3 receptor (H3R) has been investigated as a potential target for the treatment of various CNS disorders. Drugs that selectively block H3 receptors (for example, pitolisant) have been primarily evaluated for the treatment of sleep disorders (narcolepsy and obstructive sleep apnea) because they increase wakefulness. H3R antagonists/ inverse agonists were also suggested to be useful in treatment of psychiatric and substance abuse disorders. Imaging techniques are useful tools to visualize receptors and their occupancy by neurotransmitters or by a selective agonist/ antagonist drug. **Objective:** The aim of this study was to use positron emission tomography (PET) brain imaging and the radioligand H3R antagonist [^{11}C]GSK189254 to investigate occupancy by the novel H3R antagonist/ inverse agonist BF2.649 (pitolisant), a compound recently approved in the treatment of narcolepsy with or without cataplexy. **Methods:** Six healthy adult participants (age: 19-61) were scanned in a High Resolution Research Tomography (HRRT) PET scan for 90 min immediately after receiving an i.v. bolus injection of [^{11}C]GSK189254 (337±51 MBq, 2.7±0.4 μg). Subjects underwent in total two PET scans, in separate days, 3 hours after an oral drug administration. The first PET scan was performed in the placebo condition and the second PET scan, after the H_3

inverse agonist pitolisant (40 mg). Magnetic Resonance Imaging (MRI) was also conducted during the study to provide structural information for PET data analysis. **Results:** Single oral administration of pitolisant 40 mg promoted occupancy of H3R of 82.33% ± 3.55% (Mean ± SEM). The drug was well tolerated and participants experienced no side effects. **Conclusion:** The administration of pitolisant 40 mg produced a good occupancy of H3 receptors.

Disclosures: P. Sabioni: None. **P. Rusjan:** None. **P. Di Ciano:** None. **E. Mansouri:** None. **S. Houle:** None. **A. Wilson:** None. **I. Boileau:** None. **A. Laveille:** A. Employment/Salary (full or part-time): Bioprojet. **M. Capet:** A. Employment/Salary (full or part-time): Bioprojet. **T. Duvauchelle:** A. Employment/Salary (full or part-time): Bioprojet. **J.C. Schwartz:** A. Employment/Salary (full or part-time): Bioprojet. **B. Le Foll:** B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution; Bioprojet.

Poster

781. G-Protein-Coupled Receptors

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 781.12/F14

Topic: B.03. G-Protein Coupled Receptors

Support: NIH Grant GM078319

NIH Grant GM109879

Title: Activity-dependent polarization of calcium release from intracellular stores

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Abstract: In many neurons activation of G protein-coupled receptors (GPCRs) leads to activation of phospholipase C, hydrolysis of PIP2, production of IP3, and calcium release from intracellular stores. Given the different functional roles of intracellular calcium in postsynaptic and presynaptic processes we were interested in how this mechanism might differ in these compartments. Cultured cerebellar granule neurons expressing the calcium indicator GCaMP6s were stimulated with the muscarinic acetylcholine receptor (mAchR) agonist oxotremorine-M (Oxo-M), which evoked increases in cytosolic calcium in the soma and proximal dendrites but not in axons. This pattern of calcium release was not altered by overexpression of mAchRs, which were present on the surface of axons as well as the soma and dendrites. FRET

measurements using PH-domain indicators showed that activation of native mAchRs led to reversible PIP2 hydrolysis throughout both the somatodendritic and axonal compartments. The ryanodine receptor agonist caffeine and the calcium ionophore ionomycin also released calcium from intracellular stores in the soma and proximal dendrites but not in axons. In the presence of 25 mM K^+, which depolarized neurons and increased cytosolic calcium, Oxo-M, caffeine and ionomycin all produced additional increases in cytosolic calcium due to release from intracellular stores in both cell bodies and axons. Simultaneous imaging of calcium in the cytosol and endoplasmic reticulum suggested that depletion of intracellular calcium stores may contribute to the absence of calcium release in axons under non-depolarizing conditions, but that additional mechanisms are likely to be equally important. These results suggest calcium release mechanisms can be highly polarized in these neurons, and that this polarization can be regulated by neuronal activity.

Disclosures: **N.A. Lambert:** None. **S. Rajapaksha:** None. **Q. Wan:** None.

Poster

781. G-Protein-Coupled Receptors

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 781.13/F15

Topic: B.03. G-Protein Coupled Receptors

Support: NIH Grant MH073676-11

Dystonia Medical Research Foundation

Title: D_1 receptor activation in the SNr evokes GABA release and increased motor activity and is tonically inhibited by M_4 receptor signaling

Authors: ***M. S. MOEHLE**[1], T. PANCANI[1], N. BYUN[1], Z. XIANG[1], J. WESS[2], J. M. ROOK[1], C. M. NISWENDER[1], C. K. JONES[1], C. M. LINDSLEY[1], P. J. CONN[1];
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Abstract: Dysregulation of dopamine (DA) release within the basal ganglia from midbrain dopaminergic neurons of the substantia nigra pars compacta (SNpc) underlie pathological states in a wide variety of central nervous system diseases including psychiatric and movement disorders. Within the basal ganglia, DA plays a critical role in regulating striatal function by actions on two separate non-overlapping pathways, the direct and indirect pathway. Because of the critical modulatory role of DA, a great effort has been placed on understanding both how DA modulates the basal ganglia direct and indirect pathways and how other neurotransmitter systems

regulate DA signaling. Potentially opposing dopamine receptor subtype 1 (D1) signaling, are the muscarinic acetylcholine subtype 4 (M4) receptors. Recently, our lab has reported that the activation of M4 receptors on direct pathway spiny projection neurons (SPNs) can block amphetamine-induced hyperlocomotion by attenuating dopamine release from striato-nigral projections via an endocannabinoid-dependent mechanism, highlighting a previously unreported mechanism by which M4 can inhibit dopamine release and diminish dopaminergic activity in the direct pathway. However, we now report that hyperlocomotion induced by direct-acting D1 agonists can also be blocked by M4 activation, implying that M4 directly opposes D1 signaling in addition to blocking dopamine release. Using a wide range of behavioral, electrophysiological, optogenetic, pharmacological, and functional imaging techniques, we directly tested how D1 agonists induce hyperlocomotion and how M4 activation opposes D1 activation. We found that D1 activation robustly induces gamma-aminobutyric acid (GABA) release from direct pathway SPNs onto cells of the substantia nigra reticulata (SNr) and that this is attenuated by M4 activation at the level of the SNr, likely through a cAMP-dependent mechanism. We also present data to suggest that M4 activity tonically inhibits D1 activity and GABA release in the direct pathway. Additional data suggested that DA release and D1 activation, as well as acetylcholine (ACh) release, in the SNr is equally important to produce and regulate movement as their counterparts in the striatum, extending the current model for how DA regulates basal ganglia processing.

Disclosures: **M.S. Moehle:** None. **T. Pancani:** None. **N. Byun:** None. **Z. Xiang:** None. **J. Wess:** None. **J.M. Rook:** None. **C.M. Niswender:** C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); AstraZeneca. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Inventor of patents for M4 PAMs. **C.K. Jones:** C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); AstraZeneca. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Inventor of patents for M4 PAMs. **C.M. Lindsley:** C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); AstraZeneca. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Inventor of patents for M4 PAMs. **P.J. Conn:** C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); AstraZeneca. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Inventor of patents for M4 PAMs.

Poster

781. G-Protein-Coupled Receptors

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 781.14/F16

Topic: B.03. G-Protein Coupled Receptors

Support: NIH Grant 5R37-MH073853-10

NIH Grant U19-MH082441

Title: Behavioral consequences of biased D2 dopamine receptor signaling in medium spiny neurons

Authors: *S. J. ROSE[1], T. F. PACK[1], S. M. PETERSON[1], E. BORRELLI[2], M. G. CARON[1]; [1]Dept. of Cell Biol., Duke Univ. Med. Ctr., Durham, NC; [2]UC Irvine, Irvine, CA

Abstract: Dopamine signaling through the D2 dopamine receptor (D2R) in the brain is essential for motor control, reward, and cognition. It is now recognized that G protein-coupled receptors (GPCR), like the D2R, signal through canonical G-protein-mediated pathways as well as through the ability of β-arrestin2 (β-arr2) to scaffold distinct signaling complexes. Previous attempts to understand whether these distinct modes of D2R signaling are important have used cell type specific deletion of β-arr2 but this approach can also influence unrelated GPCRs function. Thus, to more precisely understand the nature of D2R signaling in normal behavior and in pharmacological responses, we used an approach where mutant D2Rs with defined signaling properties were reconstituted in the striatal D2R-positive neurons of the cortico-striato-thalamocortical circuit. D2Rs are expressed in the neuronal population of adenosine 2A receptor (A2AR) positive medium spiny neurons (iMSNs), which are the principal striatal output neurons of the classical "indirect pathway" of the basal ganglia. "Floxed" D2R mice (Anzalone et al., 2012) were crossed with A2ARCre mice, which were then virally reconstituted with four distinct Cre-dependent D2Rs, wild-type (^{WT}D2R), inactive D2R (^{D80A}D2R) and either G-protein (^{Gprot}D2R) or β-arrestin2 ($^{\beta\text{-}arr2}$D2R) selective D2Rs (Peterson et al., 2015). We found that whereas mice rescued with the inactive ^{D80A}D2R showed deficits in several behaviors that could be rescued by the ^{WT}D2R, overall locomotor behavior was rescued most efficiently by the $^{\beta\text{-}arr2}$D2R while both ^{Gprot}D2R and $^{\beta\text{-}arr2}$D2R were required for rearing behavior. Nestlet shredding, on the other hand, a form of repetitive behavior, was solely rescued by the ^{Gprot}D2R. Responses to pharmacological agents like cocaine were rescued by both D2R signaling modes, but $^{\beta\text{-}arr2}$D2R appeared more effective in rescuing amphetamine responses. Interestingly, locomotor responses to morphine could only be rescued partially with the $^{\beta\text{-}arr2}$D2R while the effect of phencyclidine (PCP) was markedly enhanced beyond the ^{WT}D2R rescue by the $^{\beta\text{-}arr2}$D2R. These results illustrate not only the complexity of D2R-signaling in the intact nervous system but argue that D2Rs can activate several distinct patterns of intracellular signals, depending on the context. These findings

should be useful to understand the profile of existing therapies and provide clues to develop more effective and selective approaches.

Disclosures: **S.J. Rose:** None. **T.F. Pack:** None. **S.M. Peterson:** None. **E. Borrelli:** None. **M.G. Caron:** None.

Poster

781. G-Protein-Coupled Receptors

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 781.15/F17

Topic: B.03. G-Protein Coupled Receptors

Support: Government of Catalonia [2014-SGR-1236]

CIBERNED [CB06/05/0064]

Spanish Ministerio de Economía y Competitividad [SAF2014-54840-R]

NIDA intramural funds

Title: Evidence for noncanonical adrenergic and dopaminergic activation: dopamine as an adrenergic alpha2 receptor agonist

Authors: *V. CASADÓ ANGUERA[1,2], M. SÁNCHEZ-SOTO[3,2,1], M. ESTEFANIA[1,2], Y. HIDEAKI[3], J. MALLOL[1,2], E. I. CANELA[1,2], A. CORTÉS[1,2], S. FERRÉ[3], V. CASADÓ[1,2]; [1]Departament de Bioquimica i Biomedicina Mol., Univ. of Barcelona, Barcelona, Spain; [2]Ctr. de Investigación Biomédica en Red sobre Enfermedades Neurodegenerativas, Spain, Spain; [3]Integrative Neurobio. Section, Natl. Inst. on Drug Abuse, Intramural Res. Program, Natl. Inst. of Hlth., Baltimore, MD

Abstract: A complex functional connection between the dopaminergic and noradrenergic systems is displayed in the brain and is involved in many brain functions. Dopamine (DA) acts on specific receptors belonging to the G protein-coupled receptor (GPCR) family and are categorized in two main groups including D_1-like and D_2-like receptors. The $G_{\alpha i/o}$-coupled dopamine D_2-like receptor family comprises three subtypes: the D2 receptor (D_2R), D_3 receptor (D_3R), and D_4 receptor (D_4R). The alpha-2 adrenergic receptor (α_2-ADR) is also a GPCR associated with inhibitory G-proteins. It has been classified in mammals into three highly homologous but distinct subtypes including α_{2A}, α_{2B}, and α_{2C}. α_{2A}-ADR is the most common subtype in the prefrontal cortex (PFC) but its expression is low in the striatum. In contrast, α_{2C}-ADR is predominantly expressed in the striatum and hippocampus but its expression is much

lower in the PFC. α_{2B}-ADR plays only a minor role in the brain, it is only weakly expressed in the central nervous system with a limited presence in the thalamus. Previous studies suggested that DA can inhibit adenylyl cyclase trough α_{2C}-ADR activation in mouse striatum and that norepinephrine (NE) can functionally interact with D_4R. Recently, we have reported that NE is a potent agonist for all D_2-like receptors. To our knowledge, inhibitory G_α subunits implicated in interactions between DA and α_2-ADR have not been determined. By using radioligand binding in brain membranes and by functional bioluminescent resonance energy transfer (BRET) assays in transfected HEK cells, the present study attempted a comparison between DA, NE and several synthetic dopaminergic ligands in their possible activation of α_{2A}- and α_{2C}-ADR. Using the non-selective α_2-ADR radioligand [^{3}H]RX821002 we determined the affinities of several DR ligands in sheep brain cortical and striatal membranes. Surprisingly, DA showed only ten-fold lower affinity than NE for α_2-ADR and the selective D_4R ligand Ro10-5824 was in the same range of NE affinity. Other assayed selective DR ligands had low to negligible ADR affinity. Functional BRET assays showed the activation of all inhibitory G_α subunits ($G_{\alpha i1}$, $G_{\alpha i2}$ $G_{\alpha i3}$, $G_{\alpha oA}$, $G_{\alpha oB}$) coupled to α_{2A} or to α_{2C}-ADR by DA and NE proving that D_2-like receptor ligands may act as potent agonists of these ADRs. Remarkably, DA binding to α_{2A} or to α_{2C}-ADR was only 2 to 25-fold less effective than NE in the activation of all inhibitory G_α subunits. Other DR ligands, such as the D_3R selective 7-OH-PIPAT, were also significantly effective. In conclusion, if α_2-ADRs promiscuously bind dopaminergic ligands in some brain regions, they should also be considered as functional dopaminergic receptors.

Disclosures: **V. Casadó Anguera:** None. **M. Sánchez-Soto:** None. **M. Estefania:** None. **Y. Hideaki:** None. **J. Mallol:** None. **E.I. Canela:** None. **A. Cortés:** None. **S. Ferré:** None. **V. Casadó:** None.

Poster

781. G-Protein-Coupled Receptors

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 781.16/F18

Topic: B.03. G-Protein Coupled Receptors

Support: NIH Grant ZIA NS002824-26

Title: Dopamine via dopamine receptor 4 alters GnRH neuron activity

Authors: ***L. DAIRAGHI**, S. CONSTANTIN, S. WRAY;
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Abstract: Gonadotropin-releasing hormone (GnRH) secreting neurons control fertility. The release of GnRH regulates the synthesis and release of both LH and FSH from the anterior pituitary. While it has been shown that dopamine is involved in the regulation of LH secretion, the mechanisms through which it does so remains unclear. Previous studies in adult rodents have reported juxtaposition of GnRH cells with fibers containing tyrosine hydroxylase, a marker of dopaminergic cells, and that application of exogenous dopamine inhibits GnRH neurons postsynaptically through D1- and/or D2-like dopamine receptors. Microchip data obtained from single GnRH neurons maintained in nasal explants indicated a high level of transcript for dopamine receptor 4 (Drd4). The present study examines the effect of Drd4 activation on GnRH neurons. Single cell RT-PCR and immunocytochemistry show a subpopulation of GnRH cells express the Drd4 transcript and receptor, respectively. Because intracellular calcium oscillations correlate with electrical activity, and many cells can be monitored simultaneously, calcium imaging was used to assess GnRH neuronal activity. Application of both apomorphine, a general dopamine receptor agonist, and PD168077, a Drd4-specific agonist, inhibited calcium oscillations in a subset of cells. Elimination of GABAergic and glutamatergic inputs to GnRH cells did not block the PD168077-mediated inhibition of GnRH neuronal activity. Together, these results indicate that dopamine directly inhibits GnRH neurons, through Drd4. Further experiments will determine the signaling pathway downstream of Drd4 activation and whether the Drd4 is the receptor subtype involved in inhibition in adult mice.

Disclosures: **L. Dairaghi:** None. **S. Constantin:** None. **S. Wray:** None.

Poster

781. G-Protein-Coupled Receptors

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 781.17/F19

Topic: B.03. G-Protein Coupled Receptors

Support: RO1MH61887

Title: Structure of LSD in complex with a human serotonin receptor

Authors: *B. L. ROTH, D. WACKER;
Pharmacol., Univ. of North Carolina At Chapel Hill, Chapel Hill, NC

Abstract: LSD is an extraordinarily potent and long-lasting psychedelic that apparently manifests its hallucinogenic effects in humans through serotonin (5-HT) G protein-coupled serotonin receptors. To gain structural insights into LSD's actions we elucidated the structure of LSD bound to a prototypical human serotonin receptor—5-HT_{2B}. The structure reveals a distinct

binding mode for LSD, along with striking conformational rearrangements required to accommodate LSD. Kinetic studies revealed that LSD has an exceptionally slow off-rate from both 5-HT_{2A} and 5-HT_{2B} receptors. We found that mutating a leucine in EL2 predicted to retain LSD in the binding pocket greatly accelerates LSD's binding kinetics, and significantly dampens LSD-mediated β-arrestin recruitment without affecting G protein signaling. These findings explain how LSD's binding mode may specify its unique kinetic and signaling properties and thereby provide an initial molecular explanation for LSD's actions at human serotonin receptors.

Disclosures: B.L. Roth: None. **D. Wacker:** None.

Poster

781. G-Protein-Coupled Receptors

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 781.18/F20

Topic: B.03. G-Protein Coupled Receptors

Title: Polychlorinated biphenyl 19 blocks G-protein coupled receptor-mediated Ca^{2+} signaling by blocking store-operated Ca^{2+} entry

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Abstract: PCB19 is one of non-dioxin-like polychlorinated biphenyls (NDL-PCBs) which are a component of Arochlor1260, ubiquitous pollutants. Especially NDL-PCBs affect cytosolic Ca^{2+} signaling via promoting Ca2+ release (from ryanodine receptor-sensitive Ca2+ pools) and inhibiting the store-operated Ca2+ entry from the extracellular space. However, the clue for NDL-PCB-mediated SOCE inhibition had accomplished with PC12 cells, of which SOCE is mainly mediated by TrpC family channels. Thus it is still unclear whether NDL-PCBs affect Orai-dependent SOCE as well. Here, we investigated the effects of PCB19 (*ortho*-substituted 2,2',6-trichlorinated biphenyl), one of NDL-PCBs on Orai-mediated SOCE in HEK293 cells, of which SOCE is solely mediated by intrinsic Orai channels. We found that PCB19 caused a rapid decline in the Ca^{2+} signaling of carbachol, a typical G_q- and phospholipase Cβ-coupled GPCR in HEK293 cells. PCB19 reduced thapsigargin-induced Ca^{2+} influx after Ca^{2+} pool depletion, suggesting that PCB19 inhibits Orai-mediated SOCE. PCB19-mediated SOCE inhibition was confirmed by demonstrating the ability of PCB19 to inhibit the SOCE current but not the TRPM7 current. These results imply that NDL-PCBs might inhibit not only TrpC-mediated SOCE as in PC12 cells, but also Orai-mediated SOCE as in many other cells including HEK293

cells, thereby interfering with GPCR signaling. **(Key words**: Polychlorinated biphenyl, PCB19, Ca^{2+} signaling, Orai, store-operated Ca^{2+} entry)

Disclosures: **S. Lee:** None. **K. Lee:** None. **S. Jo:** None. **K. Kim:** None. **S. Choi:** None.

Poster

781. G-Protein-Coupled Receptors

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 781.19/F21

Topic: B.03. G-Protein Coupled Receptors

Support: BBSRC BB/L019396/1

MRC MR/L020661/1

BBSRC BB/K009192/

Title: Peripheral or central administration of GPR4 blocker NE 52-0057 does not affect central chemosensitivity or cardio-vascular homeostasis

Authors: ***S. KASPAROV**[1], P. S. HOSFORD[2], V. MOSIENKO[1], K. KISHI[1], G. JURISIC[3], K. SEUWEN[3], B. KINZEL[3], M.-G. LUDWIG[3], J. A. WELLS[2], I. N. CHRISTIE[2], A. V. GOURINE[2], A. G. TESCHEMACHER[1];
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Abstract: G-protein coupled receptor 4 (GPR4) together with GPR65 and GPR68, comprises a family of proton-sensing receptors (http://www.guidetopharmacology.org). GPR4 is Gs coupled and drives production of cAMP. Our original study (Ludwig et al., 2003) demonstrated that it is inactive at pH >8 and essentially fully activated at neutral to slightly acidic pH. A recent publication (Kumar et al., 2015) suggested that in the mouse GPR4 is essential for central respiratory sensitivity to CO_2 and that GPR4 is selectively expressed by neurones of the retro-trapezoid nucleus (RTN) which has been extensively implicated in this phenomenon. To characterise expression of GPR4 in the brain we used a knock-in mouse where CRE is expressed from the genomic locus of GPR4. It was crossed with an EGFP-reporter mouse allowing lineage tracing of cells expressing GPR4. Consistent with Zhang et al. (2014), EGFP expression was particularly strong in endothelium throughout the CNS. Abundant expression of GPR4 was also detected in neurones of dorsal raphe and in lateral septum. Some, mainly non-noradrenergic neurones, in the locus coeruleus were also positive. Weak GPR4 expression was detected in some neurones of the RTN.

In transiently transfected HEK cells in the present series of experiments, the operational range of GPR4 was between pH~8.0 and 7.4, and at neutral pH (7.4) GPR4 was essentially fully activated. Novartis have developed a small molecule antagonist of GPR4, NE 52-0057. NE 52-0057 was highly effective in blocking GPR4-mediated cAMP accumulation with IC_{50} at pH 7.4 of 14.3 nM. We investigated whether this potent GPR4 blocker has any acute effects on cardio-vascular or respiratory activity in an anaesthetised rat model. At doses of up to 20 mg/kg (i.p.) NE 52-0057 did not affect major hemodynamic variables, cerebral blood flow and BOLD responses in somatosensory cortex to sensory stimulation. Systemic (up to 20 mg/kg i.p.) or direct central administration (1 mM onto the ventral surface of the medulla directly above RTN) of NE 52-0057 had no effect on resting respiratory activity or respiratory responses induced by increases in the level of inspired CO_2 (10%) under conditions of peripheral chemo-denervation. Thus, in the brain GPR4 is mainly expressed by endothelium but there are a few clusters of neurons which also express it. Current results argue against an essential role of GPR4 in central chemosensitivity in the rat. They also demonstrate that NE 52-0057 has no acute detrimental cardio-vascular or respiratory effects and lay the ground for further investigations of its possible uses in areas such as cancer therapy or other diseases where vascular proliferation plays an important role.

Disclosures: **S. Kasparov:** None. **P.S. Hosford:** None. **V. Mosienko:** None. **K. Kishi:** None. **G. Jurisic:** None. **K. Seuwen:** None. **B. Kinzel:** None. **M. Ludwig:** None. **J.A. Wells:** None. **I.N. Christie:** None. **A.V. Gourine:** None. **A.G. Teschemacher:** None.

Poster

781. G-Protein-Coupled Receptors

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 781.20/F22

Topic: B.03. G-Protein Coupled Receptors

Support: DGAPA PAPIIT IN219516 to AERC

DGAPA PAPIIT IN218316 to OPG

DGAPA PAPIIT IA207416 to MMD

Title: Differential expression of the cannabinoid receptor 1 (CB1) as a function of the homozygous genotypes of the single nucleotide polymorphism rs2180619

Authors: **M. A. BARRERA-TLAPA**[1], G. BENÍTEZ-KING[2], S. ALARCÓN[2], U. CABALLERO-SÁNCHEZ[1], M. VÁLDES-TOVAR[2], M. MÉNDEZ-DÍAZ[3], O. PROSPÉRO-

GARCÍA[3], *A. E. RUIZ-CONTRERAS[1];
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Abstract: The single nucleotide polymorphism rs2180619 consists of a G/A change located in the 5´ regulatory region of the CNR1 gene, which codes for the cannabinoid receptor 1 (CB1). Recently, our research group has identified an association of the homozygous G genotype with a lower efficiency in the resolution of working memory tasks, as compared to homozygous A genotype healthy young Mexican subjects. Another research group, performing an *in silico* analysis, have shown that there are allele-specific differences in the affinity to transcription factors in rs2180619. Nonetheless, the physiological effect of rs2180619 has not been elucidated. In the present work, the difference in the expression of CB1 as a function of rs2180619 in the model of neuronal precursors isolated from olfactory epithelium of living subjects was evaluated. Samples from the olfactory neuroepithelium were taken by exfoliation from four homozygous A and four homozygous G subjects. Cells were cultivated and propagated up to passage 5-9. Western blot was made with the polyclonal anti CB1 antibody made in goat H-150, 1:1,500 (Santa Cruz, Biotechnology Inc, Dallas Tx, U.S.A). GAPDH protein was used as load control and was detected by the anti-GAPDH antibody made in mouse Millipore Mab. 374, 1:20,000 (Millipore, Darmstadt, Germany). Optic densities (OD) of the bands corresponding to the glycated form of CB1 (± 63 KDa) were determined by densitometry. AA subjects showed less relative quantity (OD/mm^2) of CB1 with respect to homozygous G. This result suggest a specific-allele effect of rs2180619 in the expression of CB1 in young healthy subjects and add up to the knowledge of physiology of individual variations associated to cognitive function.

Disclosures: **M.A. Barrera-Tlapa:** None. **G. Benítez-King:** None. **S. Alarcón:** None. **U. Caballero-Sánchez:** None. **M. Váldes-Tovar:** None. **M. Méndez-Díaz:** None. **O. Prospéro-García:** None. **A.E. Ruiz-Contreras:** None.

Poster

781. G-Protein-Coupled Receptors

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 781.21/F23

Topic: B.03. G-Protein Coupled Receptors

Support: NIH Grant R15NS078645

BYU Mentoring Environment Grants

Title: The putative cannabinoid receptor gpr55: expression, modulation of hippocampal plasticity and behavior

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Abstract: Memory occurs due to experience-dependent changes in the brain. These changes are mediated by synaptic plasticity, particularly in the hippocampus. Plasticity can either strengthen or weaken synapses, the former is known as long-term potentiation (LTP). While many forms of plasticity are NMDA-dependent, endocannabinoids mediate several forms of plasticity. Endocannabinoids bind to receptors such as cannabinoid receptor 1 (CB1) and transient receptor potential vanilloid 1 (TRPV1) in various brain areas including the hippocampus. Research has demonstrates a hippocampal non-CB1/TRPV1-dependent endocannabinoid synaptic plasticity. While the receptor(s) involved is unknown, potential candidate receptors that bind the endocannabinoid anandamide have been identified, including orphan G-protein coupled receptors (GPRs) whose distribution and/or function are not well known. GPR55 is of interest as its activation enhances IP3-mediated increases in intracellular calcium. Using quantitative RT-PCR, electrophysiology and memory tasks, we examined hippocampal GPR55 expression and function. GPR55 is expressed in hippocampus of both rats and mice. Application of the GPR55 agonist LPI (2 μM) to wild-type (WT) mice significantly enhanced CA1 hippocampal LTP. This effect was absent in GPR55 knock-out (KO) mice, which exhibit significantly ($p < 0.05$) smaller LTP (146%) than WT (181%). However, LTP in WT and KO mice in the absence of LPI are not significantly different. The GPR55 antagonist CID 16020046 (10 μM) also blocked LPI enhancements in WT mice. GPR55 also appears to increase release probability (Sylantyev et al., PNAS, 2013), denoting a presynaptic role. We examined paired-pulse ratios (PPR) of KO and WT mice with or without LPI. While there is only a slight difference between KO and WT PPRs, after application of LPI there is a significant increase in PPR of WT mice not noted in KO mice, suggesting increased transmitter release but not increased probability. Whole cell patching on interneurons shows no effect on baseline when LPI is applied to the bath (n=3). IHC demonstrated GPR55 in Pyramidal cells in CA1 and CA3 layers of the hippocampus. Behaviorally, KO and WT mice did not differ in the novel object recognition test, and in the radial arm maze task examining spatial memory, KO and WT littermates performed similarly, however KO mice have a higher frequency of anxiety behavior during the task. These data suggest GPR55 is expressed and physiologically relevant in the hippocampus. Because enhanced LTP is often associated with better memory performance, this provides a potential target to enhance the cellular mechanism associated with memory formation.

Disclosures: K.M. Hurst: None. **C. Badgley:** None. **J. Edwards:** None.

Poster

781. G-Protein-Coupled Receptors

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 781.22/F24

Topic: B.03. G-Protein Coupled Receptors

Support: Czech Science Foundation (GACR P303/12/2408)

Title: Sgip1 alters internalization and modulates signaling of activated cannabinoid receptor 1 in biased manner

Authors: *J. BLAHOS[1], A. HÁJKOVÁ[2], M. DVOřÁKOVÁ[2], L. PREZEAU[3], S. RADENKOVIč[4];
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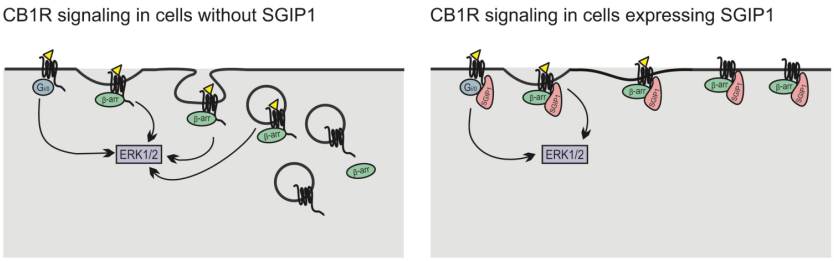
Abstract: Many diseases of the nervous system are accompanied by alterations in synaptic functions. Synaptic plasticity mediated by the endogenous cannabinoid system involves the activation of the cannabinoid receptor 1 (CB1R). The principles of CB1R signaling must be understood in detail for its therapeutic exploration. We detected the Src homology 3-domain growth factor receptor-bound 2-like (endophilin) interacting protein 1 (SGIP1) as a novel CB1R partner. SGIP1 is functionally linked to clathrin-mediated endocytosis and its overexpression in animals leads to an energy regulation imbalance resulting in obesity. We report that SGIP1 prevents the endocytosis of the activated CB1R and that it alters signaling via the CB1R in a biased manner. The CB1R mediated G-protein activation is selectively influenced by SGIP1, the β-arrestin associated signaling is changed profoundly, most likely as a consequence of the prevention of the receptor's internalization elicited by SGIP1.



Disclosures: **J. Blahos:** None. **A. Hájková:** None. **M. Dvořáková:** None. **L. Prezeau:** None. **S. Radenkovič:** None.

Poster

781. G-Protein-Coupled Receptors

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 781.23/F25

Topic: B.03. G-Protein Coupled Receptors

Support: NIH Grant DA032890

IRP/NIDA/NIH

Title: Evolutionary diversification of cannabinoid CB_1R and CB_2R genes, expression and function in human, rhesus monkey, rat and mouse

Authors: *Q.-R. LIU[1], H. ZHANG[2], C.-Y. LI[3], H. QU[4], Z.-X. XI[2], E. L. GARDNER[2], E. S. ONAIVI[5];
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Abstract: Recent studies suggest that cannabinoids may produce different pharmacological actions in experimental species, suggesting that cannabinoid effects in one species cannot be directly extrapolated to another species. We hypothesize that species differences in CB_1R and CB_2R expression, protein structure and function may contribute to different pharmacological actions produced by cannabinoids in different species. Using quantitative RT-PCR, we found species-specific differential expression of CB_1R and CB_2R isoforms in brain regions and peripheral tissues. Human *CNR1* gene may transcribe six different isoforms, and three of them encode CB_1Rs with three different N-terminal amino acid alterations - CB_1R_{472}, CB_1R_{439} and CB_1R_{411}. In contrast, rhesus monkey and rodent *Cnr1* gene transcribes isoforms encoding 472 and 473 amino acids, respectively, without N-terminal variants. Regarding CB_2 receptors, human, rhesus monkey and rat *Cnr2* genes encode 360 amino acids while mouse *Cnr2* gene encodes 347 amino acids with a premature stop codon at its C-terminus. Based on these findings, we predict that different promoters, epigenetic signatures, exons and/or different sequences in 5'-UTR and 3'-UTR of different isoforms may alter CB_1/CB_2 receptor expression in different tissues, brain regions and/or different cellular types, and therefore, contribute to different CB_1/CB_2 receptor responses in different species. Computer modeling of the 3-D structures found significant species differences in receptor structures such as opposite charged amino acid residues located in the vicinities of putative ligand binding sites. Different species also display different pharmacological responses to the same ligands. Systemic administration of ACEA (a selective CB_1R agonist) significantly inhibited spontaneous wheel running activity in rats, but it

was less effective in C57 mice, and not effective in BTBR mice. Conversely, systemic administration of WIN55212-2 (a dual CB_1/CB_2 receptor agonist) significantly reduced spontaneous wheel running activity in BTBR mice, but it was less effective in C57 mice, and not effective in rats. Similarly, systemic administration of JWH133 (a selective CB_2R agonist) significantly inhibited intravenous cocaine self-administration in mice, but not in rats. Taken together, all these findings suggest significant species differences in cannabinoid receptor structures and functions. We propose rhesus monkey (www.rhesusbase.org/) with similar CB_1R and CB_2R structure and function to Homo sapiens as a potential animal model for cannabis-based medication development for human diseases. Support NIH IRP (NIDA) and NIH grant DA032890.

Disclosures: Q. Liu: None. **H. Zhang:** None. **C. Li:** None. **H. Qu:** None. **Z. Xi:** None. **E.L. Gardner:** None. **E.S. Onaivi:** None.

Poster

782. Synaptic Integration

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 782.01/F26

Topic: B.07. Synaptic Transmission

Support: NIH R01GM095653

Title: Synaptic actions of isoflurane on hippocampal and cortical connections

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Abstract: Background/Introduction: Anesthetics are known to depress synaptic transmission, and this effect is thought to underlie the uncoupling of brain regions seen with cortical EEG recordings. We tested the hypothesis that anesthetic-induced depression of synapses leads to uncoupling of electrical activity between frontal cortex and hippocampus. Methods: The present study used electrophysiologically-guided electrode implants to record Schaffer-collateral to CA1 neuron mono-synaptic responses, as well as frontal cortical micro-EEG signals, using a IRB approved protocol. Rats were allowed to recover from surgery and then isoflurane effects were characterized after several days (>7) to several months (<7) later. Simultaneous recordings of cortical and hippocampal micro-EEG signals, evoked synaptic responses, anesthetic concentration, vital signs and behavior were made. Results: Loss of consciousness, measured as righting reflex, was consistently associated with increased synchronized delta activity, in hippocampus and cortex, as well as a novel ~15 Hz rhythmic oscillation produced by isoflurane

in hippocampal micro-EEG recordings. Surgical anesthesia, measured as loss of tail-clamp reflex, was observed on the transition to burst-suppression activity in both hippocampal and cortical micro-EEG signals. Isoflurane produced a concentration-dependent depression of mono-synaptic responses: at surgical anesthetic depths, excitatory postsynaptic potentials were depressed by 26.6 ± 4.2 % (n=5; $p<0.001$) of control amplitudes, but surprisingly, coupling between cortex and hippocampus was further enhanced. Conclusion: Clearly, our hypothesis was wrong, since increased coupling between brain regions was observed at the same time that mono-synaptic responses were depressed. We demonstrate for the first time that cortical-hippocampal coupling is increased at both low (loss of consciousness) and at high surgical concentrations of isoflurane. Support: Anesthesia Department at Stanford University, the NIH R01GM095653 to MBM

Disclosures: B. MacIver: None.

Poster

782. Synaptic Integration

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 782.02/F27

Topic: B.07. Synaptic Transmission

Support: 1SC1GM118242

5R25GM069621-11

HRD-1202008

Title: The effect of Ferrostatin-1 on intrinsic and synaptic properties of hippocampal neurons

Authors: *V. I. NAVARRO[1], L. P. MONTES[2], C. D. LOYOLA BALTAZAR[2], R. SKOUTA[2], K. FENELON[2];
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Abstract: Synaptic transmission and cellular excitability is fundamental for the normal function of brain circuits and neuronal systems. Loss or dysfunction of such neuronal communication is associated with many psychiatric and neurodegenerative disorders affecting populations worldwide. In patients suffering from these disorders, both genetic and non-genetic factors can increase cellular levels of reactive oxygen species (ROS) beyond physiological levels. Generated in excess, reactive species can damage cellular lipid membranes, proteins and DNA, leading to abnormal neural growth, differentiation and function. At the neuronal level, elevated ROS levels

have been associated with an increased synaptic transmission and excitability that could lead to cell death in *in vitro* and *in vivo* assays. Therefore, novel small antioxidant molecules able to decrease synaptic transmission and neuronal excitability would represent a promising treatment for disorders associated with increased reactive species. Ferrostatin-1 (Fer-1) is a small antioxidant molecule that can prevent the death of hippocampal neurons exposed to neurotoxic glutamate levels (Dixon et al., 2012). Fer-1 also decreases neuronal death in various disease models including Huntington's disease (HD) brain slices (Skouta R. et al., 2014). Neurons exposed to such assays are normally hyperexcitable. However, the effects of Fer-1 on synaptic transmission and neuronal excitability are unknown even under physiological conditions. The objective was to evaluate the effect of Fer-1 on synaptic and intrinsic properties of healthy hippocampal neurons using mouse brain slices. To do so, extracellular field electrophysiological recordings were performed at the CA1-Schaffer collateral synapses. Synaptic transmission, synaptic plasticity and axonal excitability were assessed in the absence (control) and in the presence of 100 μM Fer-1 (N=7). Our preliminary results suggest that Fer-1 tended to reduce synaptic transmission and axonal excitability of hippocampal neurons. We conclude that in addition to its previously described neuroprotective effects, Fer-1 might also decrease synaptic transmission and cellular excitability in diseases with an excess of ROS.

Disclosures: **V.I. Navarro:** A. Employment/Salary (full or part-time): University of Texas - El Paso. B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution; 1SC1GM118242, 5R25GM069621-11. **L.P. Montes:** A. Employment/Salary (full or part-time): University of Texas - El Paso. B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution; 1SC1GM118242, HRD-1202008. **C.D. Loyola Baltazar:** A. Employment/Salary (full or part-time): University of Texas - El Paso. B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution; 1SC1GM118242. **R. Skouta:** A. Employment/Salary (full or part-time): University of Texas - El Paso. B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution; 1SC1GM118242. **K. Fenelon:** A. Employment/Salary (full or part-time): University of Texas - El Paso. B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution; 1SC1GM118242.

Poster

782. Synaptic Integration

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 782.03/F28

Topic: B.07. Synaptic Transmission

Support: NIH Grant 1SC1GM118242

NIH Grant 5R25GM069621

NIH Grant 5G12MD007592

Title: Effects of early lead exposure on synaptic transmission and plasticity in mouse hippocampal neurons

Authors: *L. E. MARTINETTI, A. TENA, E. PERU, K. FÉNELON;
Dept. of Biol. Sci., The Univ. of Texas At El Paso, El Paso, TX

Abstract: Lead (Pb) is a ubiquitous environmental neurotoxicant that causes behavioral and cognitive deficits. Low-level Pb exposure induces learning and memory deficits in children from low socioeconomic neighborhoods found across the United States. Previous studies reported that high-levels of Pb exposure alter the function of the hippocampus, a key brain region for learning and memory. However, the neuronal mechanisms by which lowest-level chronic Pb exposure affects hippocampal function are still ill defined, due to the lack of animal models. Moreover, the long-term effects of Pb on hippocampal neurons of males and females long after exposure has ceased is unknown. Therefore, we compared control adult mice to mice exposed from birth to post-natal day 28 to either high Pb levels (330 ppm) or low Pb levels (30 ppm). Mice exposed to such low-level Pb were previously shown to exhibit poorer exploratory ambulation (Flores-Montoya and Sobin, 2014) and impaired novel odor discrimination (Flores-Montoya et al, 2015), which are hippocampus-dependent behaviors. Using both high and low Pb exposed male and female mice, extracellular field electrophysiological recordings were performed in the CA1 region of acute hippocampal slices. Our results show that synaptic transmission is decreased in low Pb-exposed mice (Control: N=17 animals; n=24 slices; High Pb: N=13 animals; n=22 slices; Low Pb: N=12 animals; n=19 slices). Interestingly, Pb-exposure had different effects when males and females were compared. In males (Control: N=10 animals; n=16 slices; High Pb: N=10 animals; n= 16 slices; Low Pb: N=4 animals; n=8 slices), low Pb exposure affected synaptic transmission and neuronal fiber excitability whereas in females (Control: N=7 animals; n=8 slices; High Pb: N=3 animals; n=6 slices; Low Pb: N=8 animals; n=11 slices), high Pb exposure affected these cellular properties. Previously, children exposed to low-level Pb showed working memory deficits (Sobin et al., 2015), suggesting an abnormal functional connection between the hippocampus and the medial prefrontal cortex (mPFC). Therefore, we performed

Optogenetics experiments in acute medial PFC slices using these Pb exposed mice to determine if hippocampus-mPFC synapses were altered. Our results show that low Pb exposure altered synaptic transmission whereas high Pb exposure affected short-term synaptic depression at the hippocampal-PFC synapses (Control: N=5 animals; n=6 slices; High Pb: N=4 animals; n=8 slices; Low Pb: N =2 animals; n=3 slices). Overall, these results contribute to better understand the long-term effects of Pb exposure on learning and memory highly relevant to children exposed to Pb early in life.

Disclosures: L.E. Martinetti: A. Employment/Salary (full or part-time): University of Texas- El Paso. B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution; 1SC1GM118242, 5R25GM069621. **A. Tena:** A. Employment/Salary (full or part-time): University of Texas- El Paso. B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution; 1SC1GM118242. **E. Peru:** A. Employment/Salary (full or part-time): University of Texas- El Paso. B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution; 1SC1GM118242. **K. Fénelon:** A. Employment/Salary (full or part-time): University of Texas- El Paso. B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution; 1SC1GM118242.

Poster

782. Synaptic Integration

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 782.04/F29

Topic: B.07. Synaptic Transmission

Support: 1SC1GM118242

Title: Characterization caudal pontine reticular nucleus afferent connections relevant to sensorimotor gating

Authors: J. C. CANO, ***S. A. PACE**, K. FÉNELON;
Univ. of Texas - El Paso, El Paso, TX

Abstract: Sensorimotor gating (SG) is a neural sensory filtering process thought to be governed by central inhibitory mechanisms to help focus attention. SG is impaired in several neuropsychiatric disorders, such as anxiety, autism spectrum disorders, schizophrenia, and post-traumatic stress disorder affecting patients worldwide. Extensive work on the circuitry underlying SG has revealed a key connection between the pedunculopontine tegmental area (PPTg) and the caudal pontine reticular nucleus (PnC), the latter being located at a crucial position between the sensory input and the motor output of the SG circuitry. Furthermore, previous studies where the PPTg-PnC connection was inhibited showed a reduced, but persistent, SG. However, how the PnC is connected to the rest of the brain is unknown. Although, previous studies have identified a few brain circuits contributing to SG, our objective was to further identify neurons directly connected to the PnC since these connected neurons could potentially contribute to SG. Therefore, we hypothesize that other brain areas anatomically connected to the PnC remained to be identified. Our hypothesis was guided by previous *in vivo* lesion studies showing that regions such as the central nucleus of the amygdala (CeA) and the medial prefrontal cortex (mPFC) are important for SG. Here, we first confirmed that the CeA and the mPFC were anatomically connected to the PnC using the retrograde neuronal tracer fluorogold in healthy adult mice (CeA-PnC, n=4; mPFC-PnC, n=2). Second, to further characterize the CeA-PnC and mPFC-PnC connections, Channelrhodopsin-2 was injected in the mouse CeA and mPFC, and extracellular field recordings were performed 6 weeks later in acute PnC slices. Photostimulation of the CeA (n=7) and mPFC (n=2) projection fibers activated PnC neurons confirming that these connections are excitatory, monosynaptic and exhibit short-term synaptic plasticity. Better understanding the CeA-PnC and mPFC-PnC connections might reveal potential therapeutic targets for future medical interventions in diseases associated with SG deficits.

Disclosures: **J.C. Cano:** A. Employment/Salary (full or part-time): University of Texas - El Paso. B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution; 1SC1GM118242. **S.A. Pace:** A. Employment/Salary (full or part-time): University of Texas - El Paso. B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution; 1SC1GM118242. **K. Fénelon:** A. Employment/Salary (full or part-time): University of Texas - El Paso. B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution; 1SC1GM118242.

Poster

782. Synaptic Integration

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 782.05/F30

Topic: B.07. Synaptic Transmission

Support: DFG SFB1089

NRW-Rückkehrerprogramm

Human Frontiers Science Program

DFG SPP1757

Title: Endocannabinoid control of NMDAR-dependent supra-linear dendritic integration via co-agonist supply

Authors: *K. BOHMBACH[1], E. M. SCHÖNHENSE[1], D. MINGE[1], A. ZIMMER[3], H. BECK[2], C. HENNEBERGER[1,4,5];
[1]Inst. of Cell. Neurosciences, [2]Dept. of Epileptology, Univ. of Bonn Med. Sch., Bonn, Germany; [3]Inst. of Mol. Psychiatry, Univ. of Bonn, Bonn, Germany; [4]German Ctr. of Neurodegenerative Dis. (DZNE), Bonn, Germany; [5]Inst. of Neurol., Univ. Col. London, London, United Kingdom

Abstract: Individual dendrites of hippocampal CA1 pyramidal cells integrate local synaptic input. Supra-linear integration of spatially clustered CA3-CA1 input depends on amplification of synaptic input by voltage-gated sodium channels and N-methyl-D-aspartate receptors (NMDARs). Our previous work demonstrated that NMDAR function at these synapses depends on astrocyte supply of the NMDAR co-agonist D-serine (Henneberger *et al.* 2010). This observation implies that also NMDAR-dependent supra-linear integration is controlled by NMDAR co-agonist supply. We used whole-cell patch clamp combined with micro-iontophoretic glutamate application and two-photon excitation fluorescence microscopy to test this hypothesis in acute hippocampal slices from Wistar rats and C57BL/6 mice. We find that, indeed, application of exogenous D-serine reduces the threshold of dendritic spikes, a hallmark of supra-linear dendritic integration, and increases their amplitude. Endogenous D-serine supply depends on astrocyte Ca^{2+} signaling and activation of astrocyte endocannabinoid receptors (CB1R) potently triggers astrocyte Ca^{2+} transients. As expected, application of the CB1R agonist WIN55-212,2 induced prominent Ca^{2+} transients in astrocytes but also boosted supra-linear integration. The latter was not observed in the presence of D-serine at a concentration that saturates the NMDAR co-agonist binding site. Thus, pharmacological CB1R activation increases NMDAR co-agonists supply, likely via astrocyte Ca^{2+} signaling, thereby lowering the threshold of dendritic spikes and increasing their amplitude. Endogenous activation of CB1R occurs when

CA1 pyramidal cells depolarize. Therefore, increasing CA1 pyramidal cell activity should activate the CB1R-dependent boost of supra-linear dendritic integration. We tested this by antidromic activation of CA1 pyramidal cells using electrical stimulation of alvear axons. Activating about 40 percent of CA1 pyramidal cells, revealed by GCaMP5G imaging, was sufficient to decrease the dendritic spike threshold and to increase their amplitudes. Again, this effect was not seen in the presence of saturating concentrations of exogenous D-serine. Importantly, blockade of CB1Rs using AM251 also prevented this effect on dendritic integration. Similarly, alveus stimulation evoked astrocyte Ca^{2+} transients that were sensitive to CB1R inhibition by AM251. In summary, we reveal a novel signaling pathway that creates a positive feedback of CA1 pyramidal cell population activity on their supra-linear dendritic integration involving CB1R-dependent NMDAR co-agonist supply.

Disclosures: K. Bohmbach: None. **E.M. Schönhense:** None. **D. Minge:** None. **A. Zimmer:** None. **H. Beck:** None. **C. Henneberger:** None.

Poster

782. Synaptic Integration

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 782.06/F31

Topic: B.01. Neurotransmitters and Signaling Molecules

Support: Whitehall Foundation

Searle Scholars Program

Title: Excitatory synaptic signaling in parvalbumin positive interneurons in mouse primary visual cortex

Authors: *L. SANCHO[1], B. L. BLOODGOOD[2];
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Abstract: Dendritic spines are small, membranous protrusions that enclose excitatory synapses and function as specialized biochemical and electrical signaling compartments. On densely spiny neurons, such as pyramidal cells, spines enhance the signaling repertoire of the enclosed synapse and support synapse-specific plasticity. On sparsely spiny interneurons such as parvalbumin basket cells (PVBCs), the majority of synapses are made directly onto the dendritic shaft. We find that in primary visual cortex of juvenile mice, layer 2/3 PVBCs have approximately 1 spine per 10 microns. Using extracellular stimulation of presynaptic terminals, whole-cell electrophysiology, pharmacology, and two-photon glutamate uncaging and calcium (Ca^{2+})

imaging we demonstrate that these spines enclose functional excitatory synapses with heterogeneous glutamate receptors and ion channels. Moreover, the complement of receptors at spine synapses is distinct from what is present at nearby dendritic synapses. Consequently, we hypothesize that spine and dendritic synapses will implement different plasticity rules to modulate synaptic Ca^{2+} signaling and to detect the co-incident activation of neighboring synapses.

Disclosures: L. Sancho: None. **B.L. Bloodgood:** None.

Poster

782. Synaptic Integration

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 782.07/F32

Topic: B.07. Synaptic Transmission

Support: KAKEN 26250003

Title: Synaptic connections between hippocampal CA2 pyramidal cells

Authors: *K. OKAMOTO[1], Y. IKEGAYA[2];
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Abstract: Among hippocampal subregions, the CA2 region is unique. CA2 neurons receive strong extrahippocampal input from the subcortical area, including the hypothalamus (Chevaleyre *et al.*, 2010), and alter their firing patterns sensitively to subtle environmental changes (Mankin *et al*., 2015) and to the current location during immobility and sleep (Kei *et a*l., 2016). Moreover, the CA2 region is associated with social recognition (Hitti *et al*., 2014). Although recent studies have increasingly focused on the function of the CA2 region, its local circuit structure remains to be elucidated. It is assumed that CA2 pyramidal neurons have many recurrent connections, based on their dense neurite arborizations (Dudek *et al*., 2016), but there is little electrophysiological evidence. Here, we used multiple whole-cell patch-clamp recordings from CA2 pyramidal cells and computed their connection probability.

Disclosures: K. Okamoto: None. **Y. Ikegaya:** None.

Poster

782. Synaptic Integration

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 782.08/F33

Topic: B.07. Synaptic Transmission

Support: ERC Advanced Grant 268548

Austrian Science Fund P24909-B24

Title: Abundance of recurrent and lateral inhibition in the dentate gyrus of the hippocampus

Authors: C. ESPINOZA, *S. J. GUZMAN, P. JONAS;
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Abstract: The dentate gyrus, the input region of the hippocampus, is thought to play a key role in several higher brain functions, such as grid-to-place code conversion and pattern separation. For these computations, the granule cell-GABAergic interneuron microcircuit plays a critical role. However, the connectivity of this important region of the brain is largely unknown. To determine the functional connectivity rules in the dentate gyrus, we made simultaneous octuple patch-clamp recordings from synaptically connected granule cells and interneurons in acute hippocampal slices. Parvalbumin (PV)-expressing interneurons were identified by epifluorescence or confocal microscopy in a parvalbumin-Cre x Ai14 mouse line before the experiment, and their identity was confirmed by the fast-spiking action potential phenotype in subsequent whole-cell recording. This allowed us to obtain an unbiased estimate of connectivity, examine the abundance of connectivity motifs, and determine the summation rules for converging excitatory inputs. In total, we found 24 synaptic connections in 15 octuples of neurons. The average probability of excitatory synaptic connections was 0.167, and the probability of inhibitory synaptic connections was 0.30. Excitatory synaptic connectivity between granule cells and PV+ interneurons declined for an inter-somatic distance of >150 μm, whereas inhibitory synaptic connectivity between PV+ interneurons and granule cells remained relatively constant. In granule cell-PV+ interneuron pairs in which the PV+ interneuron received excitation from the granule cell, the inhibitory connection probability was 0.13. However, in granule cell-PV+ interneuron pairs in which the PV+ interneuron lacked excitation from the granule cell, the inhibitory connection probability was 0.30. Thus, within dentate gyrus inhibitory microcircuits, lateral inhibition is more abundant than recurrent inhibition. In cases where multiple granule cells were connected to a given PV+ interneuron, summation of EPSPs was approximately linear. Plots of EPSP amplitude against number of stimulated inputs suggested that ~5 unitary excitatory inputs have to be synchronously activated to evoke action potentials in a postsynaptic PV+ interneuron. In conclusion, PV+ interneurons operate as coincidence detectors of local excitatory synaptic activity. Furthermore, PV+ interneurons

distribute an inhibitory output signal to a large number of granule cells by lateral inhibition. These results indicate that lateral inhibition is a major factor shaping pattern separation in the principal neuron-interneuron microcircuits of the dentate gyrus.

Disclosures: **C. Espinoza:** None. **S.J. Guzman:** None. **P. Jonas:** None.

Poster

782. Synaptic Integration

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 782.09/F34

Topic: B.07. Synaptic Transmission

Support: OTKA K83251

OTKA K115441

NNF 85659

OMFB-01678/2009

AIK 12-1-2013-0005

EU FP7 Grant 604102

LP2012-23

Title: Properties and detailed temporal dynamics of inhibitory synaptic communication between perisomatic-region targeting inhibitory neurons and pyramidal cells in mouse hippocampal CA3 region.

Authors: *D. SCHLINGLOFF, Z. KOHUS, S. KÁLI, L. ROVIRA-ESTEBAN, O. PAPP, T. F. FREUND, N. HÁJOS, A. I. GULYÁS;
Inst. of Exptl. Medicine, HAS, Budapest, Hungary

Abstract: The CA3 region of the hippocampus is able to generate synchronous network activities intrinsically, and it is crucial for cognitive functions like spatial navigation and long-term memory consolidation. Pyramidal cells and their perisomatic region-targeting interneurons, including parvalbumin (PV)-expressing basket cells, axo-axonic cells and cholecystokinin (CCK)-containing basket cells are the critical elements of the CA3 networks in the generation and control of physiological (sharp wave-ripples, gamma oscillation) and pathological (epileptic) activity patterns. Synaptic interactions among these cell types are thought to be critical for

current and rhythmogenesis. Using paired recordings in the CA3 area of mouse hippocampal slices, we determined the detailed properties and dynamics of inhibitory synaptic communication between morphologically identified inhibitory cells and their pyramidal cell and interneuron targets using action potential patterns recorded during physiological and pathological network states. PV+ and CCK+ interneurons had distinct intrinsic physiological features. Interneurons of the same type, except axo-axonic cells, formed reciprocally connected subnetworks, while the connectivity between the interneuron classes was rather sparse. The characteristics of unitary interactions depended on the identity of both pre- and postsynaptic partners, while the short-term plasticity of synaptic transmission depended mainly on the presynaptic cell type. PV+ interneuron output showed frequency-dependent depression, while more complex dynamics involving facilitation, depression, and asynchronous release characterized the output of CCK+ interneurons. We captured the dynamics of transmission at these different types of connection with simple mathematical models, and described quantitatively the response to physiological and pathological discharge patterns. Our findings support the view that intrinsic and synaptic features of PV+ cells make them ideally suited for the generation of physiological network oscillations, while the continuum of CCK+ cells implement more subtle, graded control.

Disclosures: **D. Schlingloff:** None. **Z. Kohus:** None. **S. Káli:** None. **L. Rovira-Esteban:** None. **O. Papp:** None. **T.F. Freund:** None. **N. Hájos:** None. **A.I. Gulyás:** None.

Poster

782. Synaptic Integration

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 782.10/F35

Topic: B.07. Synaptic Transmission

Support: SFB 1089 Project B01, C01

Title: Afferent synaptic connectivity of the medial septum

Authors: ***F. FUHRMANN**[1], D. JUSTUS[1], D. FRIEDRICHS[1], M. K. SCHWARZ[2], S. REMY[1,3];
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Abstract: The medial septum and the diagonal band of Broca (MSDB) modulate the activity of memory circuits in the hippocampal formation (Winson, 1978; Oddie et al., 1996). In addition to the role of MSDB parvalbuminergic neurons (PV^+) as pacemakers for hippocampal rhythmic

oscillations (Hangya et al., 2009), we have shown that MSDB glutamatergic neurons ($VGluT2^+$) mediate a hippocampal state-transition associated with locomotion (Fuhrmann et al., 2015). The activity of MSDB $VGluT2^+$ neurons underlies the speed-modulation of theta oscillations and the speed-modulation of the firing of pyramidal neurons in the hippocampus and entorhinal cortex. Since MSDB activity may contributes to a dynamic representation of self-location during navigation at different speed, it is important to understand the afferent connectivity to the MSDB. Using cre-dependent mono-transsynaptic retrograde tracing we localized specific synaptic input regions onto MSDB $VGluT2^+$ neurons. We found monosynaptic input neurons in several hypothalamic subregions and the median raphe nuclei. We identified the medial preoptic area (MPO), the median preoptic nucleus (MEPO), the periventricular hypothalamic nucleus (PVpo), the arcuate hypothalamic nucleus (ARH) , the lateral hypothalamic area (LHA), the posterior hypothalamic nucleus (PH) and the supramammillary nucleus (SUM) as specific input regions onto MSDB $VGluT2^+$ neurons.
Consistent with excitatory input from PH electrical stimulation of this area reliably evoked locomotor behavior and theta oscillations. We now combine electrical stimulation with cell-type specific silencers in the MSDB and use mono-transsynaptic retrograde tracing to understand the integration and the role of specific afferent input onto MSDB glutamatergic, parvalbuminergic and cholinergic neurons during theta oscillations and locomotor behavior.

Disclosures: **F. Fuhrmann:** None. **D. Justus:** None. **D. Friedrichs:** None. **M.K. Schwarz:** None. **S. Remy:** None.

Poster

782. Synaptic Integration

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 782.11/F36

Topic: B.07. Synaptic Transmission

Title: Modulation of neuronal excitation/inhibition balance by the light/dark cycle

Authors: ***K. HE**[1], M. D. BRIDI[2], A. KIRKWOOD[2];
[1]IRCBC, Chinese Acad. of Sci., Shanghai, China; [2]Mind/Brain institute, Johns Hopkins Univ., Baltimore, MD

Abstract: It is widely accepted that neural processing depends critically on the balanced interplay of excitation and inhibition, a balance that is dynamically maintained within permissive limits. Dysregulation of neuronal excitation/inhibition (E/I) balance has been implicated in several disorders including schizophrenia, autism, and Alzheimer's disease. Much research has focused on plastic mechanisms responsible for maintaining the E/I balance and much less is

known about how it might naturally change. Here we focused on investigating the contribution of light/dark cycle, which is correlated with the sleep/wake cycle in mouse, to the E/I regulation of the pyramidal neurons in both neocortices and hippocampus. Our results indicate that the measures of strength for excitatory and inhibitory synaptic transmission are modulated by the light/dark cycle, and surprisingly, in the opposite manner: excitation is high when inhibition is low. This leads to large fluctuations in E/I balance during the light/dark cycle. This rhythmic modulation is reflected in both single cell and network levels, and is consistent across different neocortical regions and hippocampus, suggesting that the light/dark modulation of neuronal E/I balance might be generalized to multiple brain structures.

Disclosures: K. He: None. **M.D. Bridi:** None. **A. Kirkwood:** None.

Poster

783. Tauopathies

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 783.01/F37

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: IWT (130690)

Title: Molecular analysis of Tau in canine brain and csf

Authors: *K. VAN KOLEN[1], D. VAN HAVER[2], D. DHUYVETTER[1], L. DELBROEK[1], I. VERBERNE[1], A. F. MARREIRO[3], M. VANDERMEEREN[1], K. GEVAERT[2], I. PIKE[4], M. WARD[4], D. LATTO[4], H. BORGHYS[1], M. H. MERCKEN[1];
[1]Janssen PRD, Beerse, Belgium; [2]Proteomics expertise center, VIB/UGent, Gent, Belgium; [3]Functional genomics and proteomics, KUL, Leuven, Belgium; [4]Proteome Sci., London, United Kingdom

Abstract: Background: Tau is the main component of neurofibrillary tangles and the current assumption is that neuronal loss results in passive release of this protein in the extracellular space resulting in an increase in both total and phosphorylated Tau in different neurodegenerative diseases. Nevertheless, little is known about the molecular signature of this protein in cerebrospinal fluid (CSF) and how this profile changes in response to Tau-directed therapies. Since CSF collection from mice and rats is not trivial and yields low sample volumes, other preclinical model systems are required. In this respect, studies performed in dog demonstrated spontaneous amyloid plaque formation in function of aging but changes in brain and CSF Tau are poorly documented. The aim of this study is to identify antibody combinations to detect and characterize Tau fragments in canine brain and CSF.

Methods: Pooled dog CSF samples were investigated with sandwich ELISA's and MSD assays using a panel of Tau antibodies directed to a large variety of Tau epitopes. Antibodies giving a positive signal were further validated by immunodepletion experiments combined with mass spectrometry analysis. In parallel a quantitative proteomics analysis (TMTcalibrator™, Proteome Sciences) was performed to estimate the coverage of the Tau protein and other proteins in canine CSF.
Results: Antibodies reacting with Tau in dog CSF samples could be identified. These antibodies are currently used to determine the molecular fingerprint of Tau in dog CSF. Use of the TMT calibrator™ approach showed high coverage of the tau sequence. Although, selective enrichment of phosphopeptides was not employed, it was still possible to detect multiple tau phospho-peptides, likely reflecting the most abundant epitopes in canine CSF. Despite this high coverage, IP/MS experiments showed a differential recovery of Tau peptides depending on the epitope of the antibody used for the pulldown. These data suggest that a substantial fraction of Tau in CSF is fragmented as confirmed by different MSD assays on immunodepleted CSF samples.
Conclusions: This study compared the molecular profile from Tau present in canine CSF to Tau extracted from brain. Although, we provide evidence for the presence of full length Tau, the majority of this protein seems to be fragmented in CSF. Several antibody combinations can be used to quantify those fragments and future studies will shed light on the potential use of those fragments as pharmacodynamic markers for Tau-directed therapies in AD.

Disclosures: **K. Van Kolen:** A. Employment/Salary (full or part-time): Janssen PRD. **D. Van Haver:** None. **D. Dhuyvetter:** A. Employment/Salary (full or part-time): Janssen PRD. **L. Delbroek:** A. Employment/Salary (full or part-time): Janssen PRD. **I. Verberne:** A. Employment/Salary (full or part-time): Janssen PRD. **A.F. Marreiro:** None. **M. Vandermeeren:** A. Employment/Salary (full or part-time): Janssen PRD. **K. Gevaert:** None. **I. Pike:** A. Employment/Salary (full or part-time): Proteome Sciences. **M. Ward:** A. Employment/Salary (full or part-time): Proteome sciences. **D. Latto:** A. Employment/Salary (full or part-time): Proteome sciences. **H. Borghys:** A. Employment/Salary (full or part-time): Janssen PRD. **M.H. Mercken:** A. Employment/Salary (full or part-time): Janssen PRD.

Poster

783. Tauopathies

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 783.02/F38

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH Grant AG023501

NIH Grant AG19724

NIH Grant AG033017

Title: Selective regional and neuronal vulnerability in frontotemporal dementia with MAPT mutations

Authors: *L.-C. LIN, J. A. BROWN, L. T. GRINBERG, W. W. SEELEY;
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Abstract: Autosomal dominant mutations in the gene encoding microtubule-associated protein tau (*MAPT*) present with behavioral variant frontotemporal dementia (bvFTD) due to tau aggregation and neurodegeneration in anteromedial temporal, amygdala, frontoinsula (FI), and anterior cingulate cortex (ACC). Cell type-specific vulnerability within these regions remains largely unexplored. Patients with sporadic bvFTD show early selective loss of layer 5 von Economo neurons (VENs) in the FI and ACC. Here, we investigated selective regional and neuronal vulnerability in patients with bvFTD due to mutation in *MAPT*. We performed detailed morphological and immunohistochemical analyses of tau pathomorphologies in 54 regions of 5 subjects with FTDP-17 (2 IVS10+16 C>T, 2 P301L, 1 V337M), and compared the findings to 6 patients with bvFTD due to Pick's disease (PiD), a sporadic tauopathy. Nonspecific features of neurodegeneration, including microvacuolation, astrogliosis, and neuronal loss, were semi-quantified based on hematoxylin and eosin stains. Ten tau aggregate types were semi-quantified using an early phosphorylated tau antibody CP13. To assess the overall tau pathomorphologies of each region, we calculated a composite score by adding tau and neurodegeneration scores. The top five most vulnerable regions (highest composite scores) in bvFTD-*MAPT* were entorhinal cortex, locus coeruleus, middle insula, subgenual cingulate cortex, and anterior mid-cingulate cortex. This pattern overlapped with the vulnerability seen in PiD, with 4 of the top 5 regions being identical (except for locus coeruleus). Comparing VENs and neighboring layer 5 neurons bearing tau inclusions in bvFTD-*MAPT*, our preliminary data suggested that VENs were more prone to pathological tau inclusions than neighboring layer 5 neurons in the FI and ACC. Our results indicate a common, early, regional and neuronal vulnerability in the FI and ACC to pathological tau inclusions across bvFTD due to mutations in *MAPT* and PiD. These findings begin to provide neuroanatomical grounding for further investigation of selective vulnerability in sporadic and familial tauopathies.

Disclosures: **L. Lin:** None. **J.A. Brown:** None. **L.T. Grinberg:** None. **W.W. Seeley:** None.

Poster

783. Tauopathies

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 783.03/F39

Topic: C.02. Alzheimer's Disease and Other Dementias

Title: Loss of SFPQ, an intra-nuclear counterpart of FUS causes FTLD-like phenotypes

Authors: *Y. FUJIOKA[1], S. ISHIGAKI[1], S. YOKOI[1], D. HONDA[1], H. OKADO[2], H. WATANABE[1], M. KATSUNO[1], G. SOBUE[3];
[1]Neurol., Nagoya Univ. Grad. Sch. of Med., Nagoya, Japan; [2]Dept. of Brain Develop. and Neural Regeneration, Tokyo Metropolitan Inst. of Med. Sci., Tokyo, Japan; [3]Res. Div. of Dementia and Neurodegenerative Disease, Nagoya Univ. Grad. Sch. of Med., Nagoya, Japan

Abstract: [Objective]We identified splicing factor, proline- and glutamine rich (SFPQ) as a counterpart of FUS in the nucleus. SFPQ regulates alternative splicing of the Mapt gene at Exon 10 as FUS does. Because the disease mutations in FUS affect the interaction between FUS and SFPQ, we speculated that the interaction is critical for the function of FUS, especially for maintaining the balance of Mapt isoforms. Therefore, we investigate the phenotypes of SFPQ-silenced animals. [Methods]We injected AAV encoding shRNA against SFPQ (shSFPQ) and control to the bilateral hippocampus of C57/BL6J. Next, we performed co-injection of AAV encoding shRNA against Mapt Exon10+ isoform (4-repeat tau:4R-T). These mice were subjected to various behavioral analysis. Sequentially, MRI and immunohistological analysis were performed. [Results]Silencing of SFPQ resulted in an increased ratio of 4R-T/3R-T and exhibited FTLD-like behavioral impairments as well as reduced adult neurogenesis as seen in shFUS mice. Long-term observation revealed phosphorylated tau accumulation and drastic neuronal loss in shSFPQ mice. Co-silencing of 4R-T ameliorated the behavioral phenotypes and reduced neurogenesis; however, it could not rescue neuronal loss in shSFPQ mice. [Conclusions]Loss of SFPQ caused FTLD-like phenotypes, including aberrant behaviors, reduced adult neurogenesis, and phosphorylated tau accumulation mediated by alteration of tau isoforms. These findings are similar with those in FUS-silenced mice, suggesting that SFPQ is essential for the pathogenesis of FTLD/ALS in which quality loss of FUS is associated.

Disclosures: Y. Fujioka: None. **S. Ishigaki:** None. **S. Yokoi:** None. **D. Honda:** None. **H. Okado:** None. **H. Watanabe:** None. **M. Katsuno:** None. **G. Sobue:** None.

Poster

783. Tauopathies

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 783.04/F40

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH Grant 1R21NS093442-01A1

Title: Optogenetic based regulation of autophagy against tauopathies

Authors: *J. BINDER[1], J. WEICK[2], V. DERETIC[1], K. BHASKAR[1];
[1]MGM, [2]Neurosciences, Univ. of New Mexico, Albuquerque, NM

Abstract: Filamentous aggregation of microtubule associated protein tau, as neurofibrillary tangles (NFTs), is a major pathological hallmark of tauopathies including Alzheimer's disease (AD). This pathological tau (p-Tau) impairs microtubule function, axonal transport and synaptic function, which in turn strongly correlate with cognitive decline. Multiple reports have suggested impaired autophagic clearance of p-Tau within neurons leads to NFT pathology and neurodegeneration. Transcription factor EB (TFEB), which is a master regulator of autophagy flux, has recently been shown to clear p-Tau, prevent synaptic and behavioral defects in a mouse model of tauopathy. Futhermore, our group has recently demonstrated that induction of autophagy either via FDA approved drugs (Bromhexine/Flubendazole) or by overexpressed TFEB can clear inflammation-induced p-Tau in neuronal cells. However, sustained activation of TFEB and autophagy may pose the risk of burdening cellular bioenergetics and be deleterious during conditions such as ischemic stroke, which is more prevalent in aged individuals. Here we have tested a light-based gene expression system developed by Gardner et al. (Nat Chem Biol. 2014 March ; 10(3): 196–202) to encode TFEB, with a goal to achieve precise spatio-temporal control over TFEB expression and thus regulatable autophagy flux in neuronal cells. This technology utilizes an engineered version of EL222, a bacterial transcription factor that contains a Light-Oxygen-Voltage protein, which binds DNA when illuminated with blue light (465nm). First, HEK293T cells transiently transfected with EL222 and TFEB-Flag plasmids, displayed robust TFEB-Flag expression when exposed to 465nm light (~2W/m^2) for 9 -12 hours compared to no-light condition. Second, transfection of HEK293Ts with human tau carrying T231D/S235D mutations and light-responsive TFEB-Flag followed by light induction resulted in significant increase in Flag-TFEB expression and reduction of p-Tau (transfected), but not normal tau (endogenous). Third, light-based induction of TFEB also resulted in increased expression of autophagy markers such as p62 and LC3B-II in the HEK293Ts compared to no-light condition. Finally, as a first step in testing this approach in neuronal system, we tested inducible pluripotent stem cell derived neurons (iPSNs) from Down's syndrome patient and observed significantly elevated tau oligomers, tau hyperphosphorylated at AT180 and AT8 sites. In the ongoing studies,

we are engineering lenti-viral expression system that encodes EL222 and TFEB-Flag to induce autophagy in primary neurons, iPSNs and in rTg4510 mouse model of tauopathy.

Disclosures: **J. Binder:** None. **J. Weick:** None. **V. Deretic:** None. **K. Bhaskar:** None.

Poster

783. Tauopathies

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 783.05/F41

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH Grant AG01758

NIH Grant NS044266

NIH Grant AG032953

NIH Grant AG043503

NIH Grant NR014777

NIH Grant P30 AG10124

NIH Grant PO1 AG 017586

Title: Survival in 4-repeat tauopathies is associated with cerebrospinal fluid phosphorylated tau

Authors: *K. A. FIRN[1], L. M. SHAW[2], D. J. IRWIN[1], M. GROSSMAN[1], C. T. MCMILLAN[1]; [1]Neurol., [2]Pathology and Lab. Med., Univ. of Pennsylvania, Philadelphia, PA

Abstract: Progressive Supranuclear Palsy (PSP), Corticobasal Degeneration (CBD), and Parkinson's Disease (PD), including PD with mild cognitive impairment (MCI) and dementia, are all characterized by parkinsonian motor features that may additionally include cognitive impairments. However, there are distinct sources of pathology in PSP and CBD (misfolded four-repeat protein tau, 4Rtau) compared to PD (alpha-synuclein). Both sources of pathology are associated with heterogeneous rates of survival, with a median of 5 years in PSP and 9 years in PD. Thus objective prognostic markers are essential to improve management of patient care and to stratify clinical trials. Cerebrospinal fluid (CSF) phosphorylated tau (ptau) is associated with tau pathological inclusions, and thus we hypothesize it will have specificity for 4Rtau survival, but not for PD survival. CSF total tau (ttau), in contrast, is a marker of neuronal degeneration and thus is hypothesized to lack specificity. We evaluated survival in 33 4Rtau patients and 42 age-

matched PD patients. All patients participated in a CSF lumbar puncture <3 years from disease onset, and exclusion criteria included CSF evidence of amyloid pathology (amyloid-beta<192) to exclude co-morbid AD pathology. Survival was calculated from reported age at onset to age at death, or patients were censored using reported year of last clinical visit. Cox regression models covaried gender, disease duration at CSF collection, and age at CSF collection. Ptau was associated with reduced survival in the 4Rtau cohort (β=-0.535; $p<0.005$). Ptau was not associated with survival in PD, and ttau was not associated with survival in 4Rtau or PD (all $p>0.1$). Together, these findings suggest that CSF ptau may provide a specific prognostic marker of survival in 4Rtau and should be considered as covariate in tau-targeted clinical trials.

Disclosures: K.A. Firn: None. **L.M. Shaw:** None. **D.J. Irwin:** None. **M. Grossman:** None. **C.T. McMillan:** None.

Poster

783. Tauopathies

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 783.06/F42

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH R01NS062830

Title: Amyloid induced axonal degeneration in p301L tau mice

Authors: *C. A. NISHIOKA[1,2], H.-F. LIANG[1], S.-W. SUN[1];
[1]Loma Linda Univ., Loma Linda, CA; [2]Neurosci., UC Riverside, Riverside, CA

Abstract: Evidence from post-mortem histology and in vivo diffusion tensor imaging (DTI) suggest that white matter tract damage is widespread in Alzheimer's Disease (AD). Cohort studies have revealed this damage potentially begins very early in the disease process, in patients with mild cognitive impairment. However, it remains unclear if this damage results purely from general cell loss, or from a selective axonal pathology. To study this phenomena, we attempted to induce early white matter damage in p301L tau transgenic mice using a targeted injection of Aβ into the lateral geniculate nucleus. After injections, we specifically examined retinal ganglion cells and their projections, which form the optic nerve (ON) and tract (OT). Using a combination of modalities, including DTI, optical coherence tomography (OCT) and histology, we could longitudinally tract and disentangle axonal degeneration from cell body loss. We demonstrate that early white matter damage results from selective axonal loss, and suggest that axons follow a 'dying-back' pattern of degeneration. Furthermore, our results indicate that axon loss resulting from amyloid pathology may be dependent upon tau aggregation. These results implicate axon-

specific mechanisms in the development of white matter damage and neurodegeneration during the early stages of AD.

Disclosures: **C.A. Nishioka:** None. **H. Liang:** None. **S. Sun:** None.

Poster

783. Tauopathies

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 783.07/F43

Topic: C.02. Alzheimer's Disease and Other Dementias

Title: Biochemical characterization of novel transgenic mouse tauopathy models carrying a variant of the human triple-repeat tau gene and/or the hAPP gene.

Authors: ***A. ARNER**[1], A. ADAME[2], E. ROCKENSTEIN[2], M. MANTE[2], D. MASLIAH[2], E. MASLIAH[2], R. A. RISSMAN[2];
[1]Biol., [2]UCSD, San Diego, CA

Abstract: Tauopathies encompass several of the most prevalent neurodegenerative diseases that consistently progress to severe dementia and motor impairments. They involve tau hyperphosphorylation, which leads to the proteins detachment from associated microtubules, and a decline in the structural integrity of the cytoskeleton. This disassociation is followed by intracellular tau aggregation that causes impairment of axonal function. The mortality rate of the most common tauopathy, Alzheimer disease (AD), has increased dramatically in the last decade. Due to a lack of understanding of the pathogenic mechanisms involved in AD, treatment is currently limited to minimizing symptoms, without the ability to slow the rate of neurodegeneration. Another component of AD is that it is uniquely associated with extracellular accumulation of amyloid beta plaques, which appear to disrupt synaptic function, as well as induce inflammation. Developing and researching a variety of transgenic animals meant to model these diseases is critical to advancing the efficacy of their treatment and prevention. We generated a novel transgenic mouse line carrying the human amyloid precursor protein gene (hAPP) and crossed it to our recently generated line of mice that overexpress a variant of the human triple repeat tau gene (3R Tau), to create a novel bigenic mouse AD model. We characterized the pathological and cognitive changes associated with this model, both in young and aged mice. Our results demonstrate higher levels of phosphorylated tau in the mice carrying the 3R Tau gene. Interestingly, bigenic mice had higher levels of phosphorylated tau than all other groups. Increased levels of tau kinases were observed in the 3R Tau mice, with levels in bigenic mice exceeding these levels. Our immunohistochemical data suggest increased levels of

glial scarring and neuronal loss in 3R Tau mice, and this finding was exacerbated in bigenic mice. Beta-amyloid was only detected in the particulate fraction of the hAPP mice.

Disclosures: **A. Arner:** None. **A. Adame:** None. **E. Rockenstein:** None. **M. Mante:** None. **D. Masliah:** None. **E. Masliah:** None. **R.A. Rissman:** None.

Poster

783. Tauopathies

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 783.08/F44

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: LECMA, Ligue Européenne Contre la Maladie d'Alzheimer, Research Grant 2016-2017

Paris-Sud University, PhD fellowship (Audrey Vautheny)

Title: Role of the microglial TREM2 receptor in a model of tauopathy induced by gene transfer in mice

Authors: *A.-P. BEMELMANS, A. VAUTHENY, G. AUREGAN, C. JOSÉPHINE, M.-C. GAILLARD, K. CAMBON, P. HANTRAYE;
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Abstract: Recent genomic studies have shown the correlation between neuroinflammation and Alzheimer's disease (AD) and involved notably the R47H polymorphism of TREM2, a cell-surface receptor of microglia. Subsequently, several studies have shown that microglial activation is altered in mouse models of amyloidosis deficient in TREM2. However the role of TREM2 on the tauopathy component of AD is much less studied. To fill this gap, we have applied our recently developed rodent model of tauopathy in *Trem2* knockout mice. We overexpressed different forms of the human tau protein in CA1 neurons of the hippocampus by intracerebral injection of adeno-associated virus vectors (AAV-Tau). In wild type mice, the transduced cells then gradually develop over several weeks a profile of tauopathy, including Tau hyperphosphorylation and Tau aggregation, evidenced respectively by AT8 and AT100 immunolabeling, and cell death. Based on the 1N4R form, we developed several Tau transgenes that showed different profiles of aggregation and toxicity, and we analyzed tauopathy progression one and three months after AAV administration. Wild-type Tau produced few aggregates but led to an important degeneration of CA1 pyramidal neurons. Tau-P301L, a mutant form found in familial cases of fronto-temporal dementia with Parkinsonian syndrome

linked to chromosome 17, led to significant aggregation and toxicity. We also co-expressed the wild-type form with a peptide seed which promotes its aggregation while markedly reducing its toxicity for CA1 neurons. In *Trem2* knockout mice, the different Tau vectors led to the same pattern of tauopathy as in wild type mice at one month and three months post vector administration. In addition to the tauopathy, AAV-Tau elicited a microglial activation which was more pronounced in wild-type Tau-treated animals than in mice treated with Tau-P301L or Tau co-expressed with the peptide seed. However, in Trem2 knockout mice, microglial activation was significantly reduced following wild type Tau gene transfer. This suggests that, as in amyloidosis models, TREM2 deficiency inhibits microglial activation during tauopathy. However, this does not seem to impact the progression of this cardinal feature of AD.

Disclosures: A. Bemelmans: None. **A. Vautheny:** None. **G. Auregan:** None. **C. Joséphine:** None. **M. Gaillard:** None. **K. Cambon:** None. **P. Hantraye:** None.

Poster

783. Tauopathies

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 783.09/F45

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: ARUK: ARUK-PhD2013-8

WT: WT088033MA

Title: Altered tau phosphorylation in neurons cultured from a new tau transgenic mouse model of human tauopathy

Authors: *N. YANKOVA[1], M. BONDULICH[2], W. NOBLE[2], D. HANGER[2];
[1]King's Col. London, London, United Kingdom; [2]King's Col. London, Inst. of Psychiatry, Psychology & Neuroscience, Dept. of Basic and Clin. Neurosci., London, United Kingdom

Abstract: Tauopathies comprise a broad group of neurodegenerative diseases that are characterised by the deposition of tau in the brain. It is likely that a combination of a toxic gain-of-function acquired by tau aggregates, together with a loss of normal function of tau, may be responsible for the clinical presentation in these disorders. Diseases in which 4R tau isoforms are overrepresented such as progressive supranuclear palsy, exhibit a truncated form of tau (Tau35) that is absent from age-matched controls. We have generated a new mouse model of tauopathy in which Tau35 is expressed in the absence of any mutation and under the control of the human tau promoter. Unlike most existing tau transgenic mice, expression of Tau35 in these mice is less

than 10% of that of endogenous mouse tau and comparable with tau expression in human neurodegenerative disease. Tau35 mice demonstrate key features of human tauopathy, including aggregated and abnormally phosphorylated tau, progressive cognitive and motor deficits, loss of synaptic protein, and reduced life-span. To determine the influence of a disease-relevant fragment of tau on mechanisms involved in maintaining neuronal viability, we have examined tau phosphorylation and mitochondria in primary cortical neurons derived from Tau35 mice. Many neurodegenerative diseases demonstrate abnormal mitochondrial morphology, biochemical dysfunction and mobility. Therefore, defective mitochondrial function may be critically involved in neurodegeneration cascades and may be of significance for the pathogenesis of tauopathies. This emulation of disease progression in a novel mouse model will enable identification of the molecular changes that lead to a neurodegenerative phenotype in human tauopathies.

Disclosures: **N. Yankova:** None. **M. Bondulich:** None. **W. Noble:** None. **D. Hanger:** None.

Poster

783. Tauopathies

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 783.10/F46

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: Alzheimer's Association Grant 453589

NIH Grant 5T32GM008471-23

Title: Disease-related MAPT mutations alter steady-state levels of tau protein

Authors: ***J. GAMACHE**[1], K. ASHE[2], M. KOOB[3];
[2]Neurol., [3]Lab. Med. and Pathology, [1]Univ. of Minnesota, Minneapolis, MN

Abstract: Alzheimer’s disease is one of 20 tauopathies, diseases in which the microtubule-associated protein tau becomes abnormally regulated and aggregates into neurofibrillary tangles, a hallmark of Alzheimer’s. It is not well understood how mutations in the tau gene (*MAPT)* contribute to the deleterious effects of the mutated protein in the brain. To study this, I am using a novel mouse model that harbors a regulatable human tau transgene in a targeted genomic locus. Genome editing with the CRISPR/Cas system will allow for the generation of multiple lines of mice equivalent in every way except for single mutations in the tau transgene. Preliminary work has shown that a mutation underlying a related tauopathy, Frontotemporal dementia, increased steady-state levels of human tau protein relative to wild-type tau without the mutation. This

observation led to the hypothesis that mutations increase steady-state tau levels by hindering protein degradation, possibly increasing the propensity of tau to mislocalize and aggregate within neurons. Upcoming studies will measure the half-life of this form of mutated tau to clarify whether a slower rate of degradation underlies the observed elevated levels. To determine whether other disease-related *MAPT* mutations may share a common mechanism, I will use CRISPR/Cas to introduce different classes of mutations into the transgene including those affecting the amino acid sequence, alternative splicing, or both. In the resulting mouse lines, I will measure steady-state human tau protein levels associated with each mutation. This work may show that different classes of mutations in *MAPT* have a common effect of prolonging the half-life of tau, which may underlie neurotoxicity in tauopathies.

Disclosures: J. Gamache: None. **K. Ashe:** None. **M. Koob:** None.

Poster

783. Tauopathies

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 783.11/F47

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: BBSRC grant PHPH SA5883

Title: *In vivo* imaging of mitochondrial transport in the rTg4510 mouse model of tauopathy

Authors: *J. D. JOHNSON[1], R. LEES[1], D. URSU[2], J. S. JACKSON[2], M. J. O'NEILL[2], M. ASHBY[1];
[1]Physiology, Pharmacol. and Neurosci., Univ. of Bristol, Bristol, United Kingdom; [2]Eli Lilly and Co., Windlesham, United Kingdom

Abstract: The pathological accumulation of tau is associated with a number of diseases including Alzheimer's Disease (AD). Tau is known as a microtubule stabilizing protein, enabling the replenishment and regulation of the key transport route for axonal cargoes. Tau is hyperphosphorylated, becoming aggregative, and spreads throughout the cell and brain forming intracellular neurofibrillary tangles. The small soluble aggregations of tau are linked to dysfunction within neurons. Uncovering the leading functional elements that could underpin the gross synapse loss and cell death observed in AD is crucial in slowing down or reversing this disease. Mitochondria are crucial neuronal well-being and maintenance of synaptic function. Mitochondrial malfunction is linked to degenerative pathology in dementia. Mitochondrial dysfunction can lead to decreases in ATP production, increases in damaging Reactive Oxygen Species, disruption in calcium buffering and apoptosis control. These dysfunctional and

damaging pathways can lead to synaptic damage and cell death. The changes and the time course of mitochondrial function and its relationship to synapse loss in AD patients and animal models, is unknown. It is thought mitochondria could have upstream effects related to hyperphosphorylated tau, and could also be affected by any downstream microtubule transport impairments. Here, the rTg4510 mouse, which expresses a repressible form of human tau containing the P301L mutation linked to human frontotemporal dementia with parkinsonism-17 (FTDP-17), is used to assess mitochondrial changes associated with onset of neurodegenerative pathology. Longitudinal *in vivo* two-photon microscopy is used to investigate structural and functional changes in mitochondria within cortical neurons along the time course of pathological progression. rTg4510 mice and control littermates were transduced with an AAV driving expression of mitochondrial-targeted fluorescent protein in a subset of excitatory cortical neurons. The distribution and motility of axonal mitochondria was imaged in head-fixed, anaesthetized subjects. Mitochondrial location, morphology and speed of movement were measured semi-manually using ImageJ. Repeated imaging of the same axons over the course of the disease reveals the relationship between development of tauopathy and defects in mitochondrial localization and transport. These insights will define when and how the axonal mitochondria, which are crucial for presynaptic function, are affected by pathological malfunction of tau.

Disclosures: **J.D. Johnson:** None. **R. Lees:** None. **D. Ursu:** None. **J.S. Jackson:** None. **M.J. O'Neill:** None. **M. Ashby:** None.

Poster

784. Amyloid-Beta Toxicity

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 784.01/F48

Topic: C.02. Alzheimer's Disease and Other Dementias

Title: Roles of Aβ plaques on the dynamics of soluble Aβ in the brains of APP transgenic mice

Authors: *Y. NAKA, T. WAKABAYASHI, T. HASHIMOTO, T. IWATSUBO;
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Abstract: Alzheimer’s disease (AD) is a progressive neurodegenerative disease and the most frequent cause of dementia in the elderly. Massive deposition of senile plaques (SPs) in the cerebral cortex is a pathological hallmark of AD brains. Amyloid imaging techniques revealed that SPs are present >10 years before the symptomatic onset, although the roles of SPs in the dynamic aspects of AD pathology are unclear. Based on the understanding that the imbalance between production and clearance of amyloid β peptide (Aβ), a major component of SP amyloid,

leads to AD pathology, we hypothesized that SPs influence the dynamics of soluble Aβ in the brain. To test this theory, we first quantified the level of Tris-buffered saline (TBS)-soluble Aβ and the percentage area of Aβ plaques (Aβ burden) in the hippocampus of 18-month-old APP transgenic (tg) mice (A7 line), and found a positive correlation between the levels of TBS-soluble Aβ and Aβ burden. Next, we quantified the levels of interstitial fluid (ISF) Aβ by *in vivo* microdialysis using 1,000-kDa molecular weight cut-off microprobe in the hippocampus of 18-month-old APP tg mice, and found a negative correlation between ISF Aβ and Aβ burden. These data suggest that, under the presence of Aβ plaques, brain ISF Aβ may be exchangeable with the TBS-soluble Aβ, and that a fraction of TBS-soluble Aβ represents species captured by Aβ plaques from the ISF. To determine the molecular size of TBS-soluble Aβ in APP tg mice, we separated TBS-soluble fraction from the brains of 18-month-old APP tg mice by size exclusion chromatography with tandem Superdex75 columns, and found that TBS-soluble Aβ was separated into three peaks, i.e., at ~200-300 kDa (peak 1), ~50-80 kDa (peak 2), and 10-20 kDa (peak 3). In 5~7-month-old younger APP tg mice bearing no plaques, TBS-soluble Aβ was separated into a single peak eluting at ~50-80 kDa (peak 2). The levels of Aβ in peak1 were positively correlated with the Aβ burden in the hippocampus of 18-months-old Tg mice, whereas no correlation was found between the Aβ levels in peaks 2 or peak 3 and the Aβ burden. These date suggest that Aβ separated as a ~200-300 kDa complex inTBS-soluble fraction may be the species captured by Aβ plaques. Taken together, we postulate that Aβ plaques may have a role as the pool of soluble high-molecular-weight Aβ species, thereby affecting the dynamics of soluble Aβ in the brain.

Disclosures: **Y. Naka:** None. **T. Wakabayashi:** None. **T. Hashimoto:** None. **T. Iwatsubo:** None.

Poster

784. Amyloid-Beta Toxicity

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 784.02/F49

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: Kempestiftelserna

Hjärnfonden

Alzheimerfonden

Title: Antibodies targeting the N-terminal part of the amyloid β-peptide can impair the lateral assembly of filaments and the intrinsic stability of amyloid fibrils

Authors: *A. PAMRÉN, I. IAKOVLEVA, T. ISLAM, K. BRÄNNSTRÖM, L. SANDBLAD, A. OLOFSSON;
Umeå Univ., Umeaa, Sweden

Abstract: The self-assembly of the amyloid β-peptide (Aβ) into amyloid fibrils is linked to Alzheimer's disease and factors affecting its assembly are consequently of interest to elucidate. It has recently been suggested that antibodies targeting the N-terminal part of the Aβ peptide could dissociate amyloid formations into monomers and low molecular weight oligomers. We can here present an alternative explanation suggesting that the Aβ amyloid assembly in presence of antibodies affect the lateral assembly of filaments which result in thinner fibrillar structures with a lower ability to bind thioflavine T. A full effect is already seen at an Aβ: antibody ratio corresponding to around 150:1. Both IgM and IgG isotype antibodies can mediate the response which also render the fibrillar structure less stable. The location of the epitope strongly determines the strength of the effect. Antibodies targeting the N-terminal part of Aβ show a strong effect while antibodies targeting the middle region of the peptide show no effect. Interestingly, autoantibodies of the IgM isotype targeting Aβ is almost invariable present in all humans. Through mapping of the binding pattern from a few healthy individuals, we show that the intrinsic repertoire of anti-Aβ IgM antibodies may target several different Aβ epitopes on the peptide, including the N-terminal part. The specific spectra of clonal B-cell expansion may consequently be an important modulating factor of the fibrillary architecture and the pathology.

Disclosures: **A. Pamrén:** None. **I. Iakovleva:** None. **T. Islam:** None. **K. Brännström:** None. **L. Sandblad:** None. **A. Olofsson:** None.

Poster

784. Amyloid-Beta Toxicity

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 784.03/F50

Topic: C.02. Alzheimer's Disease and Other Dementias

Title: The architecture of the amyloid fibrils controls the ability to induce fibril-catalyzed secondary nucleation

Authors: *M. ISLAM, K. BRÄNNSTRÖM, A. OLOFSSON;
Umeå Univ., Umeå, Sweden

Abstract: Self-assembly of the amyloid-beta peptide (Abeta) into amyloid fibrils is associated with the development of Alzheimer's disease. In vivo Abeta1-40 and Abeta1-42 are the dominant forms. The architectures of Abeta1-40 and Abeta1-42 fibrils differ, and Abeta1-42

assemblies generally have higher cytotoxicity. Abeta fibril formation follow a nucleation dependent polymerization process and it is known that new initiation sites, from which the incorporation of monomers can propagate into a fibril, can be generated through at least three different routes, these include; primary nucleation where nuclei spontaneously form in solution, the breaking of fibrils to form new fibrillar ends, and fibril-catalyzed secondary nucleation where formation of new nuclei is catalyzed laterally along already formed fibrils .The overall rate of conversion into amyloid is consequently dependent on the number of initiation sites from which the template-dependent polymerization can start. Under stagnant conditions fibril-catalyzed secondary nucleation dominates. We have performed cross-seeding studies and show that fibrils of Abeta1-42 are impaired to induce fibril-catalyzed secondary nucleation of Abeta1-40 while the elongation process is unaffected. Intriguingly the formed Abeta fibril acquire the same properties as the Abeta1-42 and is, in contrast to spontaneously formed fibrils of Abeta1-40, impaired to induce fibril-catalyzed secondary nucleation of monomeric Abeta1-40. The results suggest that the incorporated Abeta1-40 acquired the structure of Abeta1-42 fibrils and that the architecture of the Abeta fibrils rather than the sequence controls the ability to induce fibril-catalyzed secondary nucleation.

Disclosures: **M. Islam:** None. **K. Brännström:** None. **A. Olofsson:** None.

Poster

784. Amyloid-Beta Toxicity

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 784.04/F51

Topic: C.02. Alzheimer's Disease and Other Dementias

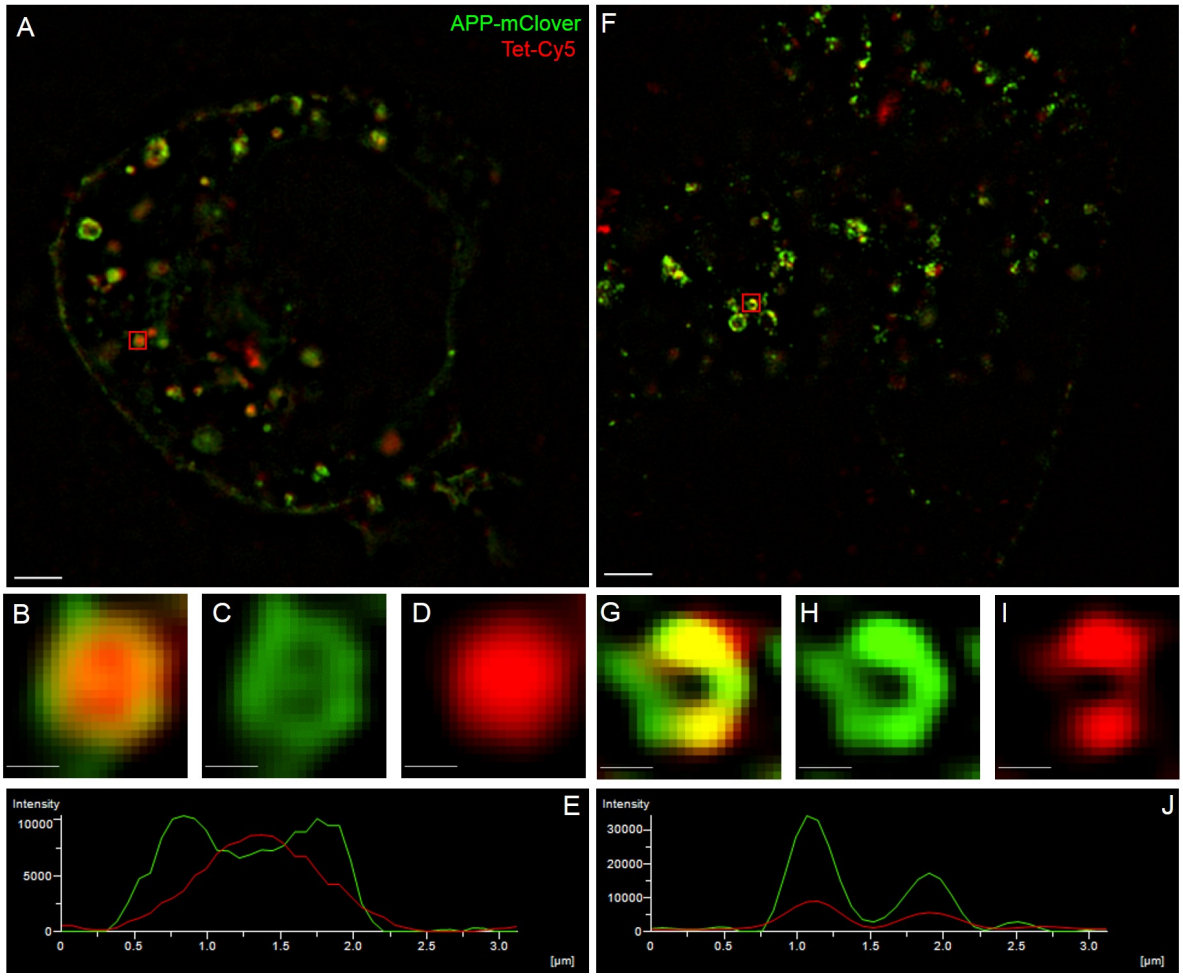
Support: NIH Grant R21NS083529

NSF GRFP DGE-1143954

Title: Tracking de novo intracellular amyloid beta generation using fluorogenic click-labeled amyloid precursor protein and super-resolution microscopy

Authors: ***L. R. CZERNIEWSKI**[1], S. CRICK[2], J.-M. LEE[3], P. I. HANSON[4], A. CASHIKAR[4], Q. XIAO[3], M.-I. KIM[3];
[1]Washington Univ. In St. Louis, Saint Louis, MO; [2]Washington Univ. in St. Louis, St. Louis, MO; [3]Dept. of Neurol. and the Hope Ctr. for Neurolog. Disorders., [4]Dept. of Cell Biol. and Physiol., Washington Univ. Sch. of Med., St. Louis, MO

Abstract: The cellular location of the amyloid precursor protein (APP) influences its processing; on the cell surface APP is cleaved by α-secretase to produce non-amyloidogenic fragments, or APP is endocytosed and cleaved by β- and γ-secretase to generate Aβ. Little is known about the subcellular site of interaction between the amyloidogenic secretases and APP and ultimately the site of Aβ generation due to the lack of probes that can interrogate the *de novo* cleavage of Aβ from APP. Using unnatural amino acids and fluorogenic click chemistry, we have site-specifically labeled Aβ within APP with a small fluorophore and fused mClover to the C-terminus of APP to distinguish full-length APP and its β-C-terminal fragment (βCTF) from Aβ. We sought to use this bifluorescent APP construct to detect intracellular Aβ generation by monitoring the separation of click-labeled Aβ from the mClover-tagged APP intracellular domain (AICD-mClover). However, visualization of cleavage events in some intracellular organelles are diffraction limited. We have circumvented this limitation by using super-resolution microscopy. Live mouse neuroblastoma cells were incubated with a cell-impermeable red tetrazine-fluorophore to click-label cell surface APP-mClover within the Aβ segment. This resulted in endocytosis and trafficking of the bifluorescent APP construct. Super-resolution structured illumination microscopy distinguished uncleaved APP or βCTF from Aβ and the AICD providing a subcellular readout of Aβ production (A-D). Following γ-secretase cleavage of APP to generate Aβ, AICD-mClover was localized to the limiting membrane of vesicles while the click-labeled Aβ signal was localized to the lumen of the vesicle (B-D, E shows intensity profile through B). Uncleaved APP resulted in colocalization of the bifluorescent APP probes on the limiting membrane of vesicles (F-I, J shows intensity profile through G). Using this method, we have directly monitored *de novo* Aβ generation at the subcellular level for the first time. This will enable the delineation of intracellular pathways critical for Aβ production.



Disclosures: **L.R. Czerniewski:** None. **S. Crick:** None. **J. Lee:** None. **P.I. Hanson:** None. **A. Cashikar:** None. **Q. Xiao:** None. **M. Kim:** None.

Poster

784. Amyloid-Beta Toxicity

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 784.05/F52

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: Arizona Biomedical Research Commission

National Institute on Aging

Title: The effects of apoe genotype on aβ levels in human liver

Authors: *G. E. SERRANO[1], C. MAAROUF[2], J. WALKER[2], A. GARCIA[2], L. SUE[2], T. G. BEACH[2];
[1]Brain and Body Donation Program, [2]Banner Sun Hlth. Res. Inst., Sun City, AZ

Abstract: It is well known that Apolipoprotein E (APOE) genotype alters the risk of developing Alzheimer's disease (AD), but the molecular mechanism of this effect is still unknown. The most accepted general hypothesis is that the E4 allele-coded form of APOE influences the metabolism of amyloid precursor protein and/or its critical cleavage product, amyloid-β (Aβ), resulting in brain accumulation of Aβ as senile plaques. It has also been assumed that the critical molecular events all take place in the brain, but as the liver is a major site for both the synthesis of APOE as well as the metabolism of circulating Aβ, it is possible that alterations of liver function could affect brain Aβ levels through changes in blood Aβ concentration. In this study we hypothesized that APOE genotype may affect the rate of Aβ degradation in the liver. An Aβ degradation assay was developed using fluorescein-labeled Aβ40 and 42 spiked into liver homogenates. Our preliminary data suggest that Aβ degradation rates in the liver do not vary between subjects with different APOE alleles. However, Aβ40 appears to degrade three times faster in non-demented control subjects (ND) than in individuals with AD. The expression of potential Aβ-degrading enzymes presenilin, β-site APP-cleaving enzyme (BACE), and neprilysin were not different in liver samples from AD, while cathepsin D and Insulin-degrading enzyme are significantly affected in AD subjects. The protein Levels in the Liver of both Aβ degrading enzymes significantly correlates with the pathological aggregation of Aβ in the brain. This suggests that inefficient degradation of Aβ in the liver could results in abnormal levels of Aβ in the brain.

Disclosures: G.E. Serrano: None. **C. Maarouf:** None. **J. Walker:** None. **A. Garcia:** None. **L. Sue:** None. **T.G. Beach:** None.

Poster

784. Amyloid-Beta Toxicity

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 784.06/F53

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: MRC DTP PhD studentship

Title: The anti-inflammatory annexin A1 induces the clearance and degradation of the amyloid β peptide

Authors: *M. RIES[1], R. LOIOLA[2], U. N. SHAH[1], S. GENTLEMAN[1], E. SOLITO[2], M. SASTRE[1];
[1]Div. of Brain Sci., Imperial Col. London, London, United Kingdom; [2]William Harvey Res. Insitute, Queen Mary Univ. of London, London, United Kingdom

Abstract: The brain of Alzheimer's disease (AD) patients is characterised by the deposition of amyloid β (Aβ) peptide and tau phosphorylation, and also shows extensive glial activation and neuronal loss. Apart from secreting pro-inflammatory mediators, activated microglia can also have neuroprotective effects by reducing Aβ accumulation through increasing its clearance, as well as through the release of anti-inflammatory molecules including certain cytokines, growth factors, and the inflammation-resolving molecule annexin A1 (ANXA1). The aim of this study was to determine the effect of ANXA1 on the generation and clearance of Aβ, as well as on microglial activation and phagocytosis. Our data show that ANXA1 is increased in the brains of AD patients and animal models of AD at early stages of the disease. ANXA1 was able to reduce the levels of Aβ in N2a neuroblastoma cells by increasing its enzymatic degradation by neprilysin, and to stimulate Aβ phagocytosis by microglia. In addition, ANXA1 inhibited the microglial secretion of inflammatory mediators induced by Aβ. Our data suggest that ANXA1 plays a key role in the clearance of Aβ and supports the use of ANXA1 as potential therapeutic tool for AD.

Disclosures: M. Ries: None. **R. Loiola:** None. **U.N. Shah:** None. **S. Gentleman:** None. **E. Solito:** None. **M. Sastre:** None.

Poster

784. Amyloid-Beta Toxicity

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 784.07/G1

Topic: C.02. Alzheimer's Disease and Other Dementias

Title: The redox state of methionine 35 in amyloid-beta (1-42) peptide (A-betaP) determines the amplitude of prostaglandin E_2 (PGE_2) release from rat microglia *In vitro*.

Authors: *G. POZZOLI[1], F. MISITI[2], E. CLEMENTI[3], G. TRINGALI[1], C. DELLO RUSSO[1], L. LISI[1], P. NAVARRA[1];
[1]Catholic Univ. Sch. Med., 00168 Rome, Italy; [2]Dept. of Hlth. and Motor Sci., Univ. of Cassino, Cassino, Italy; [3]Inst. of "Chimica del Riconoscimento Molecolare", Natl. Council of Res., Rome, Italy

Abstract: Alzheimer's disease (AD) is a brain pathology characterized by the presence of senile plaques in several regions of the central nervous system. A major protein component of the plaques is the amyloid-beta peptide (A-betaP), which possesses direct neurotoxic activity; such neurotoxicity has been associated to the *redox* state of methionine residue in position 35 (Met-35) of A-betaP. The plaques are also the foci of local inflammatory responses, as shown by the activation of surrounding microglia, with increased synthesis and release of several pro-inflammatory mediators; the latter may account for indirect toxic effects of A-betaP. In the present study, we used 3 variants of A-betaP, namely, A-betaP(1-42), where the Met-35 is present in the reduced state, a modified peptide with oxidized Met-35 and an A-betaP derivative in which Met-35 is substituted with norleucine, to investigate the relationship between Met-35 *redox* state and the ability of A-betaP to induce a pro-inflammatory activation in glial cells. The latter was assessed by measuring the levels of prostaglandin E_2 (PGE_2) released after 24-h exposure to test peptides in primary cultures of rat cortical microglia or astrocytes. Under basal conditions, microglia produced and released significant amounts of PGE_2 (100 - 150 pg/ml after 24 h of incubation). 5 microM A-betaP(1-42) induced a 4-fold increase in PGE_2 secretion compared to controls, whereas A-betaP(1-42)Met-35^{Ox} and A-betaP(1-42)Nle35, both at the concentration of 5 microM, had no effect on PGE_2 release. Under basal conditions, astrocytes produced and released tiny amounts of PGE_2, roughly 4 - 6 pg/ml after 24-h incubation, and none of A-beta peptides tested produced significant changes on PGE_2 levels. Moreover, A-betaP(1-42) strongly increased interleukin-1 beta (IL-1beta) mRNA accumulation in microglial cells, whereas A-betaP(1-42)Met-35^{Ox} effect was significantly smaller, and A-betaP(1-42)Nle-35 had no effect. No toxic effects were observed in microglia or astrocytes after treatment with the different peptides. The results of the present study are consistent with previous reports showing that A-betaP increases PGE_2 secretion in activated microglia; in addition, our findings suggest that the reduced state of Met-35 in A-betaP is necessary to induce a pro-inflammatory activation in microglial cells.

Disclosures: **G. Pozzoli:** None. **F. Misiti:** None. **E. Clementi:** None. **G. Tringali:** None. **C. Dello Russo:** None. **L. Lisi:** None. **P. Navarra:** None.

Poster

784. Amyloid-Beta Toxicity

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 784.08/G2

Topic: C.02. Alzheimer's Disease and Other Dementias

Title: Probing amyloid beta-induced cell death using a fluorescence-peptide conjugate in Alzheimer's disease mouse

Authors: *J.-S. BAE[1,2], H. JIN[3];
[1]Sch. of Med., Kyungpook Natl. Univ., Daegu, Korea, Republic of; [2]Cell Matrix Res. Institute, Kyungpook Natl. Univ., Daegu, Korea, Republic of; [3]Col. of Vet. Medicine, Kyungpook Natl. Univ., Daegu, Korea, Republic of

Abstract: With the increasing worldwide incidence of Alzheimer's disease (AD), there is a critical need for the discovery of more effective diagnostic methods. However, development of diagnostic tools in AD has been hindered by obstacles such as the absence of exact biomarkers. Apoptosis caused by amyloid-**β (Aβ)** plays an important role in AD pathology; therefore, provides an attractive biological target for the diagnosis of AD. The present study aimed to evaluate the potential of small peptide, named ApoPep-1 (Apoptosis-targeting peptide-1) as a new apoptosis imaging agent in AD. The fluorescein-conjugated ApoPep-1, but not the control peptide, targeted apoptotic cells in the brain of **amyloid precursor protein (APP)/presenilin 1 (PS1)** mice. We also observed fluorescence signals during *in vivo* imaging of apoptotic cells using ApoPep-1, and fluorescence levels increased in an age-dependent manner in APP/PS1 mice. *Ex vivo* imaging of isolated brains in APP/PS1 mice further confirmed the targeting of ApoPep-1 to apoptotic cells. The fluorescein-labeled ApoPep-1 co-localized with brain cells such as neurons, astrocytes, and microglia, all of which undergo apoptosis in the APP/PS1 mice brain. These findings demonstrate that ApoPep-1 can target apoptotic brain cells, and be used for experimental investigations relevant to apoptosis in AD.

Disclosures: J. Bae: None. **H. Jin:** None.

Poster

784. Amyloid-Beta Toxicity

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 784.09/G3

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: Magnus Bergwall

Hjärnfonden

Vetenskapsradet

Title: The determinants of amyloid-β fibril formation

Authors: *K. K. BRÄNNSTRÖM[1], T. ISLAM[2], L. SANDBLAD[4], A. OLOFSSON[3];
[1]Med. chemistry, Umeå Univ., Umea, Sweden; [2]Med. chemistry, Umea, Sweden; [3]Med. chemistry, umea, Sweden; [4]Dept. of Mol. Biol., Umea, Sweden

Abstract: Self-assembly of the amyloid-β peptide (Aβ) into amyloid fibrils is associated with the development of Alzheimer's disease. Several different lengths of Aβ are found *in vivo*, but $A\beta_{1-40}$, $A\beta_{1-42}$, and N-terminally truncated variants thereof, are the dominant forms. The architectures of $A\beta_{1-40}$ and $A\beta_{1-42}$ fibrils differ, and $A\beta_{1-42}$ assemblies generally have higher cytotoxicity. We performed cross-templating experiments using surface plasmon resonance and discovered that monomeric $A\beta_{1-42}$ can be readily incorporated onto the ends of immobilized $A\beta_{1-40}$ fibrils, but that monomeric $A\beta_{1-40}$ is poorly incorporated onto immobilized $A\beta_{1-42}$ fibrils. Intriguingly, the most N-terminal residue, Asp1, controls this barrier. We further showed that the monomers that are incorporated onto the fibrillar ends also adopt the properties of the templating fibril. This consequently implies an important role in the mechanism behind the formation and architecture of nuclei from which a fibril subsequently propagates. These results demonstrate a complicated interplay between different Aβ variants where the ability to incorporate monomers control the properties and formation of the amyloid fibrils. We describe a possible pathological mechanism for the N-terminally truncated Aβ variants, and thus expose a novel avenue for intervention.

Disclosures: K.K. Brännström: None. **T. Islam:** None. **L. Sandblad:** None. **A. Olofsson:** None.

Poster

784. Amyloid-Beta Toxicity

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 784.10/G4

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: Alzheimer's Assoc. Grant NIRG-15-363387

Title: Picalm mediates autophagic abeta clearance and toxicity mitigation in pericytes

Authors: *E. LAWSON, B. V. ZLOKOVIC, Z. ZHAO;
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Abstract: Background: Alzheimer's disease (AD) is the most common form of dementia in the elderly, manifesting the occurrence of amyloid plaques, neurofibrillary tangles and the destruction of the neurovascular unit. Vascular factors are considered as a major risk factor for dementia due to AD. Recent studies have demonstrated pericytes degenerate in AD and potentially play a key role in pathogenesis. However the cellular and molecular mechanisms underlying pericyte degeneration during AD pathogenesis remain elusive. Methods: We examined: i) Abeta accumulation and pericyte degeneration during AD pathogenesis in post mortem AD brain tissues using immunohistochemistry; ii) internalization of soluble Abeta and

clearance of aggregated Amyloid oligomers via autophagy in primary brain pericytes using in vitro culture models; iii) the role of PICALM in mediating the clearance of oligomeric Abeta via autophagy in pericytes in vitro. Results: Our study showed that: a) pericytes internalize soluble Abeta species via LRP1 mediated endocytosis with the assistance of PICALM; b) pericytes clear aggregated Abeta oligomers via PICALM dependent autophagic pathway; c) PICALM-mediated autophagic clearance of intracellular Abeta protects pericytes from Abeta toxicity and cell death. Conclusions: The data suggest that PICALM-mediated autophagy of Abeta regulates its clearance and is a protective mechanism in pericytes in AD.

Disclosures: E. Lawson: None. **B.V. Zlokovic:** None. **Z. Zhao:** None.

Poster

784. Amyloid-Beta Toxicity

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 784.11/G5

Topic: C.02. Alzheimer's Disease and Other Dementias

Title: Justicidin A decreases amyloid β peptide via inhibiting endocytosis of amyloid β precursor protein

Authors: *Y. CHUN[1,2], S. CHUNG[2], G. FOUCHE[3], V. MAHARAJ[4], H. YANG[1];
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Abstract: Alzheimer's disease (AD) is a progressive neurodegenerative disorder that is characterized by the accumulation of neurotoxic amyloid β (Aβ) peptides, with eventual cognitive decline and memory impairment. Therapeutic drug for the AD is still unavailable. *Monsonia angustifolia* (coded as BP21) is used for food as indigenous vegetables consumed in Tanzania. In this study, we tested the effect of BP21 on Aβ production and spatial learning ability to investigate its protection against AD. BP21 extract is effective in memory function recovery as well as reduction of Aβ secretion. We next identified its active compounds, Justicidin A. It was known that amyloid β precursor protein (APP) is transported to the plasma membrane, where it is sequentially cleaved by α-secretase and γ-secretase (non-amyloidogenic pathway). Alternatively, once APP undergoes clathrin-dependent endocytosis, it can be sequentially cleaved by β-secretase and γ-secretase at endosomes, producing Aβ (amyloidogenic pathway). O-GlcNAcylation is a novel type of O-linked glycosylation attaching the monosaccharide β-N-acetylglucosamine (GlcNAc) to serine and threonine residues. Recently, we found that O-GlcNAcylation of APP increases the non-amyloidogenic processing of APP and

decreases the production of Aβ. Here, we confirmed specific increase of O-GlcNAcylation of APP by Justicidin A, which is one of lignin derivatives. Justicidin A increased the level of APP in the plasma membrane. We also found that Justicidin A selectively attenuated the endocytosis of APP, but not that of transferrin receptor. The level of sAPPα increased, while the level of sAPPβ and Aβ was concomitantly decreased by Justicidin A. Blocking the clathrin-dependent endocytosis by inhibitor prevented the effect of Justicidin A, suggesting that the effect of Justicidin A on Aβ production was mainly mediated through the decrease of APP endocytosis. These results strongly indicate that O-GlcNAcylation by Justicidin A selectively decreases endocytosis rate of APP, thereby enhancing non-amyloidogenic processing of APP. Thus, O-GlcNAcylation of APP could be a new novel therapeutic target for AD.

Disclosures: Y. Chun: None. **S. Chung:** None. **G. Fouche:** None. **V. Maharaj:** None. **H. Yang:** None.

Poster

784. Amyloid-Beta Toxicity

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 784.12/G6

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH Grant AG016574-17

Title: Apolipoprotein E isoforms impact pericyte-mediated Aβ metabolism.

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Abstract: Pericytes are an important component of the neurovascular unit. While pericytes regulate cerebral blood flow, angiogenesis and the integrity of the blood-brain barrier (BBB), these cells also play a critical role in brain metabolism of amyloid-β (Aβ). The ε4 allele of the *APOE* gene encoding apolipoprotein E (apoE) is the strongest genetic risk factor for late-onset Alzheimer's disease (AD) among the three human *APOE* alleles (ε2, ε3, ε4). ApoE4 not only exacerbates Aβ accumulation in the brain but also triggers a cascade of events that causes vascular dysfunction including BBB breakdown. Although pericytes and astrocytes are the major cell types producing apoE in the brain, how apoE isoforms influence pericyte-mediated Aβ clearance remains unclear. We isolated primary pericytes from the brains of apoE3 targeted-replacement (TR) mice, apoE4-TR mice or *Apoe*$^{-/-}$ mice at the age of 3-8 weeks. These cells were cultured and incubated with 500 nM of Aβ40 or Aβ42 in the presence or absence of lysosomal inhibitors, and cellular Aβ binding, uptake and degradation were analyzed by FACS,

ELISA and immunocytochemistry. As an alternative approach, apoE particles were purified from conditioned medium of pericytes from apoE3-TR or apoE4-TR mice and their effects on Aβ metabolism was similarly assessed in pericytes from *Apoe*$^{-/-}$ mice. FACS demonstrated that binding of both FAM-labelled Aβ40 and Aβ42 to pericytes from apoE4-TR mice were significantly less than those of pericytes from apoE3-TR mice. The amounts of cell-associated Aβ following uptake were also reduced in apoE4-pericytes compared to apoE3-pericytes. Similar results were obtained by ELISA. However, these apoE isoform-dependent effects on Aβ binding and uptake were not seen using exogenous apoE3 and apoE4 particles in pericytes from *Apoe*$^{-/-}$ mice. Furthermore, when lysosomal inhibitors were used to assess the capacity of lysosomal mediated Aβ degradation, we found that apoE3-pericytes have a greater capacity to degrade Aβ than apoE4-pericytes. Taken together, our results support a superior role of pericytes expressing apoE3 than apoE4 in mediating Aβ cellular metabolism and suggest that the apoE isoform-dependent effects on brain Aβ pathology likely involve both parachyma and vasculature.

Disclosures: **M. Tachibana:** None. **Y. Yamazaki:** None. **G. Bu:** None. **T. Kanekiyo:** None.

Poster

784. Amyloid-Beta Toxicity

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 784.13/G7

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH Grant AG 044486 (OB)

NIH Grant AG 15379 (OB)

Title: Reciprocal crosstalk between amyloid beta and presenilin 1

Authors: ***K. M. ZOLTOWSKA**, M. MAESAKO, O. BEREZOVSKA;
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Abstract: Extracellular amyloid plaques composed of fibrillogenic amyloid β (Aβ) are well-established pathological hallmark of Alzheimer's disease (AD). The potential spreading of the amyloid pathology within the brain from region to region has recently gained widespread interest but the concept raises several controversies and the mechanisms are unclear. The amyloid fibril formation is determined by a relative ratio of longer (i.e., Aβ42/Aβ43) to shorter (i.e. Aβ40) species, which are yielded by the intramembranous cut of amyloid precursor protein (APP) C-terminal stub by the γ-secretase complex, the catalytic component of which is presenilin 1 (PS1). The latter exists in equilibrium of the dynamic conformational states characterized by varied

proximity between PS1 N-terminus and loop/C-terminus, as monitored by the FRET assay in live cells. The close proximity between PS1 domains shifts the γ-secretase cleavage towards the production of longer Aβ species.
Using fluorescence lifetime imaging microscopy, calcium imaging and cytotoxicity assays, we explored mechanistic link between Aβ42 and Aβ40 peptides present at various ratios, and PS1 conformation in primary neurons. Pathogenic conformational changes within the PS1 subdomain architecture were triggered in neurons exposed to Aβ peptides at a relatively high ratio of Aβ42/40. This effect was mediated by increased intracellular calcium load. The pathogenic rearrangement within PS1 shifts further the equilibrium of Aβ peptides towards the longer, aggregation prone species.
Our findings link elevated calcium, Aβ42 and PS1/γ-secretase conformation, provide novel cell- and non-cell autonomous mechanisms of Aβ action, and offer possible mechanistic explanation of the impending spread of the amyloid pathology.

Disclosures: **K.M. Zoltowska:** None. **M. Maesako:** None. **O. Berezovska:** None.

Poster

784. Amyloid-Beta Toxicity

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 784.14/G8

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: Ministry of Science and Technology in Taiwan (MOST 104-2321-B-001-061)

Research fund from Institute of Biomedical Sciences, Academia Sinica, Taiwan

Title: Epigenetic regulation of HDAC1 SUMOylation protects against amyloid-beta toxicity in a mouse model of Alzheimer’s disease

Authors: ***E. H. LEE**[1], C.-C. TAO[2], W.-L. HSU[1], Y.-L. MA[1], S.-J. CHENG[1];
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Abstract: Amyloid-β (Aβ) produces neurotoxicity in the brain and causes neuronal death. But the endogenous defense mechanism that is activated on Aβ insult is less well understood. Here we found that acute Aβ increases the expression of protein inhibitor of activated STAT1 (PIAS1) and Mcl-1 *via* activation of MAPK/ERK. Aβ increases the association between PIAS1 and HDAC1 and Aβ induction of PIAS1 enhances the SUMOylation of HDAC1 at Lys-444 and Lys-476 in rat hippocampus. Knockdown of PIAS1 decreases endogenous HDAC1 SUMOylation. It

also blocks the effect of Aβ on Mcl-1 expression. HDAC1 SUMOylation is induced by BDNF, IGF-1 and CRF in the rat brain. Sumoylated HDAC1 reduces it association with CREB, increases CREB binding to the *Mcl-1* promoter and mediates Aβ induction of Mcl-1 expression. Transduction of SUMO-modified lenti-HDAC1 vector to the hippocampus of APP/PS1 mice rescues deficits of spatial learning and memory, contextual fear memory and LTP observed in APP/PS1 mice. It also reduces amyloid plaque in APP/PS1 mice. These results together reveal an important role of HDAC1 SUMOylation as an endogenous protection mechanism against Aβ toxicity.

Disclosures: E.H. Lee: None. **C. Tao:** None. **W. Hsu:** None. **Y. Ma:** None. **S. Cheng:** None.

Poster

784. Amyloid-Beta Toxicity

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 784.15/G9

Topic: C.02. Alzheimer's Disease and Other Dementias

Title: Genome wide screening of molecules involved in Aβ uptake by CRIPSR/Cas9 system

Authors: *I. EBINUMA, Y. HORI, T. TOMITA;
Lab. of Neuropathology and Neurosci., The Univ. of Tokyo, Tokyo, Japan

Abstract: Amyloid-β protein (Aβ) is one of the pathologically important molecules in the etiology of Alzheimer's disease (AD). Recent studies suggest that impaired clearance of Aβ from the central nervous system is involved in the development of late-onset AD (LOAD). To date, several mechanisms have been implicated in the Aβ clearance; phagocytosis, proteolytic degradation, transport across the blood-brain barrier, or transport via cerebrospinal fluid. Intriguingly, recent genome wide association studies identified molecules related to phagocytic uptake of Aβ (e.g., CD33 or TREM2) as genetic risk factors for LOAD. However, a detailed mechanism of Aβ uptake has not been well characterized. To elucidate molecular mechanism of Aβ uptake in detail, we carried out genome-wide screening of Aβ uptake using CRISPR/Cas9 system-mediated genome editing. We first transduced Cas9-expressing murine neuroblastoma N2a cells with whole genome targeting gRNA lentiviral library to obtain cell population in which each genome was edited at single locus. To screen cells with altered ability in Aβ uptake, fluorescent-labeled Aβ was treated to the genome-edited cell population, and the cells with abnormal fluorescent intensity were collected using FACS. gRNA-target sequences transduced by recombinant lentiviruses in the sorted cells were amplified and analyzed by deep sequencing. In combination with over-representation analysis, we found that genes involved in endocytic machinery and immune response pathway affected the Aβ uptake. In addition, interactome

analysis revealed that INPP5D and CD2AP, which are known as genetic LOAD risk factors, were mapped in same protein-protein interaction network with genes identified by the screening. These results suggest that these risk factors play a role in Aβ clearance in the pathogenesis of LOAD.

Disclosures: I. Ebinuma: None. **Y. Hori:** None. **T. Tomita:** None.

Poster

784. Amyloid-Beta Toxicity

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 784.16/G10

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: CONACYT 250870

PAPIIT-UNAM IN208616

Title: Oligomeric amyloid β 1-42 induces a reversible loss of catecholaminergic afferents in the rat insular cortex.

Authors: *R. PEREZ ORTEGA, P. MORENO-CASTILLA, O. URREGO MORALES, F. BERMÚDEZ-RATTONI;
Dept. de Neurociencia Cognitiva, Inst. de Fisiología Celular, Univ. Nacional Autónoma De México, Ciudad de México, Mexico

Abstract: Alzheimer's Disease (AD) is the most common form of dementia in the elderly and is characterized by a progressive neurodegeneration and an overall time-dependent cognitive decline. One of the first symptoms of AD is episodic memory loss. In recent years, the role of catecholaminergic (predominantly dopamine and noradrenaline) systems in AD memory loss and pathology has become increasingly significant. Catecholaminergic systems are important for memory encoding in the hippocampus and cortex and its AD-related dysfunction accounts for behavioral and functional plasticity impairments. Amyloid beta (Aβ) is considered a hallmark in AD pathology and the soluble, oligomeric form of 42 residues long ($A\beta_{42}$) is the most toxic form of Aβ. In this study, we aimed to determine the effect of $A\beta_{42}$ on catecholaminergic afferents in the insular cortex (IC), an area where dopamine (DA) is important for the encoding of recognition and taste memories. We injected $A\beta_{42}$ or a control peptide in the rat insular cortex and analyzed catecholaminergic afferents density by means of tyrosine hydroxylase (TH) immunosignal 2 h, 24 h, 7 days, 15 days, and 30 days after injection. We found that TH afferents density decreased at 24 hours, but was surprisingly restored at 7 days. Furthermore, retrograde

tracer analysis showed that $A\beta_{42}$ impairs the ventral tegmental area (VTA)-IC dopaminergic pathway 24 h after peptide injection. We set to determine if an astroglial response was responsible for afferents density restoration at 7 days. GFAP immunosignal showed that astrocytes were mostly activated at 7 days but not 24 hours after peptide injection. Together, these results suggest that $A\beta_{42}$ has a detrimental effect on catecholaminergic afferents in the insular cortex at immediate times, and that astrocyte activation might be involved in axonal regeneration in subsequent days.

Disclosures: R. Perez ortega: None. **P. Moreno-castilla:** None. **O. Urrego morales:** None. **F. Bermúdez-rattoni:** None.

Poster

784. Amyloid-Beta Toxicity

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 784.17/G11

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: HNDC grant

Title: Large soluble oligomers of amyloid β-protein from Alzheimer brain are far less bioactive than the smaller oligomers to which they dissociate

Authors: *T. YANG, S. LI, H. XU, D. WALSH, D. SELKOE;
Ann Romney Ctr. for Neurologic Dis., Brigham and Women's Hosp., Boston, MA

Abstract: Soluble oligomers of amyloid β-protein (Aβ) isolated from brains of Alzheimer's disease (AD) patients have been shown experimentally (in the absence of amyloid plaques) to impair hippocampal synaptic plasticity, decrease synapses, induce tau hyperphosphorylation and neuritic dystrophy, activate microglial inflammation, and impair memory in normal adult rodents. Nevertheless, there has been confusion and controversy about what types of oligomers actually confer these AD-like phenotypes. Here, we show that the vast majority of soluble Aβ species obtained from typical AD brains elute at high MW on non-denaturing size-exclusion chromatography. These species have little or no cytotoxic activity in several bioassays. However, incubation of this HMW oAβ in mildly alkaline buffer led to their quantitative dissociation into low MW oligomers (~8-70 kDa), and these were now highly bioactive: they impaired hippocampal LTP, decreased neuronal levels of β_2-adrenergic receptors, and activated microglia *in vivo*. We conclude that most Aβ assemblies in AD cortex are large and inactive but under certain circumstances can dissociate into smaller but highly bioactive species. Amyloid plaques likely sequester HMW oligomers, limiting their potential to dissociate. Conditions which de-

stabilize HMW oligomers or retard the incorporation of their smaller more bioactive components may be important drivers of Aβ toxicity. Consequently, targeting these small, cytotoxic forms should be therapeutically beneficial.

Disclosures: **T. Yang:** None. **S. Li:** None. **H. Xu:** None. **D. Walsh:** None. **D. Selkoe:** None.

Poster

784. Amyloid-Beta Toxicity

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 784.18/G12

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH Grant 5R00AG043552-05

Alzheimer's Association 2015-NIRG-339422

Title: Rho-associated protein kinase 1 (ROCK1) is increased in Alzheimer's disease and ROCK1 depletion reduces amyloid-β levels in brain

Authors: B. W. HENDERSON[1], E. G. GENTRY[1], T. RUSH[1], J. C. TRONCOSO[2], M. THAMBISETTY[3], T. J. MONTINE[4], *J. H. HERSKOWITZ[5];
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Abstract: Alzheimer's disease (AD) is the leading cause of dementia and mitigating amyloid-β (Aβ) levels may serve as a rational therapeutic avenue to slow AD progression. Pharmacologic inhibition of the Rho-associated protein kinases (ROCK1 and ROCK2) is proposed to curb Aβ levels, and mechanisms that underlie ROCK2's effects on Aβ production are defined. How ROCK1 affects Aβ generation remains a critical barrier. Here, we report that ROCK1 protein levels were elevated in mild cognitive impairment due to AD (MCI) and AD brains compared to controls. Aβ42 oligomers marginally increased ROCK1 and ROCK2 protein levels in neurons but strongly induced phosphorylation of Lim kinase 1 (LIMK1), suggesting that Aβ42 activates ROCKs. RNAi depletion of ROCK1 or ROCK2 suppressed endogenous Aβ40 production in neurons, and Aβ40 levels were reduced in brains of ROCK1 heterozygous knock-out mice compared to wild-type littermate controls. ROCK1 knockdown decreased amyloid precursor protein (APP) in neurons, and treatment with bafilomycin accumulated APP levels in neurons depleted of ROCK1. These observations suggest that reduction of ROCK1 diminishes Aβ levels

by enhancing APP protein degradation. Collectively, these findings support the hypothesis that both ROCK1 and ROCK2 are therapeutic targets to combat Aβ production in AD.

Disclosures: B.W. Henderson: None. **E.G. Gentry:** None. **T. Rush:** None. **J.C. Troncoso:** None. **M. Thambisetty:** None. **T.J. Montine:** None. **J.H. Herskowitz:** None.

Poster

784. Amyloid-Beta Toxicity

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 784.19/G13

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: CNPq-Brazil

FAPERJ-Brazil

CAPES-Brazil

Title: Alzheimer-associated Aβ oligomers impact the central nervous system to induce peripheral metabolic deregulation

Authors: *J. R. CLARKE[1], N. M. LYRA E SILVA[2], C. P. FIGUEIREDO[1], W. L. KLEIN[3], D. P. MUÑOZ[4], L. A. VELLOSO[5], S. T. FERREIRA[2], F. G. DE FELICE[2];
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Abstract: Alzheimer's disease (AD) is associated with peripheral metabolic disorders. Clinical/epidemiological data indicate increased risk of diabetes in AD patients. Here, we show that intracerebroventricular infusion of AD-associated Aβ oligomers (AβOs) in mice triggered peripheral glucose intolerance, a phenomenon further verified in two transgenic mouse models of AD. Systemically injected AβOs failed to induce glucose intolerance, suggesting AβOs target brain regions involved in peripheral metabolic control. Accordingly, we show that AβOs affected hypothalamic neurons in culture, inducing eukaryotic translation initiation factor 2α phosphorylation (eIF2α-P). AβOs further induced eIF2α-P and activated pro-inflammatory IKKβ/NF-κB signaling in the hypothalamus of mice and macaques. AβOs failed to trigger peripheral glucose intolerance in tumor necrosis factor-α (TNF-α) receptor 1 knockout mice. Pharmacological inhibition of brain inflammation and endoplasmic reticulum stress prevented glucose intolerance in mice, indicating that AβOs act via a central route to affect peripheral

glucose homeostasis. While the hypothalamus has been largely ignored in the AD field, our findings indicate that AβOs affect this brain region and reveal novel shared molecular mechanisms between hypothalamic dysfunction in metabolic disorders and AD.

Disclosures: **J.R. Clarke:** None. **N.M. Lyra e Silva:** None. **C.P. Figueiredo:** None. **W.L. Klein:** None. **D.P. Muñoz:** None. **L.A. Velloso:** None. **S.T. Ferreira:** None. **F.G. De Felice:** None.

Poster

784. Amyloid-Beta Toxicity

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 784.20/G14

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: a Grant-in-Aid for JSPS Fellows (PD, 25-6016), Japan

Title: Spatial distribution of Raman shifts within amyloid beta aggregates *In vitro*

Authors: *Y. NAGASHIMA, A. IWATA;
Dept. of Neurology, The Univ. of Tokyo, Tokyo, Japan

Abstract: Amyloid beta (Aβ) plays an important role in pathogenesis of Alzheimer's disease. This protein is prone to aggregate and is known to form senile plaques in brains of patients with Alzheimer's disease. In the present study, we were interested in investigating molecular vibrational spectra of Aβ aggregates in *vitro*. Raman scattering provides vibrational information intrinsic to and characteristic of chemical species without any extrinsic labeling procedures. Therefore Raman spectroscopy enables us to observe somewhat small peptides, such as Aβ, aggregating in physiological condition without involvement of labeling molecules of a size relatively larger. Recombinant human Aβ1-42, pretreated with TFIP (1,1,1,3,3,3-hexafluroro-2-propanol) to dissolve fibrous state in advance, were incubated for 24 hours at 37°C to form protein aggregates in *vitro*. Two dimensional spontaneous Raman spectral images of the aggregates were obtained using laser confocal Raman microspectroscopy. We found that several vibrational modes such as 1003cm^{-1}, 1162cm^{-1}, 1417cm^{-1}, 1449cm^{-1}, 1520cm^{-1}, 1612cm^{-1} and 1656cm^{-1} were prominently observed within the aggregates. Previous studies of molecular vibrations showed that the mode of 1003cm^{-1} originates from phenylalanine residue, and the mode of 1449cm^{-1} originates from CH_2 bond. The modes 1612cm^{-1} and 1656cm^{-1} are reported to originate from Amide I bond and are related to beta-sheet structure of protein, explaining insoluble feature of Aβ aggregates. As for the other modes (1162cm^{-1}, 1417cm^{-1} and 1520cm^{-1}), we currently do not know the origin, but we found some of these Raman shifts were

heterogeneously distributed in the 2D spectral images of aggregates. It is interesting that some of them seemed to form core-like structures around the center of aggregates purely made of Aβ. This indicates that Aβ aggregates are not homogeneous structure in terms of chemical bonds or groups corresponding to these observed vibrational modes of Aβ molecules.
This is the first attempt to reveal spatial distribution of chemical Raman shifts within Aβ aggregates. These results provide a clue about generation and growth mechanism of Aβ aggregation.

Disclosures: **Y. Nagashima:** None. **A. Iwata:** None.

Poster

784. Amyloid-Beta Toxicity

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 784.21/G15

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: LuMind

Title: Biologically produced Abeta species induce pathological endosomal phenotypes *In vitro*

Authors: ***M. SAWA**, X. CHEN, O. NATERA, M. PEARN, W. MOBLEY;
UCSD, La Jolla, CA

Abstract: Alzheimer’s disease (AD) is a progressive neurodegenerative disorder that is growing in prevalence. The molecular pathogenesis of AD starts decades prior to clinical diagnosis; so early detection and intervention is critical to halting it’s progression; perhaps even abating symptoms altogether. An early and critical neuronal phenotype of AD is accumulation and enlargement of early endosomes (EE) and increased activation of Rab5. EE enlargement contributes to neurodegeneration by impairing axonal transport of trophic factors necessary for neuronal survival. To better understand the molecular mechanisms underlying the abnormalities, we employed the conditioned medium (CM) of a CHO cell line (7PA2) which expresses the human Indiana mutation of APP (APP V717F); CM7 is used to designate this CM. Wild type CHO cells are used as a control; CMC is used to refer to this CM. CM7 contains biologically relevant amyloid beta (Abeta) species. We assessed the effects of CM7 in PC12 cells and rat primary neurons. We observed that 2hr-treatement of CM7 induced abnormalities in; endosomal pathways, neurotrophin signaling, axonal trafficking and synaptic structures. Immunodepletion analysis showed that Abeta is responsible for these phenotypes. We conclude that CM7 recapitulates AD conditions in vitro. We will discuss the molecular linkages between Abeta species and the AD-related pathologies.

Disclosures: **M. Sawa:** None. **X. Chen:** None. **O. Natera:** None. **M. Pearn:** None. **W. Mobley:** None.

Poster

784. Amyloid-Beta Toxicity

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 784.22/G16

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: UCSD CTRI Pilot Grant UL1TR001442

NIA Grant AG005131

Alzheimer Association Grant NIRGD-13-284795

Title: Circadian alterations impact the regulation of insulin degrading enzyme in the brain of Alzheimer patients.

Authors: T. KIM[1], J. MOTT[1], I. TRINH[1], B. SPENCER[1], *P. A. DESPLATS[2];
[1]Neurosciences, Univ. California San Diego, La Jolla, CA; [2]Neurosciences and Pathology, UCSD, LA Jolla, CA

Abstract: Alzheimer disease (AD) is the most prevalent neurodegenerative disorder of the elderly, manifested by progressive memory loss and decline in cognitive functions, with underlying accumulation of amyloid-β (Aβ) and phosphorylated Tau in the neocortex and the hippocampus. Disturbance of circadian rhythmicity is a common ailment for more than 80% of AD patients, evidenced by altered sleep/wake cycles and exacerbated cognitive impairment during the evening (sundowning).
Circadian rhythms coordinate physiology with the environment. About 15% of expressed genes are controlled by the circadian clock, including those involved in insulin metabolism. Disruption of core clock genes Per2 and Bmal1 leads to insulin resistance and diabetes in mice. Normal functioning of the insulin-signaling pathway is important for the maintenance of cognitive performance during aging and hyperinsulinemia, insulin resistance and diabetes increase the risk for AD. Still, the role of circadian deregulation in insulin balance and its contribution to AD pathology is underexplored.
We investigated the role of the circadian protein BMAL1 in the regulation of the insulin-degrading enzyme (*IDE*), which participates in the clearance of both, insulin and Aβ. We hypothesized that alterations in *BMAL1* transcription associated with AD may impair brain insulin metabolism via deregulation of IDE, aggravating neurodegeneration.

We profiled frontal cortex samples from mild cognitively impaired (MCI) and severe AD patients in comparison to age and gender-matched healthy control subjects (N=66), evaluating IDE transcript and protein abundance as a function of the time of death. We detected significant alterations in BMAL1 expression in MCI and AD cases, with reduced amplitude of oscillation and advanced phase of expression. In addition, we observed circadian-like oscillation of *IDE* transcripts in control brains, but the rhythmic patterns of expression were significantly altered in MCI and AD cases for both transcription and protein levels, with changes in amplitude and peak expression time. Moreover, IDE alterations associated with aberrant insulin signaling, including increased IRS-1 phosphorylation in AD brains, and also correlated with cognitive decline. Lastly, *in silico* analysis of the *IDE* proximal promoter identified multiple canonical E-boxes, for the binding of *BMAL1* to the DNA, supporting the role of this clock factor on the regulation of IDE. We conclude that alteration of brain circadian rhythms impact insulin metabolism and potentially Aβ deposition by deregulation of IDE expression, a pathway mediated by *BMAL1*.

Disclosures: T. Kim: None. **J. Mott:** None. **I. Trinh:** None. **B. Spencer:** None. **P.A. Desplats:** None.

Poster

784. Amyloid-Beta Toxicity

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 784.23/G17

Topic: C.02. Alzheimer's Disease and Other Dementias

Title: p53 dependent SIRT6 expression protects Aβ induced DNA damage

Authors: *H. CHOI[1], E. JUNG[1], H. SONG[1], A. KIM[1], Y. HWANG[2], H. RYU[2], I. MOOK-JUNG[1];
[1]Seoul Natl. Univ. Col. of Med., Seoul, Korea, Republic of; [2]Ctr. for Neuro-Medicine, Brain Sci. Institute, KIST, Seoul, Korea, Republic of

Abstract: Alzheimer's disease (AD) is the most common type of dementia and age-related neurodegenerative disease. Elucidating the cellular changes that occur during ageing is an important step towards understanding the pathogenesis and progression of neurodegenerative disorders. *SIRT6* is a member of the mammalian sirtuin family of anti-aging genes. However, the relationship between SIRT6 and AD has not yet been elucidated. Here, we report that SIRT6 protein expression levels are reduced in the brains of both the 5XFAD AD mouse model and AD patients. Aβ42, a major component of senile plaques, decreases SIRT6 expression, and Aβ42-induced DNA damage is prevented by the overexpression of SIRT6 in HT22 mouse hippocampal neurons. Also, there is a strong negative correlation between Aβ42-induced DNA damage and

p53 levels, a protein involved in DNA repair and apoptosis. In addition, upregulation of p53 protein by Nutlin-3 prevents SIRT6 reduction and DNA damage induced by Aβ42. Taken together, this study reveals that p53-dependent SIRT6 expression protects cells from Aβ42-induced DNA damage, making SIRT6 a promising new therapeutic target for the treatment of AD.

Disclosures: H. Choi: None. **E. Jung:** None. **H. Song:** None. **A. Kim:** None. **Y. Hwang:** None. **H. Ryu:** None. **I. Mook-Jung:** None.

Poster

784. Amyloid-Beta Toxicity

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 784.24/G18

Topic: C.02. Alzheimer's Disease and Other Dementias

Title: Mechanisms of suppression of Kv1.1 channel activity by Aβ(1-42)

Authors: *K. DEBOEUF[1,2], M. ISLAM[2], J. FARLEY[1,2];
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Abstract: Many studies have found that Aβ-peptides participate in the pathogenesis of Alzheimer's disease (AD), leading to disruption of Ca^{2+} homeostasis and eventual cell death. The mechanisms underlying these effects remain unclear. Our work suggests that Aβ-inhibition of voltage-dependent K^+ channel (e.g., Kv1.1) activity is among the earliest steps. Using murine Kv1.1 expressed in *Xenopus* oocytes, we previously elucidated a pathway in which Ca^{2+}-dependent activation of protein phosphatase 2B (PP2B), PKC, PTKs, and RhoA all participated to produce rapid strong suppression of Kv1.1 activity (Hallahan et al., 2016, under revision). This pathway is recruited by a variety of stimuli that increase $[Ca^{2+}]_i$, including GPCRs that couple to $G_{q/11}$ -PLC, Ca^{2+} ionophore (A23187), and LGICs that flux Ca^{2+}. Because Kv1.1 and related channels are activated during an action potential, regulate depolarization Ca^{2+} influx, and inhibition of Kv1 channels can be neurotoxic, we speculate that Aβ-suppression of Kv1 channels could lead to hyperexcitability, altered synaptic transmission, disrupted Ca^{2+} homeostasis, and neurotoxicity. We assessed the effects of Aβ(1-42) peptide (Anaspec, monomers and low-*n* oligomers) on Kv1.1 channels in oocytes. Aβ(1-42) [10 nM -1 uM] produced dose-dependent inhibition of macroscopic Kv1.1 current: ~50% reductions within 30 m for 1 uM. Reverse sequence (40-1) peptide and other controls failed to suppress Kv1.1. Aβ suppression of Kv1.1 was partially Ca^{2+}- and PP2B-dependent, being reduced by ~50% when cells were loaded with BAPTA-AM, or exposed to the PP2B-inhibitor cyclosporine A. Patch-clamp results suggest that Aβ-suppression of Kv1.1 involves both PP2B-dephosphorylation and direct protein-protein

interaction of Aβ with Kv1.1 channel subunits. Exposure of inside-out single Kv1.1 in ripped-off oocyte patches to application of purified, catalytically-active PP2B produced gradual reductions in *p*(open), followed by abrupt disappearance of Kv1.1 activity. Heat-inactivated PP2B had no effect. Application of Aβ to the intracellular face of Kv1.1 channels under conditions where little enzymatic activity could occur (zero Ca^{2+}, absence of Mg^{2+}/ATP) also produced dramatic reductions in *p*(open).

Disclosures: K. Deboeuf: None. **M. Islam:** None. **J. Farley:** None.

Poster

784. Amyloid-Beta Toxicity

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 784.25/G19

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: Division of Applied Life Science (BK 21)

Title: Suppression of Adiponectin receptor 1 exacerbates $A\beta_{1-42}$ -induced memory impairment and neurodegeneration via down-regulating insulin signaling

Authors: *M. KIM, S. U. REHMAN, N. B. ABID, M. KIM;
Gyeongsang Natl. Univ., Jinju-Si, Gyeongsangnam-Do, Korea, Republic of

Abstract: Illuminating metabolic dysfunction in brain have elaborated a new paradigm in Alzheimer's disease (AD) research. Adiponectin a fat derived hormone binds to Adiponectin receptor 1 (AdipoR1) a major switch to activate metabolic pathway encompasses various organs including brain, liver, heart, pancreas, kidney etc. A Role of AdipoR1 has not established so far and need to be explored. We previously reported the role of Osmotin- a homolog of mammalian adiponectin, in mitigating AD pathology via AdipoR1-AMPK-SREBP2 pathway. To further elucidate osmotin mode of action to ameliorate AD pathology, role of AdipoR1 needs to be elaborated. Present study elucidates relationship between AdipoR1 and $A\beta_{1-42}$ -induced neurodegeneration. For this purpose PEI-based AdipoR1 shRNA-mediated knockdown mice with intravenous injection and induced AD pathology with intracerebral injection of $A\beta_{1-42}$ peptide were generated. Results shows that AdipoR1 knockdown mice showed decreasing pattern of spontaneous alternation behavior as well as long-term spatial learning memory. Evidences from both *in vitro* and *in vivo* models highlighted AdipoR1 deficiency induced activation of apoptotic cascades including caspase3/7 activity, cleaved caspase3, PARP1. Furthermore, insulin signaling correlation to AdipoR1-neuronal cell death have been addressed.

Present study is a first report of AdipoR1 role in neurodegenerative disease and illuminating new therapeutic paradigm of AD.

Disclosures: **M. Kim:** None. **S.U. Rehman:** None. **N.B. Abid:** None. **M. Kim:** None.

Poster

784. Amyloid-Beta Toxicity

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 784.26/G20

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: CNPq

INNT

FAPERJ

CAPES

Title: Oxidative damage impairs cholinergic function in cultured neurons exposed to Alzheimer's-linked Aβ-oligomers

Authors: ***L. E. SANTOS**, C. FIGUEIREDO-FREITAS, N. NUNES-TAVARES, S. T. FERREIRA, F. G. DE MELLO;
UFRJ, Rio De Janeiro, Brazil

Abstract: Acetylcholine is a major neurotransmitter in both central and peripheral nervous systems, usually synthesized near pre-synaptic terminals, in a reaction involving the transfer of an acetyl group from acetyl-coenzyme A to choline. This reaction is carried out by an enzyme known as choline acetyltransferase (ChAT, EC 2.3.1.6), also regarded as a marker of cholinergic neurons. Disturbances of cholinergic neurotransmission have long been implicated in the development of several central nervous system (CNS) pathologies. Among them, Alzheimer's disease (AD) - an alarmingly prevalent form of dementia - stands out for having one of the most well established cholinergic hypotheses, first presented formally in the 1980s. Early work by our group, using chick retina as a CNS model, showed that ChAT activity in cultured or *ex vivo* neurons can be markedly and quite specifically down-regulated by excitotoxic stimuli, such as excitatory amino-acid (EAA) treatments, long before any significant changes in cell viability or enzyme levels occur. This effect was shown to be dependent on calcium influx and at least partially on nitric oxide (NO) production [J Neurochem. 2001; 77:1136-1144]. Recently, we observed similar results in a more specific context. After treating cultured cholinergic neurons

with oligomeric forms of the amyloid-β peptide (AβOs), we found that ChAT activity was significantly down-regulated, without any concurrent loss of neuron viability or enzyme expression. AβOs are diffusible synaptic toxins found in AD brains, which are currently regarded as possible culprits of the disease. Notably, we also showed that this effect of AβOs on ChAT activity is linked to excitotoxicity and the production of reactive oxygen species (ROS), being likely mediated by oxidative damage to the enzyme [JBC 2012; 287:19377-19385]. In the current work, we expand these observations to cultured neurons of the rat septal region, and identify oxidative modifications involved in the loss of cholinergic activity associated with AβOs. Using S-nitrosothiol resin-assisted capture (SNO-RAC) and 4-acetamido-4'-maleimidylstilbene-2,2'- disulfonic acid (AMS) labeling of reduced thiols we show that cysteine modifications are apparently unrelated to this inactivation of the enzyme. Tyrosine nitration, in the other hand, is shown by immunoassay to be induced in the enzyme by treatments with EAAs, AβOs or NO donors, and to correlate well with the loss of ChAT activity. These results suggest a novel mechanism for cholinergic dysfunction, which precedes neuronal death, and may be relevant in early-stage AD pathology.

Disclosures: L.E. Santos: None. **C. Figueiredo-Freitas:** None. **N. Nunes-Tavares:** None. **S.T. Ferreira:** None. **F.G. de Mello:** None.

Poster

784. Amyloid-Beta Toxicity

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 784.27/G21

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: CONACYT 220006

CONACYT220342

Vicerrectoria académica Universidad de Monterrey 15027 and 16504

Title: Modification of aggregation kinetics and cytotoxicity of amyloid beta peptide through insertion of aminoacid point mutations

Authors: A. ESTRADA-RODRIGUEZ[1], J. TREVIÑO-GARZA[2], H. MARTINEZ-RODRIGUEZ[2], R. VIDALTAMAYO[4], *V. ZOMOSA[3];
[1]Bioquimica y Medicina Mol., [2]BIOQUIMICA Y MEDICINA MOLECULAR, [3]UANL, Monterrey, Mexico; [4]Dept. de Ciencias Basicas, Univ. de Monterrey, Monterrey, Mexico

Abstract: Alzheimer´s Disease (AD) is the most common type of senile dementia. Deposition of Amyloid beta (Aβ) peptide in the brain is one of the most important events in AD progression. Current evidence implicates soluble oligomers as primary toxic agents in amyloid diseases. Preventing formation of these soluble oligomers could stop amyloid β-sheet self-assembly. For that reason, formation of Aβ oligomers is being considered a target for therapeutic strategies for AD. It is well known that the amino acid sequence of Aβ peptide is essential for its aggregation and amyloid plaque formation. In this work, we used two variants of Aβ peptide: One containing amino acids 1-40 and other restricted to amino acids 25-35. We inserted point mutations at positions: A30W, K28A and M35C to assess the role of the amino acids in these positions in Aβ-peptide aggregation kinetics and to evaluate if changes in aggregation kinetics correlate with changes in cytotoxicity of the peptides. We used thioflavin S (ThS) as a fluorescent probe to determine amyloid-like structure formation and 8-anilinonaphthalene-1-sulfonic acid (ANS) as a fluorescence probe to determine formation of unstructured hydrophobic aggregates. Our results show that Aβ(25-35), Aβ(25-35)-K28A and Aβ(1-40)-K28A formed more amyloid aggregates, while Aβ(25-35)-A30W did not aggregate at all. We evaluated whether the mutants could modulate aggregation of the wild-type sequence Aβ peptide. We observed that Aβ(25-35)-A30W, Aβ(25-35)-K28A and Aβ(1-40)-A30W acted as inhibitors of amyloid formation, while Aβ(25-35)-M35C, Aβ(1-40)-K28A and Aβ(1-40)-M35C acted as enhancers of amyloid aggregation. We tested the effects of the mutant peptides on cell viability using the rat C6 glioma cell line. Wild-type sequence Aβ-(25-35) and all its mutants decreased cell viability to 45%. In contrast, wild-type Aβ(1-40) decreased cell viability to 55%, while the Aβ(1-40)-A30W mutant increased cell viability to 65%. Remarkably, Aβ(1-40)-K28A and Aβ(1-40)-M35C did not decrease cell viability with respect to control conditions. Our result demonstrate that point mutations change the aggregation kinetics and cytotoxicity of the Aβ peptide, and the strategy of introducing these point mutations could be used to design new therapeutic agents for Alzheimer's disease.

Disclosures: A. Estrada-rodriguez: None. **J. Treviño-garza:** None. **H. Martinez-rodriguez:** None. **R. Vidaltamayo:** None. **V. Zomosa:** B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution; CONACYT CB 2013-2014 GRANT: 220006.

Poster

784. Amyloid-Beta Toxicity

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 784.28/G22

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: Swedish Research Council

Petrus and Augustas Hedlund Foundation

Crafoord Foundation

Åke Wiberg Foundation

Swedish Dementia Foundation

Swedish National Graduate School for Competitive Science on Ageing and Health

Title: Aggregation dependent effects of Aβ1-40 on human brain pericyte

Authors: *N. SCHULTZ[1], K. BRÄNNSTRÖM[2], A. OLOFSSON[2], M. WENNSTRÖM[1]; [1]Dept. of Clin. Sci., Lund Univ., Malmoe, Sweden; [2]Dept. of Med. Biochem. and Biophysics, Umeå, Sweden

Abstract: The amyloid beta (Aβ)1-40 peptide is known to form depositions, so called cerebral amyloid angiopathy (CAA) in the vessel walls. These depositions are suggested to cause vascular changes such as impaired blood circulation, decreased angiogenesis, dysfunctional and leaking vessels as well as blood brain barrier (BBB) damage. Since Aβ1-40 is toxic for pericytes, a cell type important for vessel function and BBB maintenance, it can be hypothesized that Aβ1-40 induced pericyte loss underlies the vascular changes linked to CAA. Pericytes are recognized by their expression of NG2, a transmembrane glycoprotein important for proliferation, migration and survival. Although the impact of Aβ1-40 on pericyte viability has been shown before, there are few studies examining whether these effects are aggregation dependent. In the current study we use lactate dehydrogenase assay to analyze cell death and immunoassays to analyze caspase 3/7 activity, proliferation and NG2 shedding in primary fetal human brain pericytes (HBVP) after exposure to fibril, oligomer or monomer Aβ1-40. Our study shows that exposure to fibril Aβ1-40 increase cell death. In contrast, monomer Aβ1-40 decreased cell death while unaltered cell viability was found after oligomer Aβ1-40. Further, fibril Aβ1-40 induced an increased shedding of NG2 whereas neither monomer nor oligomer Aβ1-40 affected shedding of this pericyte protective proteoglycan. Moreover, fibril Aβ1-40 induced cell death was ablated when HBVPs were incubated together with either anti-NG2 or anti-low density lipoprotein (LRP)-1 antibodies. Interestingly, monomer Aβ1-40 dramatically increased proliferation of pericytes and co-incubation with anti-NG2 antibody ablated this effect. Fibril Aβ1-40 on the other hand decreased proliferation and oligomer Aβ1-40 had no effect on this event. These results demonstrate that the aggregation form of Aβ1-40 determines the impact of Aβ1-40, as fibril and monomer had quite the opposite effect on pericytes. The results also suggest that LRP-1 and NG2 are involved in the fibril Aβ1-40 toxicity and that the mitogenic effect of monomer Aβ1-40 is mediated via NG2. The findings add knowledge on how Aβ1-40 affects the microvascularity and contribute thereby to a further understanding of the role of CAA in brain vascular pathology.

Disclosures: **N. Schultz:** None. **K. Brännström:** None. **A. Olofsson:** None. **M. Wennström:** None.

Poster

784. Amyloid-Beta Toxicity

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 784.29/G23

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: Fondecyt 40473

CMA BIO BIO PIA ECM12

Title: Possible role of membrane fluidity in the modulation of neurotoxicity of Alzheimer's amyloid beta peptide

Authors: *E. J. FERNANDEZ, F. J. SEPULVEDA, N. RIFFO, D. BASCUÑAN, S. A. SANCHEZ, L. G. AGUAYO;
Univ. De Concepcion, Concepcion, Chile

Abstract: The beta-amyloid peptide (Aβ), crucially involved in Alzheimer's Disease (AD), has been described to have the ability to associate and aggregate on the cell surface, disrupting the plasma membrane through the formation of pores and membrane breakage. However, the molecular determinants involved in this interaction, as well as the role played by the physicochemical properties of the cell membrane, are largely unknown. Since cholesterol is an important molecule for membrane integrity and fluidity, we examined the effect of varying cholesterol content with the association and subsequent perforation of the plasma membrane by Aβ in hippocampal neurons.
Using cultured rat hippocampal neurons and methyl-β-cyclodextrin (MβCD) as a tool to increase or decrease the levels of cholesterol in the cellular membrane, we analyzed if membrane fluidity affected membrane association and perforation using confocal/spectral microscopy, generalized polarization (GP), and electrophysiologal techniques. The results showed that cholesterol removal produced an increase in membrane fluidity (30% decrease in GP value compared to control cells) and facilitated membrane perforation by Aβ with respect to control cells (time to establish perforated configuration (TEPC): control=8±2 vs. MβCD=2.3±0.5 min, $p<0.01$). Interestingly, under this condition, a decrease in the association of Aβ to neuronal membranes was observed (fluorescent-punctas/20µm: control=18±2 vs. MβCD=10±1, $p<0.05$). On the contrary, increasing cholesterol levels by 25%, which is known to increase membrane rigidity (40% increase in GP value compared to control cells) enhanced the association and clustering of the peptide with the membrane (fluorescent-punctas/20µm: control=18±2 vs. MβCD=10±1, $p<0.01$), but inhibited membrane disruption.
In conclusion, our results strongly suggest the importance of plasma membrane organization in the toxic effects of Aβ in hippocampal neurons, since fluidity can regulate the distribution and insertion of the Aβ peptide in the neuronal membrane.

Disclosures: **E.J. Fernandez:** None. **F.J. Sepulveda:** None. **N. Riffo:** None. **D. Bascuñan:** None. **S.A. Sanchez:** None. **L.G. Aguayo:** None.

Poster

784. Amyloid-Beta Toxicity

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 784.30/G24

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: Fondecyt Grant 1130068

Fondecyt Grant 1150736

CONICYT PhD fellowship 21130445

Title: The distribution of neuronal pserstat3 is affected by a mediator released by astrocytes in response to AβOs

Authors: ***Y. A. MUÑOZ**[1], A. PAULA-LIMA[2], M. T. NUÑEZ[1];
[1]Dept. of Biol., [2]Inst. for Res. in Dent. Sci., Univ. of Chile, Santiago, Chile

Abstract: Astrocytes are essential for neuronal survival; however, under pathological conditions astrocytes participate in the degeneration of adjacent neurons. Amyloid-beta oligomers (AβOs) have been found in Alzheimer's disease (AD) brains and astrocytes respond to AβOs through a process called reactive astrogliosis, which generates reactive oxygen/nitrogen species (ROS/RNS) and inflammatory cytokines that affect surrounding neurons. Stat3 is a crucial transcription factor involved in maintenance and function of nervous system and its deregulation has been implicated in AD. Growth factors induce serine-727 phosphorylation and this modification is associated with modulation of transcriptional activity of Stat3. The main goal in this work is determine if hippocampal neuronal Stat3 is affected by reactive astrocytes. **Methods**: Primary hippocampal neuron and astrocytes cultures were used. Changes in pSerStat3 distribution were detected by immunocytochemistry. The oxidative tone and ROS production were evaluated by microscopy and fluorimetry. Protein and mRNA levels were determined by Western blotting and PCR, respectively. **Results:** Here, we show that AβOs does not induce changes in protein neither mRNA Stat3 levels in neurons but it produces pSerstat3 redistribution in mixed neuron-astrocytes cultures. The mediator released by astrocytes-stimulated by AβOs in the media increase neuronal oxidative tone. **Conclusion:** We propose that in hippocampal neurons, pSerStat3 is a sensor for stressor astrocyte-produced induced by AβOs activation.

Disclosures: **Y.A. Muñoz:** None. **A. Paula-Lima:** None. **M.T. Nuñez:** None.

Poster

785. Alzheimer's Disease: Anti-Amyloid Beta Therapeutics

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 785.01/G25

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: Alberta Prion Research Institute (Alberta Innovates Bio Solutions)

Alzheimer Society of Alberta

Alberta Innovates Health Solutions

Title: Identification of short brain penetrant amylin receptor based peptides as potential therapeutic agents for Alzheimer's disease

Authors: *R. N. SOUDY[1], W. FU[1], K. KAUR[2], J. JHAMANDAS[1];
[1]Dept. of Med., Univ. of Alberta, Edmonton, AB, Canada; [2]Chapman Univ. Sch. of Pharm. (CUSP), Chapman Univ., Irvine, CA

Abstract: Aggregation and deposition of β-amyloid (Aβ) peptides in brain play a pivotal role in Alzheimer's disease (AD) pathogenesis. We have identified the amylin receptor as a putative target for the deleterious effects of Aβ in the brain, and chronic administration of AC253 (a 24-amino acid peptide), an amylin receptor antagonist, improves age-dependent deficits in spatial memory and learning in transgenic mouse model of AD. Identification of shorter amylin receptor antagonist peptides, that are proteolytically stable and brain penetrant when administered systemically could provide novel therapies for AD. An AC253 based peptide library of 14 peptide fragments was synthesized on cellulose membrane and screened for binding to amylin receptor using transfected HEK-293 that express the amylin 3 (AMY3) receptor subtype (AMY3). Promising sequences were synthesized using Fmoc synthesis, and labeled with Cy5.5 dye for further studies. *In vitro* cell uptake was evaluated in AMY3 cells using flow cytometry and fluorescence microscopy. *Ex-vivo* brain uptake was done using near infrared imaging, and fluorescence microscopy. Peptides R5 (12 aa), and R14 (14 aa) showed significant binding to HEK293-AMY3 cells compared to other library fragments. *In vitro* studies showed that both peptides blocked human amylin cellular responses in HEK293-AMY3 cells with equal the potency as full length AC253. Flow cytometry and fluorescence microscopy cell uptake studies demonstrated that R5, and R14 peptides have selective and significant specific binding to HEK293-AMY3 cells similar to AC253. *Ex vivo* brain imaging in wild type mice after intra-peritoneal administration of Cy5.5 labelled peptides revealed that both R5, and R14 peptides can cross the Blood Brain Barrier, and peptide R5 showed superior brain penetration to that observed in AC253. Microscopy studies showed that labeled peptides were mainly distributed in the hippocampal and cortical regions, which coincides with the amylin receptor localization in the

brain. Our data identify novel promising peptides amylin receptor antagonists for future pre-clinical and clinical studies in AD.

Disclosures: **R.N. Soudy:** None. **W. Fu:** None. **K. Kaur:** None. **J. Jhamandas:** None.

Poster

785. Alzheimer's Disease: Anti-Amyloid Beta Therapeutics

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 785.02/G26

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: Alberta Prion Research Institute (Alberta Innovates Bio Solutions)

The Alzheimer Society of Alberta and NWT

Alberta Innovates Health Solutions

Title: Effects of amylin receptor antagonist AC253 fragments on beta amyloid (Aβ) - and human amylin-induced depression of hippocampal long-term potentiation.

Authors: ***R. KIMURA**[1], R. SOUDY[2], W. FU[2], D. WESTAWAY[2,3], J. JHAMANDAS[2]; [1]Ctr. for Liberal Arts and Sci., Tokyo Univ. of Science, Yamaguchi, Sanyo-Onoda, Japan; [2]Medicine. (Neurology) and Inst. of Neurosci. and Mental Hlth., [3]Ctr. for Prions and Protein Folding Dis., Univ. of Alberta, Edmonton, AB, Canada

Abstract: Alzheimer's disease (AD) is characterized by accumulation of amyloid-β peptide (Aβ) in the brain regions that subserve memory and cognition. We have previously demonstrated that effects of $A\beta_{1-42}$ and human amylin on hippocampal long-term potentiation (LTP) are blocked by the amylin receptor antagonists, AC253 and pramlintide. In this study, we examined the effects of several peptidergic fragments, that were derived from AC253, on $A\beta_{1-42}$ and human amylin-evoked depression of LTP at Schaeffer collateral-CA1 hippocampal synapses. In mouse hippocampal brain slices, field excitatory postsynaptic potentials (fEPSPs) were recorded from the stratum radiatum layer of the CA1 area in response to electrical stimulation of Schaeffer collateral afferents. LTP was induced by either high frequency (HFS) or 3-theta burst stimulation (TBS) protocols. $A\beta_{1-42}$ (50 nM) and human amylin (50 nM) depressed LTP evoked using both stimulation protocols. Pre-application of fragment #5 (R5, 250 nM) and #14 (R14, 250 nM), but not #11 (R11, 250 nM), blocked both Aβ- and human amylin-induced reduction of LTP without affecting baseline transmission or LTP on their own. We also examined the effects of these fragments on LTP in Aβ-over-expressing transgenic mice (TgCRND8). In contrast to wild-type age matched control mice, 6-12-month old TgCRND8 mice show blunted LTP. In TgCRND8

mice, basal depression of LTP is enhanced by application of R5 and R14 but not R11 fragments. Our data show that specific shorter sequence peptides derived from AC253, possess amylin receptor antagonist activity to reverse the effects of $A\beta_{1-42}$ and human amylin on LTP, and furthermore, also increase LTP in TgCRND8 mice with increase brain amyloid burden. These peptidergic fragments by virtue of their ability to block the amylin receptor may thus serve as potentially useful therapeutic agents in treatment of AD.

Disclosures: **R. Kimura:** A. Employment/Salary (full or part-time): Center for Liberal Arts and Sciences, Tokyo University of Science, Yamaguchi, Japan. B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution; Alberta Prion Research Institute (Alberta Innovates Bio Solutions), the Alzheimer Society of Alberta and NWT, Alberta Innovates Health Solutions. **R. Soudy:** None. **W. Fu:** None. **D. Westaway:** None. **J. Jhamandas:** None.

Poster

785. Alzheimer's Disease: Anti-Amyloid Beta Therapeutics

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 785.03/G27

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: Canadian Institute of Health Research

Alberta Innovaties Health Solutions

Title: Systemic administration of amylin receptor antagonist, cyclic AC253, improves spatial memory in Aβ over-expressing (TgCRND8) mice

Authors: ***A. N. PATEL**[1,2], R. SOUDY[1], W. FU[1], D. MACTAVISH[1], J. YANG[2], D. WESTAWAY[2], J. JHAMANDAS[1];
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Abstract: Alzheimer's disease (AD) is characterized by accumulation of amyloid-β peptide (Aβ) in the brain regions that subserve memory and cognition. We have previously demonstrated that electrophysiological and neurotoxic effects of Aβ can be blocked by the amylin receptor antagonist, AC253. Furthermore, chronic intracerebroventricular infusions of AC253 restore spatial memory deficits in APP over-expressing transgenic mice (TgCRND8). In this study, we performed systemic administrations of cyclized AC253 (cAC253) that is proteolytically stable

and brain penetrant, to examine the effects of this peptide on memory and learning in TgCRND8 mouse model.
TgCRND8 and wild-type (Wt) littermate control mice (3.5 months of age) received daily intraperitoneal injections for 10 weeks of either cAC253 or saline. Hippocampal-dependent spatial learning and memory was assessed at baseline and 10 weeks after drug administration using standard Morris Water Maze (MWM) and Novel Object Recognition tests. In the acquisition phase (escape latency) in MWM task, TgCRND8 mice had significantly longer escape latencies over the 5-day testing period than Wt littermate controls at 6 months of age. However, TgCRND8 mice receiving cAC253 for showed significant shorter escape latencies in MWM at 6 months of age compared to TgCRND8 treated with saline. Western blot analysis of brains from Tg cAC253 treated group showed increase (15%) in synapsin-1 and synaptophysin compared to Tg saline treated group. Other markers of AD pathology from treatment groups are being evaluated. These studies provide evidence for the utility of systemic administrations of the brain penetrant amylin receptor antagonist, cyclic AC253, in mitigating spatial memory learning deficits in an AD mouse model.

Disclosures: **A.N. Patel:** None. **R. Soudy:** None. **W. Fu:** None. **D. MacTavish:** None. **J. Yang:** None. **D. Westaway:** None. **J. Jhamandas:** None.

Poster

785. Alzheimer's Disease: Anti-Amyloid Beta Therapeutics

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 785.04/G28

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH GRANT RO1AG040092

PROBIODRUG UNRESTRICTED GIFT

Title: Plaque-clearing by a murine anti-pyroglutamate-3 Aβ IgG2a monoclonal antibody with and without a CDC mutation

Authors: *H. CREHAN[1,2], B. LIU[1,2], M. KLEINSCHMIDT[3,4], J.-U. RAHFELD[3,4], K. X. LE[1], M.-A. PARK[2,5], M. DI CARLI[2,5], V. REISER[6], W. TRIGG[7], B. HUTTER-PAIER[8], I. LUES[3], S. SCHILLING[3,4], C. A. LEMERE[1,2];
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MA; [6]GE Healthcare, Princeton, NJ; [7]GE Healthcare, Amersham, United Kingdom; [8]QPS, Grambach, Austria

Abstract: Pyroglutamate-3 Aβ (pGlu-3 Aβ) is an N-terminally truncated and modified Aβ species found in plaques and vascular amyloid in Alzheimer's disease (AD) brain (Saido et al., 1995; Lemere et al., 1996). Following truncation of the first 2 Aβ residues, pGlu-3 Aβ is formed by the cyclization of glutamate at residue 3 by glutaminyl cyclase (QC) and is associated with increased aggregation and neurotoxicity (Russo et al., 2002; Schilling et al., 2006; Nussbaum et al., 2012). Previously, we reported that chronic treatment in plaque-rich 12 mo-old APP/PS1dE9 mice with an anti-pGlu-3 Aβ IgG2a mAb (07/2a), demonstrated significant cognitive improvement and plaque reduction compared to PBS-control mice and was more effective than an anti-pGlu-3 Aβ IgG1 mAb (07/1) (SfN 2015). Here, we treated hAPP/hQC double transgenic (Tg) mice, an hAPP mouse model with enhanced pGlu3-Aβ generation due to overexpression of human QC, with: i) 07/2a at two doses (150μg and 500μg); ii) 07/2a-k (500 μg), 07/2a bearing a CDC mutation to avoid complement activation; and iii) PBS. Passive i.p. immunization was performed weekly from 8 to 12 months of age. PyroGlu-3 Aβ immunoreactivity (IR), measured by 07/2b IgG2b (k17) mAb, was significantly reduced in the hippocampus in 07/2a-treated (150μg dose, $p<0.05$; 500μg dose, $p<0.01$), and 07/2a-k-treated ($p<0.05$) compared to PBS-control hAPP/xhQC mice. General Aβ (R1282 IR) was significantly decreased in hippocampus in all three pGlu-3 Aβ vaccinated groups compared with PBS-control hAPP/hQC mice. Although a few hemosiderin-positive microhemorrhages were seen in all groups, no differences were observed immunized vs. PBS-control hAPP/hQC mice. In a separate study, we performed longitudinal ^{18}F-GE180 TSPO microPET imaging of microglial activation at baseline and Days 3 and 30 following a single injection of 07/1, 07/2a and 07/2a-k in young, pre-plaque vs. aged, plaque-rich APP/PS1dE9 mice. Differences were observed in hippocampal and whole brain uptake of ^{18}F-GE180, suggesting that the IgG isotype and CDC mutation of the anti-pyroGlu3 Aβ mAbs, as well as aging and the presence of plaques, differentially affected microglial activation. In summary, we demonstrate that: 1) murine anti-pGlu-3 Aβ IgG2a antibodies with and without a CDC mutation significantly lowered pyroGlu3 and general Aβ plaques without increasing microhemorrhage in a mouse model with enhanced pyroGlu3 Aβ deposition, and 2) microglial activation was differentially altered by a single injection of 07/2a and 07/1 mAbs but unchanged by immunization with 07/2a-k. Further studies are underway to better understand the clearance mechanisms for each of these anti-pyroGlu3 Aβ antibodies.

Disclosures: **H. Crehan:** C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Antibodies from Probiodrug. GE-180 Cassettes from General Electric.. **B. Liu:** None. **M. Kleinschmidt:** None. **J. Rahfeld:** None. **K.X. Le:** None. **M. Park:** None. **M. Di Carli:** None. **V. Reiser:** None. **W. Trigg:** None. **B. Hutter-Paier:** None. **I. Lues:** None. **S. Schilling:** None. **C.A. Lemere:** F. Consulting Fees (e.g., advisory boards); Serves on the Probiodrug Scientific Advisory Board.

Poster

785. Alzheimer's Disease: Anti-Amyloid Beta Therapeutics

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 785.05/G29

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: JSPS KAKENHI 26290022, I.T. and 15K16321, D.Y., Japan Society for Promotion of Science

Long-Term Research Grant Scheme LRGS/BU/2012/UKM-UKM/K/04, Ministry of Education Malaysia

Title: Tocotrienol-rich fraction inhibits amyloid β fibrillation *In vitro* and in transgenic mouse model of Alzheimer's disease

Authors: *N. F. IBRAHIM[1,2], D. YANAGISAWA[1], L. W. DURANI[1,2], H. S. HAMEZAH[1,2], H. A. DAMANHURI[2], W. Z. WAN NGAH[2], I. TOOYAMA[1];
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Abstract: Aim and Background
Abnormal aggregation of amyloid β (Aβ) peptides may result in formation of insoluble Aβ fibrils that deposit outside neurons, known as senile plaques in Alzheimer's disease (AD). Therapeutic approaches aimed at modulation of Aβ pathology have been studied, and one such approach involves vitamin E. Tocotrienol-rich fraction, (TRF) an extract of palm oil containing large amounts of vitamin E analogs (mostly tocotrienols) has been shown to reduce Aβ-induced toxicity in cell culture. Therefore, the present study investigated the effects of TRF, in potentially modulating Aβ fibril formation *in vitro* and in APP/PS1 transgenic mice.
Methods
The effect of TRF on Aβ (1-42) fibrillation was investigated with thioflavin T (ThT) assay and SDS-PAGE (sodium dodecyl sulfate electrophoresis on polyacrylamide gel). APP/PS1 mice were daily supplemented with either water (n = 9), or palm oil stripped of vitamin E (PO, n = 10), or TRF (60 mg/kg; n = 11) from ages 5 to 15 months. Meanwhile wild type mice (n = 13) received water. Novel object recognition tests were done at age 14.5 months. After that, Thioflavin S staining and immunohistochemistry using anti-Aβ (N) antibody were performed. Immunoreactive areas were measured using ImageJ software.
Results
Under cell-free conditions, ThT assay fluorescence intensity for Aβ (1-42) incubated alone increased progressively with incubation time. Interestingly, TRF dose-dependently inhibited the formation of Aβ fibrils, as shown by a reduction of fluorescence intensity. In SDS-PAGE, TRF treatment showed relatively more intense bands of low molecular weight Aβ (1-42) aggregates in

a dose-dependent manner.
In animal experiments, APP/PS1 mice supplemented with TRF showed significantly more exploration of the novel object as indicated by recognition index, compared to water-supplemented APP/PS1 mice. This result indicated preservation of cognitive function comparable to wild type mice. Moreover, thioflavin-S-positive fibrillar load was significantly reduced in APP/PS1 mice supplemented with TRF. In addition, Aβ immunoreactivity was decreased in the brains of TRF-supplemented mice. No significant benefit was seen in PO-supplemented mice. These results indicated that TRF reduced Aβ pathology in the brain of APP/PS1 mice.
Conclusion
These findings suggest potential beneficial effect of TRF as a therapeutic agent to reduce amyloid fibrillation *in vitro* and in transgenic mouse model of AD.

Disclosures: N.F. Ibrahim: None. **D. Yanagisawa:** None. **L.W. Durani:** None. **H.S. Hamezah:** None. **H.A. Damanhuri:** None. **W.Z. Wan Ngah:** None. **I. Tooyama:** None.

Poster

785. Alzheimer's Disease: Anti-Amyloid Beta Therapeutics

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 785.06/G30

Topic: C.02. Alzheimer's Disease and Other Dementias

Title: Antioxidative stress effect of epicatechin and catechin induced by $A\beta_{25-35}$ in rats and use of the electrostatic potential and the Fukui function as a tool to elucidate specific sites of interaction

Authors: *M. MUNOZ ARENAS[1], T. CRUZ-GONZÁLEZ[1], E. CORTEZ-TORRES[2], F. PEREZ-SEVERIANO[3], B. ESPINOSA[4], J. GUEVARA[5], A. PEREZ-BENITEZ[1], F. MELENDEZ-BUSTAMÁNTE[1], A. DÍAZ[1], R. RAMÍREZ[1];
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Abstract: Alzheimer's disease (AD) is a neurodegenerative disorder caused by the aggregation of the amyloid-beta peptide (Aβ) in senile plaques and cerebral vasculature. The $A\beta_{25-35}$ fraction

has shown the most toxicity; its neurotoxic mechanisms are associated with the generation of oxidative stress and reactive astrogliosis that induce neuronal death and memory impairment. Studies indicate that pharmacological treatment with flavonoids reduces the rate of AD, in particular, it has been shown that antioxidants are compounds that could interact with this peptide due to their antioxidant properties. In this study, experimental and computational tools were used to calculate the molecular electrostatic potential and the Fukui function with the Gaussian 09 computational program, to predict the most reactive parts of these molecules and make the complex between $A\beta_{25-35}$ and two flavonoids (catechin and epicatechin) in the absolute gas-phase, where a possible interaction between them was observed. This is important for understanding the $A\beta_{25-35}$-Flavonoid (A-F) interaction as a therapeutic strategy to inhibit the neurotoxic effects that this peptide causes in AD, which currently is still considered an ambiguous process.

Disclosures: **M. Munoz Arenas:** None. **T. Cruz-González:** None. **E. Cortez-Torres:** None. **F. Perez-Severiano:** None. **B. Espinosa:** None. **J. Guevara:** None. **A. Perez-Benitez:** None. **F. Melendez-Bustamánte:** None. **A. Díaz:** None. **R. Ramírez:** None.

Poster

785. Alzheimer's Disease: Anti-Amyloid Beta Therapeutics

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 785.07/G31

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: Deutsche Forschungsgemeinschaft (DFG)

ERC Grant Agreement No. 321366-Amyloid

The general legacy of Mrs. Ammer

The MetLife award

The Cure Alzheimer's fund

Title: TREM2-deficiency reduces the efficacy of immunotherapeutic amyloid clearance

Authors: *X. XIANG[1], G. WERNER[1], B. BOHRMANN[2], F. MAZAHERI[3], A. CAPELL[1], R. FEEDERLE[4], I. KNUESEL[2], G. KLEINBERGER[1], C. HAASS[1];
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Abstract: Alzheimer's disease (AD) is the most abundant neurodegenerative disorder and threatens our ageing society. Immunotherapeutic approaches are currently the most advanced therapies for treatment of AD. Antibodies raised to amyloid β-peptide (Aβ) cross the blood-brain-barrier and bind to amyloid plaques in the brain of AD patients. Bound antibodies induce clearance of amyloid plaques by microglia via Fc receptor-mediated phagocytosis. Dysfunctions of microglia may play a pivotal role in AD pathogenesis and could result in reduced efficacy of antibody-mediated Aβ clearance. Recently, heterozygous mutations in the triggering receptor expressed on myeloid cells 2 (*Trem2*), a microglial gene involved in phagocytosis, were genetically linked to late onset AD. Loss of TREM2 has been shown to reduce the ability of microglia to engulf Aβ. We have now investigated if loss of TREM2 affects the efficacy of immunotherapeutic approaches. Using CRISPR/Cas9 modified N9 microglial cell lines as well as bone marrow derived macrophages (BMDM) and primary microglia cells from wild-type (wt) or *Trem2* knockout (ko) mice, we investigated the potential of these cells for antibody-dependent phagocytosis of pre-formed Aβ fibrils or engulfment of antibody covered amyloid plaques from brain slices of APP/PS1 mice. We showed that anti-Aβ antibodies stimulate fibril Aβ uptake and amyloid plaque clearance in a dose-dependent manner in the presence or absence of TREM2. However, TREM2-deficient N9 cells, as well as macrophages and primary microglia derived from *Trem2* ko mice showed significantly reduced uptake of antibody bound Aβ and as a consequence reduced clearance of amyloid plaques. The level of Fcγ-receptors I-IV increased in *Trem2* ko BMDM, indicating a compensatory increase of TREM2 independent antibody/antigen uptake pathways and probably explaining why *Trem2* ko cells still response to increasing concentrations of anti-Aβ antibodies. Antibody titration experiments revealed that reduced efficacy of amyloid plaque clearance and fibril Aβ uptake in *Trem2* ko cells can be compensated by elevating the concentration of therapeutic antibodies. Taken together, our findings suggest that patients with compromised TREM2 function may require a higher dose of the therapeutic antibody to achieve efficient Aβ clearance.

Disclosures: **X. Xiang:** None. **G. Werner:** None. **B. Bohrmann:** A. Employment/Salary (full or part-time): Roche Innovation Center Basel. **F. Mazaheri:** None. **A. Capell:** None. **R. Feederle:** None. **I. Knuesel:** A. Employment/Salary (full or part-time): Roche Innovation Center Basel. **G. Kleinberger:** None. **C. Haass:** Other; C.H. is an advisor of F. Hoffmann - La Roche..

Poster

785. Alzheimer's Disease: Anti-Amyloid Beta Therapeutics

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 785.08/G32

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: the Convergence of Conventional Medicine and Traditional Korean Medicine R&D program funded by the Ministry of Health & Welfare through the Korea Health Industry Development Institute (HI15C0214).

Title: Aβ vaccination with bee venom derived phospholipase A2 (bvPLA2) ameliorates Alzheimer's disease pathology through the induction of Aβ-specific Treg population in 3xTg-AD mice

Authors: *H. BAE, H. BAEK, C. LEE, G. LEE, D. CHOI;
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Abstract: Alzheimer's disease (AD) is the most common form of dementia and characterized by an imbalance between the production and clearance of amyloid-beta (Aβ) and tau proteins. Vaccination against Aβ peptide results in dramatic reduction of Aβ pathology in experimental mouse models. Our recent study demonstrated that bvPLA2, the major component of BV, causes immune tolerance by increasing the population of CD4+ CD25+ Foxp3+ Tregs in cisplatin-induced nephrotoxicity, an allergic asthma and Parkinson disease murine model. Here, we investigated that the effect of bvPLA2 to induce antigen-specific Tregs to ameliorate Alzheimer's disease pathology through linked immunosuppression. First, we investigated whether bvPLA2 would improve the cognitive function and the pathological features of AD in Aβ-vaccinated-3xTg-AD mice. bvPLA2 treatment dramatically ameliorated learning and memory deficits in Aβ-vaccinated-AD mice. In addition, bvPLA2 significantly reduced Aβ deposits in the hippocampus and cortex region of AD mice, compared with the Aβ-vaccinated-AD mice group. Next, we systemically administered Aβ-specific Treg populations generated in the absence or presence of bvPLA2 into 3xTg-AD mice. Systemic transplantation of Aβ-specific Tregs into 3xTg-AD mice improved cognitive function and reduced deposition of Aβ plaques. Furthermore, adoptive transfer of Tregs generated in the presence of bvPLA2 showed reduced Aβ plaques and diminished learning and memory ability compared with Tregs generated in the absence of bvPLA2. This opens the possibility of new therapeutic strategy to target Tregs to tissue-specific antigens for the treatment of AD.

Disclosures: H. Bae: None. **H. Baek:** None. **C. Lee:** None. **G. Lee:** None. **D. Choi:** None.

Poster

785. Alzheimer's Disease: Anti-Amyloid Beta Therapeutics

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 785.09/G33

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: Grant # 5AZ09, Ed and Ethel Moore Alzheimer's Disease Research Program, State of Florioda Department of Health

Grant # 6AZ08, Ed and Ethel Moore Alzheimer's Disease Research Program, State of Florioda Department of Health

Title: Epigenetic modulation of amyloid precursor protein (APP) metabolites and other Alzheimer's disease biomarkers *In vitro* and *In vivo*

Authors: *C.-H. VOLMAR, H. SALAH-UDDIN, P. HALLEY, G. LAMBERT, A. WODRICH, S. MANOAH, N. PATEL, N. MEHTA, G. SARTOR, K. JANCZURA, S. DESSE, D. DORCIUS, C. WAHLESTEDT;
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Abstract: Alzheimer's disease (AD) is the most common form of dementia in the elderly. Currently approved treatments are not efficacious and are palliative at best. The "amyloid cascade hypothesis" places beta amyloid (Aβ) at the origin of AD, causing a chain of molecular events leading to neuronal degeneration, memory loss, motor impairment, and eventually death. No FDA-approved treatment presently reduces Aβ accumulation (the main constituent of plaques) in the brain of patients. With the recent clinical trial shortcomings of Alzheimer's immunotherapy and γ-secretase inhibitors, experts in the field agree that "drug cocktails" are desirable but present challenges in terms of clinical and regulatory hurdles. We therefore took an epigenetic approach where a single drug would simultaneously affect the expression of a number of defined AD-related targets.
Screening of our in-house comprehensive library of epigenetic compounds in an AD cell model over-expressing APP with the Swedish mutation resulted in the identification of small molecules that are able to significantly reduce Aβ. Confirmed non-toxic Hits were then tested in RT-QPCR and western blots to hone in on compounds that affect AD-related and neuro-protective genes and proteins. We identified an atypical small molecule histone deacetylase inhibitor (HDACi), CTI-309, that reduces beta amyloid (Aβ), decreases tau gene expression, and increases the expression of the following genes: BDNF, α-secretase (ADAM10), Mint2, Fe65 and REST. This molecule increases the production of sAPPα, the cleavage product of ADAM10, in line with the increased gene expression observed for ADAM10. This molecule also increases levels of immature APP, supporting an effect on APP trafficking, as do the increases in Mint2 and Fe65. Treatment of the triple transgenic (APP/PS1/tau) (3xTg AD) mouse model with CTI-309 resulted in significant increases in spontaneous alternations in the Y-maze compared to controls. We also observed, in these CTI-309 treated mice, significant increases in frequency and time spent with the novel object in the novel object recognition test. Interestingly, no differences were observed in the open field test. Taken together, our data suggest that the newly identified epigenetic molecule CTI-309 is brain penetrant, targets the non-amyloidogenic pathway, affects APP trafficking, increases neuroprotective genes, shows less toxicity than other HDACis tested and increases memory in an AD model. We are currently conducting experiments to decipher the exact mechanism of this molecule.

Disclosures: **C. Volmar:** None. **H. Salah-Uddin:** None. **P. Halley:** None. **G. Lambert:** None. **A. Wodrich:** None. **S. Manoah:** None. **N. Patel:** None. **N. Mehta:** None. **G. Sartor:** None. **K. Janczura:** None. **S. Desse:** None. **D. Dorcius:** None. **C. Wahlestedt:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Co-founder of Epigenetix and IntelliSyn RD.

Poster

785. Alzheimer's Disease: Anti-Amyloid Beta Therapeutics

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 785.10/G34

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: Tata Trusts / CSIR

Title: Lipoprotein receptor related protein 1 as a therapeutic target for alzheimer’s disease

Authors: *A. RAMACHANDRAN[1], S. KUMAR[1], K. V. RUPANAGUDI[1], H. S. ILAMATHI[2], S. S. THAKUR[2], M. CHAND[3], P. KHANNA[3], S. C. JAIN[3], V. RAVINDRANATH[1]; [1]Indian Inst. of Sci., Bangalore, India; [2]Ctr. for Cell. and Mol. Biol., Hyderabad, India; [3]Univ. of Delhi, Delhi, India

Abstract: Alzheimer’s disease (AD), a debilitating neurodegenerative disorder is characterised by progressive loss of memory, cognitive, and executive functions. Accumulation of β-Amyloid 42 (Aβ42) is considered to be the causative factor in Alzheimer’s disease, either due to the over production of Aβ42 (in familial AD) or decreased clearance as seen in sporadic forms of the disease. The drugs currently used for treatment of AD provide symptomatic relief but do not cure or alter the progression of the disease. We have previously shown that partially purified extract of root of *Withania somnifera* (WS) reverses behavioural deficits and pathological hallmarks of AD in middle aged and old APPswe/PS1ΔE9 (APP/PS1) mice via upregulation of liver lipoprotein receptor related protein 1 (LRP1) leading to clearance of Aβ42 from brain (Sehgal *et al*, Proc. Natl. Sci, 2012) to the periphery through the peripheral sink, sLRP in the plasma. In order to identify the active principle(s) in the partially purified extract of WS, we fractionated it into twelve sub-fractions and studied the effect of these sub-fractions on LRP1 expression, *in vitro* using luciferase based reporter system. Different regions of LRP promoter were cloned into pGL3 basic promoterless vector such that the luciferase gene is expressed under LRP promoter. This construct was transfected into H6 cells and the cells were further treated with each sub-fraction followed by luciferase assay. Two sub-fractions showed significant increase in reporter induction as compared to the crude extract. We further studied the effects of these two sub-fractions *in vivo* and found that treatment of 9 month old APP/PS1 mice for 15 days results in a

three fold increase in liver LRP expression. Identification of the active principle(s) in these two sub-fractions will help in generation of a class of drugs that help clearance of Aβ42 from the brain leading to reversal of cognitive deficits.

Disclosures: **A. Ramachandran:** None. **S. Kumar:** None. **K.V. Rupanagudi:** None. **H.S. Ilamathi:** None. **S.S. Thakur:** None. **M. Chand:** None. **P. Khanna:** None. **S.C. Jain:** None. **V. Ravindranath:** None.

Poster

785. Alzheimer's Disease: Anti-Amyloid Beta Therapeutics

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 785.11/G35

Topic: C.02. Alzheimer's Disease and Other Dementias

Title: Inflammation induces natural anti-amyloid beta antibodies in a murine Alzheimer's disease model

Authors: ***M. J. CHUMLEY**[1], M. A. THOMPSON[1], K. C. PAULHUS[1], M. J. EIMERBRINK[2], J. L. PETERMAN[2], J. D. WHITE[2];
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Abstract: Alzheimer's disease is the leading cause of dementia, and amyloid beta (Aβ) plaques are one of the main pathologies associated with the disease. Anti-Aβ immunotherapy has been investigated as a means of reducing the Aβ burden seen in Alzheimer's patients. Studies in transgenic mice have shown that immunization with anti-Aβ antibody or with the Aβ protein itself causes a significant decrease in the Aβ burden. Immunohistochemistry of the brains of these mice reveals increased IgG binding to Aβ plaques in the brain, correlating with decreased overall plaque burden (Schenk et al., 1999; Wilcock et al., 2004). Furthermore, recent studies in humans have shown increased levels of naturally produced anti-Aβ antibodies in Alzheimer's patients (Kellner et al. 2009). Previous research from our lab as shown that CD57BL6/J mice given seven daily intraperitoneal injections of lipopolysaccharide exhibit a significant increase of Aβ in the brain. Additionally, when mice were given a two-week recovery period followed by a second bout of LPS injections, there was no additional Aβ production, suggesting a protective effect initiated by the first LPS bout. The objective of the present study was to determine if anti-Aβ immunoglobulin production increases with LPS stimulation, and to investigate whether this IgG crosses the blood brain barrier and aggregates around Aβ plaques. Female Alzheimer's transgenic mice were injected with LPS for one week, followed by a two-week recovery period and a second week of LPS injections. After injections, mice were euthanized in accordance with IACUC-approved methods, immediately after which brains and blood samples were collected.

The blood was analyzed by ELISA to determine antibody concentration, and brains were analyzed by immunohistochemistry to determine IgG presence around Aβ plaques. We found an increase of anti-Aβ IgG in the blood, correlating with an increased amount of IgG around plaques as compared to controls. These results demonstrate that mice can be stimulated to produce natural anti-Aβ antibodies as a response to inflammation and the increased Aβ burden caused by inflammation.

Disclosures: M.J. Chumley: None. **M.A. Thompson:** None. **K.C. Paulhus:** None. **M.J. Eimerbrink:** None. **J.L. Peterman:** None. **J.D. White:** None.

Poster

785. Alzheimer's Disease: Anti-Amyloid Beta Therapeutics

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 785.12/G36

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH Grant NS083175

NIH Grant AG037337

NIH Grant AG047059

NIH Grant AG052249

Michael J Fox Foundation Grant 11709

Title: Sigma-2/PGRMC1 antagonist pharmacodynamic target engagement biomarker discovery for Alzheimer's disease

Authors: *C. REHAK, N. IZZO, K. MOZZONI, C. SILKY, R. YURKO, H. SAFFERSTEIN, S. CATALANO;
Cognition Therapeut. Inc., Pittsburgh, PA

Abstract: Cognition Therapeutics Inc. (CogRx) discovered CT1812, a novel Abeta oligomer receptor antagonist which is the only drug candidate demonstrated to prevent and displace Abeta oligomer binding to neuronal receptors. By stopping the initiating event in the Abeta oligomer cascade, this first-in-class drug blocks downstream synaptotoxicity and restores memory to normal in transgenic mouse models of Alzheimer’s disease (AD). CT1812 displaces receptor-bound oligomers by allosterically antagonizing the sigma-2/PGRMC1 receptor (Izzo et al., 2014a, b). CT1812 is the first disease modifying therapeutic that will test the oligomer

hypothesis of AD. Biomarkers in patient biofluids that change following CT1812 engagement with the target receptor enable independent verification of compound activity. Despite prior clinical experience with sigma-2 ligands, biomarkers of sigma-2/PGRMC1 antagonist functional target engagement are not reported in the literature. Sigma-2/PGRMC1 has been demonstrated to regulate expression levels and subcellular localization of several proteins, including EGF receptor (Ahmed et al., 2010), mPRα receptor (Thomas et al., 2014), UNC 40/DCC (Runko et al., 2004), and GLP-1 receptor (Zhang et al 2014). We hypothesize that sigma-2/PGRMC1's role in regulating expression levels and subcellular localization of several proteins may provide an opportunity to measure drug-target engagement, which may manifest as changes in target protein expression or downstream signaling in clinically relevant samples. In 21DIV neurons, sigma-2/PGRMC1 localization was visualized by immunocytochemistry and quantified via image processing. In neurons, GLP-1R was expressed predominantly in the cytoplasm at low levels. Addition of Abeta oligomers caused a significant increase in GLP-1 receptor protein expression in the nucleus. Treatment with sigma-2/PGRMC1 antagonist CT1344 (analog of clinical candidate CT1812) at therapeutic brain concentrations blocked this increase, restoring GLP-1R expression pattern to normal, but did not affect expression in the absence of Abeta oligomers. The magnitude of protein concentration changes associated with the effects of Abeta oligomers on expression levels of GLP-1R was modest (i.e. 20%), but was completely reversed by CogRx sigma-2/PGRMC1 antagonist. Target engagement "fingerprints" (patterns of consistent changes in amounts of several proteins, each modest in magnitude) have been used successfully as pharmacodynamic biomarkers in clinical studies (Paweletz et al. 2009; Tsitoura et al. 2015).

Disclosures: **C. Rehak:** A. Employment/Salary (full or part-time): Cognition Therapeutics Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Cognition Therapeutics Inc. **N. Izzo:** A. Employment/Salary (full or part-time): Cognition Therapeutics Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Cognition Therapeutics Inc. **K. Mozzoni:** A. Employment/Salary (full or part-time): Cognition Therapeutics Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Cognition Therapeutics Inc. **C. Silky:** A. Employment/Salary (full or part-time): Cognition Therapeutics Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Cognition Therapeutics Inc. **R. Yurko:** A. Employment/Salary (full or part-time): Cognition Therapeutics Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Cognition Therapeutics Inc. **H. Safferstein:** A. Employment/Salary (full or part-time): Cognition Therapeutics Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Cognition Therapeutics Inc. **S. Catalano:** A. Employment/Salary (full or part-time): Cognition Therapeutics Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Cognition Therapeutics Inc..

Poster

785. Alzheimer's Disease: Anti-Amyloid Beta Therapeutics

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 785.13/G37

Topic: C.02. Alzheimer's Disease and Other Dementias

Title: Prevention of Aβ-induced deficits in long term potentiation (LTP) *In vitro* and *In vivo* by MRZ-99030 and MRZ-14042

Authors: *G. RAMMES[1], R. D. JEGGO[2];
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Abstract: β-Amyloid (Aβ) plays a pivotal role in the aetiology of Alzheimer's disease (AD) and other neurodegenerative, protein aggregation disorders. Recently, increasing evidence indicates that small soluble toxic Aβ species are the more synaptotoxic form. MRZ-99030 and MRZ-14042 are both small dipeptide molecules that interfere with Aβ aggregation. MRZ-14042 was more potent than MRZ 99030 in binding to Aβ as determined by surface plasmin resonance – affinities for monomeric $A\beta_{1-42}$ were 10nM and 30 nM respectively. Atomic force microscopy and diffuse light scattering experiments revealed that both MRZ-99030 and MRZ-14042 prevent the formation of toxic oligomeric species by promoting aggregation into non-toxic, off-pathway MRZ-99030 / Aβ assemblies and thereby suppressing the toxic effect of Aβ oligomers. MRZ-14042 had lower stoichiometric requirements than MRZ 99030 i.e. was also effective at a 1:1 ratio, whereas MRZ-99030 required a 10-20 fold excess over Aβ.
Long term potentiation (LTP) is regarded as an electrophysiological correlate of neuronal synaptic plasticity and is impaired by acute administration of Aβ oligomers. MRZ-99030 fully prevented deficits in LTP *in vitro* induced by $A\beta_{1-42}$ oligomers (10 - 50 nM) when applied at a 10:1 ratio e.g. 100 nM of MRZ-99030 against $A\beta_{1-42}$ 10 nM, whereas at a 1:1 ratio MRZ-99030 was ineffective. Surprisingly, MRZ-14042 (100nM) did not reverse deficit in *in vitro* LTP evoked by $A\beta_{1-42}$ (10nM).
MRZ-99030 50 mg/kg s.c. had little effect *per se* on LTP *in vivo* but almost completely prevented the deficits in synaptic plasticity induced by $A\beta_{1-42}$ oligomers (6μL, 1.8 μM). The dose-dependency of this effect was further investigated with MRZ-14042 which was effective even at doses as low as 0.4mg/kg MRZ-14042 (~10nM brain ECF). The reasons for this apparent discrepancy in *in vitro* and *in vivo* LTP are unclear.
In addition, MRZ-14042 (1μM) almost completely prevented depolarization of retinal ganglion cells and retinal epithelial cells by $A\beta_{1-42}$ oligomers (50nM) *in vitro* whereas MRZ-99030 (1μM) was somewhat less efficacious – around 50% effect size.
These data provide proof of concept for both compounds as potential treatments for Alzheimer´s

disease and retinal pathologies associated with toxic effects of Aβ oligomers e.g. glaucoma and age-related macular degeneration.

Disclosures: G. Rammes: None. **R.D. Jeggo:** None.

Poster

785. Alzheimer's Disease: Anti-Amyloid Beta Therapeutics

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 785.14/G38

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: Alzheimer’s Drug Discovery Foundation 20131002

NIH/NIA T32 AG029796

Center on Aging, College of Pharmacy, and Academic Health Center of the University of Minnesota

Title: Treatment with a Clusterin/ApoJ peptide reduces amyloid pathology in APP/PS1 mice

Authors: *D. A. HOTTMAN[1], D. S. CHERNICK[2], Y. ZHANG[1], A. GRAM[1], R. OMTRI[3], K. KANDIMALLA[3], L. LI[1];
[1]Exptl. and Clin. Pharmacol., [2]Pharmacol., [3]Pharmaceutics, Univ. of Minnesota, Minneapolis, MN

Abstract: Alzheimer’s disease (AD) is a progressive neurodegenerative disorder that poses a growing challenge to health care systems and economies across the globe. Currently there is no cure for AD. Recent genetic studies have identified the clusterin gene (*CLU*, also known as apoJ) as one of the top-ranking loci associated with late-onset AD. Like apoE (a primary genetic risk factor for AD), apoJ is a multifunctional protein; apoJ binds Aβ, inhibits Aβ aggregation, enhances phagocytosis of Aβ aggregates, and facilitates the clearance of Aβ across the blood-brain barrier (BBB) as well as modulates inflammatory and immune functions in the brain. Previous studies have shown that a 10-amino acid peptide derived from an integral sequence of apoJ, apoJ[113-122], recapitulates several beneficial properties of full length apoJ. In preliminary studies, we have found that apoJ[113-122] inhibits Aβ aggregation, protects neuronal cells against Aβ-induced cytotoxicity, enhances hippocampal synaptic plasticity in mouse brain slices, promotes anti-inflammatory activity of plasma HDL, and crosses the blood-brain barrier *in vitro* . Following these findings, an *in vivo* daily injection study of apoJ[113-122] was conducted for 3 months in the APP/PS1 mouse model of AD. The cerebral Aβ load was markedly reduced in apoJ[113-122] treated mice, compared with PBS treated controls.

Intriguingly, there was a corresponding increase in the level of Aβ in the plasma of apoJ[113-122] treated mice, indicating that apoJ[113-122] enhances Aβ efflux from the brain across the BBB. Additional biochemical analysis are underway to further elucidate the mechanisms by which apoJ[113-122] elicits these observed effects. These findings suggest that the apoJ[113-122] peptide could be a potential new therapeutic agent against AD.

Disclosures: D.A. Hottman: None. **D.S. Chernick:** None. **Y. Zhang:** None. **A. Gram:** None. **R. Omtri:** None. **K. Kandimalla:** None. **L. Li:** None.

Poster

785. Alzheimer's Disease: Anti-Amyloid Beta Therapeutics

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 785.15/G39

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH P30 NS47466

Title: Treatment with Aβ oligomer eliminating D-peptide causes uptake of Aβ species by neurons in Tg AD model mice.

Authors: *T. VAN GROEN[1], I. KADISH[1], M. TUSCHE[2], N. JIANG[2], D. WILLBOLD[2]; [1]Cell, Developmental and Integrative Biol., Univ. Alabama-Birmingham, Birmingham, AL; [2]Forschungszentrum Juelich, Juelich, Germany

Abstract: Our two transgenic mouse lines express two AD mutations, i.e., PS1 (ΔE9 mutation) and APPswe or APPswe/dutch/iowa. They develop plaques at about four months of age, and we have described that two types of deposits are present, plaques (with a thioflavine S [and Congo red] positive core) and diffuse deposits. Furthermore, plaques are surrounded by activated glial cells, but diffuse deposits are not. We hypothesized that these distinct amyloid deposits would label differently following intracerebral anti Aβ42 targeted D-peptide injections in these mice. We sacrificed and transcardially perfused the mice at 1, 2 and 4 days following the injections. The brains were cut and immunohistochemically stained for APP and Aβ, and GFAP and Iba-1. Following the 1 and 2 days survival time the AD mice displayed a clear labeling of Aβ in the cortex and hippocampus, after 4 days retrograde transport was seen (related to specific terminal fields, i.e., connected to the injected area), however they do not show a change in the number of plaques. Further, the labeled Aβ is present in lysosomes in neurons near the injection site. Labeled Aβ deposits stay labeled over the researched timeframe, whereas the diffuse labeling (not bound) disappears over 2 days. It should be noted that none of these injections is associated with any glial activation, neither in the cortex nor in the hippocampus, except for the injection

track. Thus, the D-peptides label amyloid deposits that develop in these AD model mice, and the D-peptides are taken up with Aβ by neurons and transported.

Disclosures: **T. Van Groen:** None. **I. Kadish:** None. **M. Tusche:** None. **N. Jiang:** None. **D. Willbold:** None.

Poster

785. Alzheimer's Disease: Anti-Amyloid Beta Therapeutics

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 785.16/G40

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: AIM-CTI

Title: Stem cells treatment for alzheimer's disease

Authors: ***T. BOLMONT**[1], A. LUKASHEV[2];
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Abstract: Adult human stem cells constitute a promising therapeutic approach for the treatment of various neurodegenerative disorders including Alzheimer's disease (AD). We have investigated the impact of intravenous human stem cell delivery on cerebral Abeta amyloid pathology in a mouse model of AD. The cells used in the study were human mesenchymal stem cells (hMSC), bone marrow derived, ischemia-tolerant, cultured under a controlled, low physiological level of oxygen, manufactured under cGMP conditions and currently used in FDA-approved clinical trials in the US. Importantly, these hMSC express negligible levels of human leukocyte antigen-D related (HLA-DR) cell surface receptor. Both young pre-depositing APPPS1 mice as well as aged APPPS1 mice were used in experiments with either single or repeated intravenous delivery of hMSC or control Lactated Ringers Solution (LRS). Intravenous delivery of hMSC safely reduced cerebral Abeta pathology in both aged and young APPPS1 mice. Concomitantly, microglial activation was diminished in hMSC-treated APPPS1 mice, with no increase of vascular amyloid or manifestation of microhemorrhages. Quantitative RT-PCR biodistribution analysis revealed that intravenously delivered hMSC migrate to the brain and could be detected in this organ with the highest value at 1 hour post-delivery. These preclinical results were used to substantiate an IND application with placebo-controlled, crossover study to assess the safety, tolerability, and preliminary efficacy of a single intravenous dose of allogeneic human mesenchymal stem cells to subjects with mild to moderate dementia due to AD. Although all the details of the action of hMSC on AD are not yet fully understood, solid clinical safety

profile and preclinical efficacy of hMSC may open a new area of their application for this devastating disease.

Disclosures: **T. Bolmont:** A. Employment/Salary (full or part-time): Stemedica International. **A. Lukashev:** A. Employment/Salary (full or part-time): Stemedica International.

Poster

785. Alzheimer's Disease: Anti-Amyloid Beta Therapeutics

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 785.17/G41

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: CNPq Grant

CAPES Grant

FAPERJ Grant

Title: Mesenchymal stem cells protect hippocampal neurons from oxidative stress and synapse damage induced by amyloid-β oligomers

Authors: ***M. GODOY**[1], L. SARAIVA[2], L. CARVALHO[2], A. VASCONCELOS-DOS-SANTOS[2], H. BEIRAL[2], L. SINIS[2], N. CUNHA-E-SILVA[2], A. GALINA-FILHO[2], A. VIEYRA[2], F. DE FELICE[2], S. FERREIRA[2], R. MENDEZ-OTERO[2];
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Abstract: Background: Alzheimer's disease (AD) is a neurodegenerative disease with high prevalence and morbidity, for which there are no effective therapies. Soluble oligomers of the amyloid-β peptide (AβOs) are the main neurotoxins involved in the early synaptic dysfunction and oxidative stress associated with the disease. The therapeutic potential of bone marrow mesenchymal stem cells (MSCs) has been investigated in several models of neurological diseases and the main mechanism of action of these cells is based on paracrine signaling, through the release of trophic or neuroprotective factors.The aim of the current study was to evaluate the neuroprotective actions of MSCs against the deleterious effects caused by exposure of hippocampal neurons to AβOs. Methods: For this, we established a model of indirect coculture of neurons and MSCs.Results: Here, we report for the first time that MSCs protect neurons against oxidative stress and synaptic failure through internalization and degradation of the extracellular AβOs, as well as by the release of extracellular vesicles containing the antioxidant enzyme catalase. Conclusions: Taken together, our data suggest that mesenchymal stem cells may represent a promising therapeutic alternative for the treatment of Alzheimer’s disease.

Disclosures: **M. Godoy:** None. **L. Saraiva:** None. **L. Carvalho:** None. **A. Vasconcelos-dos-Santos:** None. **H. Beiral:** None. **L. Sinis:** None. **N. Cunha-e-Silva:** None. **A. Galina-Filho:** None. **A. Vieyra:** None. **F. De Felice:** None. **S. Ferreira:** None. **R. Mendez-Otero:** None.

Poster

785. Alzheimer's Disease: Anti-Amyloid Beta Therapeutics

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 785.18/G42

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NSFC grant

Title: Anti-Aβ42 camel heavy-chain variable domain counteracts Aβ42-induced pathological effects

Authors: ***G. HE**[1], X. YANG[1], Y. WAN[2], Z. JIA[3], Z. ZHOU[1];
[1]Inst. of Life Sciences, Southeast Univ., Jiangsu, China; [2]CAS Key Lab. of Receptor Research, Shanghai Inst. of Materia Medica, Chinese Acad. of Sci., Shanghai, China; [3]Neurosciences and Mental Health, The Hosp. for Sick Children, Dept. of Physiology, Univ. of Toronto, Toronto, ON, Canada

Abstract: The accumulation and deposition of beta amyloid play a major role in the pathogenesis of Alzheimer’s disease. In vivo and in vitro studies suggest that soluble beta-amyloid is the critical toxic component, which significantly induce the dendritic spine loss, synaptic plasticity impairment and memory deficit. We generated a naïve camel heavy-chain variable domain antibody (VHH) phage display library against human amyloid beta 42 (Aβ42) peptide. The 2 clones of VHH anti-Aβ42 VHH effectively inhibited the assembly of monomer Aβ into oligomeric or fibrillary forms. Electrophysiological, biochemical and immunostaining assays showed significant ameliorating effects of anti-Aβ42 VHH on Aβ42-induced impairment of neuronal functions. Memory deficit caused by soluble Aβ42 oligomers is rescued through VHH co-injection. Together, the anti-Aβ42 VHH may be a therapeutic application for treating Alzheimer’s disease.

Disclosures: **G. He:** None. **X. Yang:** None. **Y. Wan:** None. **Z. Jia:** None. **Z. Zhou:** None.

Poster

785. Alzheimer's Disease: Anti-Amyloid Beta Therapeutics

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 785.19/G43

Topic: C.02. Alzheimer's Disease and Other Dementias

Title: Prevention of tau increase in cerebrospinal fluid of APP transgenic mice suggests downstream effect of BACE1 inhibition

Authors: *J. SCHELLE[1,2,3], L. HÄSLER[1,2,4], J. GÖPFERT[4], T. JOOS[4], H. VANDERSTICHELE[5], E. STOOPS[5], U. NEUMANN[6], D. SHIMSHEK[6], M. STAUFENBIEL[2], M. JUCKER[1,2], S. KÄSER[1,2];
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Abstract: The inhibition of the beta-site amyloid precursor protein-cleaving enzyme 1 (BACE1) is a main therapeutic approach for the treatment of Alzheimer's disease (AD). The characterization of BACE1 inhibitors has largely focused on direct effects, i.e. the reduction of β-amyloid (Aβ) generation and deposition in the brain. We previously reported an age-related increase of tau protein in the cerebrospinal fluid (CSF) of Aβ precursor protein (APP) transgenic mice reminiscent of changes in the CSF of AD patients. Using a novel high-sensitivity tau sandwich immunoassay we now demonstrate that BACE1 inhibition prevents CSF tau increase both in early-depositing APP tg mice and APP tg mice with moderate Aβ pathology. Our results demonstrate that BACE1 inhibition not only reduces Aβ generation but also downstream AD pathophysiology. The tight correlation between Aβ aggregation in brain and tau levels in CSF renders CSF tau a valuable marker to predict the effectiveness of BACE inhibitors in current clinical trials.

Disclosures: **J. Schelle:** A. Employment/Salary (full or part-time): Ulf Neumann, Novartis Institutes for BioMedical Research, Neuroscience, 4056 Basel, Switzerland, Derya R. Shimshek, Novartis Institutes for BioMedical Research, Neuroscience, 4056 Basel, Switzerland, Hugo Vanderstichele, ADx NeuroSciences, 9052 Gent, Belgium, Erik Stoops, ADx NeuroSciences, 9052 Gent, Belgium. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Matthias Staufenbiel, Department of Cellular Neurology, Hertie Institute for Clinical Brain Research, University of Tübingen, 72076 Tübingen, Germany. **L. Häsler:** None. **J. Göpfert:** None. **T. Joos:** None. **H. Vanderstichele:** A. Employment/Salary (full or part-time): Hugo Vanderstichele, ADx NeuroSciences, 9052 Gent, Belgium. **E. Stoops:** A. Employment/Salary (full or part-time): Erik

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Poster

785. Alzheimer's Disease: Anti-Amyloid Beta Therapeutics

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 785.20/G44

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH Grant AG05108601

NIH Grant AG04280402

Title: Regulation of amyloid-beta precursor protein (APP) and beta-secretase 1 (BACE1) expression by transcription factor modulating compounds mithramycin A and tolfenamic acid in human cells

Authors: *B. L. BAYON[1], K. NHO[2], B. MALONEY[3], N. CHOPRA[3], D. K. LAHIRI[4]; [1]Dept. of Med. & Mol. Genet., [2]Radiology, [3]Psychiatry, [4]Psychiatry, Med. & Mol. Genet., Indiana Univ. Sch. of Med., Indianapolis, IN

Abstract: Transcription factors (TFs) play a role in the survival of neuronal cells and regulate genes associated with Alzheimer's disease (AD). Expression levels of some TFs, such as Sp1, are perturbed in AD. BACE1 is responsible for the rate-limiting cleavage of APP to amyloid-β (Aβ). Sp1 positively regulates APP and induces BACE1. To test the involvement of Sp1 in regulation of APP, we treated human cells with mithramycin A (MTM), an Sp1 inhibitor, and tolfenamic acid (TA), which induces Sp1 degradation. We also transfected a variety of mammalian cell lines, a primary human fetal neuron culture, and mixed brain cultures derived from human fetal neurospheres with siRNAs. Minimal changes in confluence, cytotoxicity, neurite length, and neurite outgrowth were seen after Sp1 knockdown via siRNA or treatment with Sp1 modulating drugs. Treatment with TA did not change Aβ42 levels, or affect APP and BACE1 levels. Treatment with MTM led to a significant decrease in the expression of APP and BACE1, and significantly decreased Aβ42 levels. Neither treatment with Sp1-inhibiting drugs

alone nor transfection with Sp1 siRNA alone affected cell viability of human cells illustrating that Sp1 levels can be safely reduced in cells. However, combination treatments of MTM plus TA or of Sp1 inhibition by siRNA in combination with TA treatment led to high cytotoxicity in human cells. To understand the relationship between genetic variants in Sp1 and AD-related endophenotypes, we performed an association analysis of single nucleotide polymorphisms (SNPs) in Sp1 with an AD imaging biomarker (entorhinal cortex thickness) in the AD Neuroimaging Initiative cohort, and identified a SNP (rs11170553) in Sp1 significantly associated with entorhinal cortex thickness. We found that rs11170553 was also associated with global cortical Aβ load measured by Florbetapir PET, demonstrating a possible correlation with Sp1 and AD pathology. To better understand the activation of multiple TFs and elucidate the status of signaling pathways after MTM or TA treatment, we used a TF luciferease transactivation reporter array. This array revealed decreased activation of several TFs with MTM treatment that correspond with a decrease or no change with TA treatment. These, as well as TFs with binding sites on the BACE1 promoter or those known to be implicated in AD were used as a preliminary screen for future assays targeting these alongside Sp1. Compounds that can modify Sp1 or other TF binding to sites on the BACE1 and APP promoters could provide a means to limit the production of Aβ peptide and may slow the symptoms of AD. These results show that appropriate modulation of a specific TF could potentially be a novel drug target for AD.

Disclosures: **B.L. Bayon:** None. **K. Nho:** None. **B. Maloney:** None. **N. Chopra:** None. **D.K. Lahiri:** None.

Poster

785. Alzheimer's Disease: Anti-Amyloid Beta Therapeutics

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 785.21/G45

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NMRC/CBRG/0041/2013

Title: Amelioration of abeta (1-42) induced plasticity impairment by inhibition of g9a/glp complex in ca1 hippocampal neurons

Authors: *M. SHARMA[1], T. DIERKES[2], S. SREEDHARAN[1];
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Abstract: Alzheimer’s disease (AD) is the most common form of age-related neurodegenerative disorder and the leading cause of dementia among the elderly. AD is characterised by the

formation of extracellular amyloid plaques and intracellular neurofibrillary tangles (NFTs); and is featured with progressive memory loss. Altered epigenetic mechanisms are implicated in the impairment of memory. G9a/GLP histone methyltransferase complex is an important epigenetic regulator that is reported to regulate gene transcription in the hippocampus during memory consolidation. We hypothesized that modulating G9a/GLP complex could alleviate the effects of A-beta (1-42) on neuronal plasticity. We aim to address the role of epigenetic complex G9a/GLP in A-beta induced plasticity impairments and elucidate the underlying molecular pathway using vitro electrophysiology, neuropharmacology and biochemical analyses. We studied late long-term potentiation (late-LTP), a cellular correlate of memory and its associative mechanisms such as synaptic tagging and capture (STC) in the CA1 area of hippocampal slices from 5-7 week old male Wistar Rats. Our findings demonstrate that A-beta (1-42) impairs the late-LTP as well as STC in the CA1 pyramidal neurons. Inhibition of G9a/GLP complex activity restores the late-LTP and re-establishes the STC. We noticed that the restoration of LTP and STC by G9a/GLP complex inhibition is mediated by BDNF. We provide evidence for the promotion of plasticity in AD like conditions by G9a/GLP complex inhibition and hence propose G9a/GLP complex as the possible target for preventing A-beta induced plasticity deficits in hippocampal neurons.

Disclosures: **M. Sharma:** None. **T. Dierkes:** None. **S. Sreedharan:** None.

Poster

785. Alzheimer's Disease: Anti-Amyloid Beta Therapeutics

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 785.22/G46

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH Grant K99 AG050764

Fellowship German Academic Exchange Service (DAAD)

Title: Characterization of novel, highly stable, and cytotoxic oligomers in the context of transthyretin amyloid disorders

Authors: ***Y. S. EISELE**[1,2], L. PLATE[1,2], G. J. MORGAN[1,2], G. C. LANDER[3], N. REIXACH[1], J. N. BUXBAUM[1], L. R. WISEMAN[1,4], E. T. POWERS[2], J. W. KELLY[2,1,5];
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Abstract: Transthyretin (TTR) is one of over 30 amyloidogenic proteins that are known to misfold and form amyloid fibrils in neurodegenerative diseases. In its native form TTR is a well-

folded, homotetrameric protein that is mainly secreted from the liver into the blood, but also from the choroid plexus into the cerebrospinal fluid. TTR-related amyloid disorders present as age-related peripheral neuropathies, cardiomyopathies, or cerebral amyloid angiopathy (CAA). Importantly, TTR amyloidosis is the only amyloid disorder for which a regulatory agency approved disease-modifying treatment is available. Tafamidis, a small molecule, kinetically stabilizes the native TTR tetramer and thereby prevents TTR amyloidogenesis. However, the amyloid load does not appear to change in patients that respond to tafamidis. Thus, smaller, non-native TTR oligomers are hypothesized to be a driver of the degenerative pathology.
Here, we report the time- and concentration-dependent formation of novel TTR oligomers *in vitro* from monomeric TTR as well as from destabilized initially tetrameric TTR variants at near physiological pH at 37°C. Oligomers were biochemically and biophysically characterized in regard to their molecular weight, stability, and ligand binding. TTR oligomer formation requires the dissociation of the native TTR tetramer and likely involves partial misfolding that compromises the small molecule-binding site present in the native TTR tetramer. Interestingly, once formed, the oligomers seem relatively stable and their stability further increases over time, probably owing to conformational annealing. Atomic force microscopy and negative-stain electron microscopy reveal a filamentous, protofibrillar appearance. These TTR oligomers exhibit cytotoxicity in a *C. elegans* pharyngeal pumping assay in contrast to the native TTR tetramer. In addition, our findings suggest that similar TTR oligomers are present in blood samples of patients with TTR amyloidosis. All these traits indicate that the newly characterized, highly stable and cytotoxic non-native TTR oligomers might be highly relevant in the TTR pathogenesis cascade. Ongoing studies focus on deciphering the precise structure of these TTR oligomers and delineating a structure-toxicity relationship.

Disclosures: **Y.S. Eisele:** None. **L. Plate:** None. **G.J. Morgan:** None. **G.C. Lander:** None. **N. Reixach:** None. **J.N. Buxbaum:** None. **L.R. Wiseman:** None. **E.T. Powers:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Pfizer Inc. **J.W. Kelly:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Pfizer Inc, Misfolding Diagnostics Inc. F. Consulting Fees (e.g., advisory boards); Pfizer Inc, Misfolding Diagnostics Inc.

Poster

786. Pharmacology for Alzheimer's Disease Therapeutics

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 786.01/G47

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: National natural science fundation of China (81473374)

Title: Neuroprotective, anti-amyloidogenic and neurotrophic effects of total flavonoids from Dracoephalum Mololariea L in Alzheimer's deficits

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Abstract: Alzheimer's disease (AD) is a progressive neurodegenerative disease, marked by extracellular senile plaques and intracellular neurofibrillary tangles (NFT). Amyloid-β peptides (Aβ) has relationship with both two hallmark pathologies. Total flavonoids from *Dracoephalum Mololariea* L (TFDM) is a traditional Chinese medicine, which has been proved to show a significant therapeutic effect on cardiovascular diseases from the epidemiological data. But no available study has reported that whether TFDM has any therapeutic activity on neurological disorders including Alzheimer's disease or not. In this study, we investigated the effects of TFDM on both APP/PS1 double transgenic AD mice and APPsw overexpressing SH-SY5Y cells. The results from our experiments showed that TFDM treatment improved the learning and memory capability of APP/PS1 mice, and increased the cell viability when subjecting to Aβ toxicity. These results demonstrated that TFDM has neuroprotective effects against AD related deficits. Besides, TFDM has anti-amyloidogenic effect, involving decreasing the Aβ burden through APP processing pathway by BACE1 and insoluble Aβ levels. In addition, TFDM exhibited antioxidative effects on both mice and cells through decreasing superoxide anion and improved enzyme activity of superoxide dismutase and glutathione peroxidase. Furthermore, TFDM up-regulated neurotrophic ERK/CREB/BDNF pathway in both cerebral cortex and APPsw over-expressing SH-SY5Y cells, which illustrated its neurotrophic effect. In general, TFDM may lightened the toxicity of Aβ by decreasing Aβ burden, inhibited amyloidogenic pathway, down-regulated oxidative stress, and up-regulated ERK/CREB/BDNF pathway. In one word, TFDM would be an alternative drug on curing or ameliorating AD.

Disclosures: R. Liu: None. **H. Jiang:** None. **Y. Wang:** None. **M. Hu:** None. **J. Li:** None. **L. Wang:** None. **T. Zhang:** None. **J. Xing:** None.

Poster

786. Pharmacology for Alzheimer's Disease Therapeutics

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 786.02/G48

Topic: C.02. Alzheimer's Disease and Other Dementias

Title: TFEB activation and protective effects by ouabain in Alzheimer's disease models

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Abstract: Autophagy is impaired in AD and especially the late steps of autophagy, autophagosome-lysosome fusion and degradation, is thought to be impaired in AD, hence resulting in accumulation of autophagosomes and tau aggregates. Several world-wide groups have tried to find novel autophagy-enhancing compounds which inhibit mTOR or increase LC3-II (+) autophagosomes. Transcription factor EB (TFEB) is a recently known mater regulator of autophagy and lysosomal degradation. TFEB is a transcription factor which transcribes lysosomal and autophagy genes. Hence, TFEB activation can enhance not only the initial steps of autophagy but also the late steps of autophagy-lysosomal degradation. Thus, we developed high content screening (HCS) of TFEB activity system and screened with huge compounds library. Several hit compounds were found, and ouabain, one of which, will be discussed about neuroprotective effects in AD models.

Disclosures: **H. Song:** A. Employment/Salary (full or part-time): ulsan university. **S. Yoon:** A. Employment/Salary (full or part-time): ulsan university. **D. Kim:** A. Employment/Salary (full or part-time): ulsan university.

Poster

786. Pharmacology for Alzheimer's Disease Therapeutics

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 786.03/G49

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: MOST 104-0210-01-09-02

MOST 105-0210-01-13-01

Title: Modulation of adenosine homeostasis is associated with the improvement of neuronal dysfunction in a mouse model of Alzheimer's disease

Authors: *C.-C. LEE[1], C.-P. CHANG[1], C.-J. LIN[2], H.-L. LAI[1], Y.-H. KAO[2], Y.-G. CHANG[1], S.-J. CHENG[1], H.-M. CHEN[1], D. BLUM[3], J.-M. FANG[4], Y.-L. LIN[5], Y. CHERN[1];
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Abstract: Alzheimer's disease (AD) is a neurodegenerative disorder, which is characterized by cognitive impairment and synaptic dysfunction. Adenosine plays an important role in regulating various physiological functions and notably plasticity through four adenosine receptors (i.e., A_1R, $A_{2A}R$, $A_{2B}R$, and A_3R) and several adenosine transporters (e.g., ENT1, ENT2). We developed a group of dual-function adenosine compounds, which exhibit ability, at low affinities, to activate $A_{2A}R$ and inhibit ENT1. Previous studies demonstrated that these adenosine compounds show therapeutic effects on several neurodegenerative diseases, such as Huntington's disease, spinocerebellar ataxia type 3, and amyotrophic lateral sclerosis. Here, we investigated the effect of a dual-function adenosine compound (J4) on the impairment of cognitive functions in a mouse model of AD (APP/PS1dE9). Chronic oral intake of J4 (0.02 g/L in drinking water) from the age of 3 to 10 months significantly enhanced the impaired spatial memory of APP/PS1dE9 mice, and normalized the decremental long-term potentiation (LTP) in the CA1 region of hippocampus as well as the reduced levels of several proteins associated with neuronal plasticity. These findings suggest that modulation of adenosine homeostasis by J4 is beneficial in a mouse model of AD. Our study provides a potential therapeutic approach to delay the progression of AD.

Disclosures: **C. Lee:** None. **C. Chang:** None. **C. Lin:** None. **H. Lai:** None. **Y. Kao:** None. **Y. Chang:** None. **S. Cheng:** None. **H. Chen:** None. **D. Blum:** None. **J. Fang:** None. **Y. Lin:** None. **Y. Chern:** None.

Poster

786. Pharmacology for Alzheimer's Disease Therapeutics

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 786.04/G50

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: LECMA/Alzheimer Forschung Initiative, Inserm, Université Lille 2, PIA LabEx (excellence laboratory) DISTALZ (Development of Innovative Strategies for a Transdisciplinary approach to ALZheimer's disease) Université Lille 2, Région Nord/Pas-de-Calais

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ANR (ADORATAU)

LVL is an Investigator FCT (Fundação para a Ciência e Tecnologia, Portugal)

Title: Oral administration of MSX-3, an adenosine $A_{2A}R$ antagonist, reduces amyloid load and memory déficits of APP/PS1dE9 mice

Authors: *E. FAIVRE[1,2], J. COELHO[3], K. ZORNBACH[4], E. MALIK[5], E. MARCINIAK[2,1], L. CELLAI[2,1], K. CARVALHO[2,1], V. FLATEN[2,1], D. DEMEYER[2,1], S. EDDARKAOUI[2,1], R. CAILLIEREZ[2,1], M. SCHNEIDER[5], S. HUMEZ[2,1], N. SERGEANT[2,1], Y. CHERN[6], C. MUELLER[5], L. BUÉE[2,1], A. HALLE[4], L. LOPES[3], D. BLUM[2,1];
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Abstract: Alzheimer's disease (AD) is a neurodegenerative disorder characterized by extracellular amyloid-beta deposits and neurofibrillary tangles. Its occurrence depends on different genetic and environmental factors. Epidemiological and experimental studies on Tau and amyloid models have shown that caffeine, a non-selective adenosine receptor antagonist, may be protective in AD, an effect thought to be ascribed to the blockade of adenosine A_{2A} receptors ($A_{2A}R$). Our recent report of a significant protection achieved by $A_{2A}R$ genetic deletion and pharmacological blockade in a Tau transgenic mouse model reinforces this idea. However so far, the outcome of $A_{2A}R$ blockade on amyloïdogenesis and related brain impairments have remained unclear.
The present study was aimed to study the impact of $A_{2A}R$ blockade on memory deficits and pathological development in the APP/S1dE9 transgenic mouse model of AD, using a specific $A_{2A}R$ antagonist, MSX-3. This pro-drug was chronically administered at the dose of 0.3g/L through drinking water to APP/PS1dE9 mice and littermate controls from 3 to 9 months of age. At completion of the treatment, MSX-3 was detectable in plasma and brain of treated mice. MSX-3 treatment improved spatial memory of APP/PS1dE9 mice. This was associated with a reduction of amyloid-beta plaques and a decrease of the levels of $A\beta_{42/40}$ ratio in the cortex, but not with an improvement of neuroinflammation. Furthermore, treatment with MSX3 did not improve microglial phagocytic activity, which additionally argues against immune processes as the main effector mechanism.
These results show that chronic blockade of A_{2A} receptors using MSX-3 is beneficial in a mouse model of amyloïdogenesis, but the underlying mechanisms still remain to be uncovered. Combined with our previous data in a Tau transgenic mouse model, our data suggest that caffeine-analogues specifically targeting $A_{2A}Rs$ constitute important novel therapeutic options in the treatment of AD.

Disclosures: **E. Faivre:** None. **J. Coelho:** None. **K. Zornbach:** None. **E. Malik:** None. **E. marciniak:** None. **L. Cellai:** None. **K. Carvalho:** None. **V. Flaten:** None. **D. Demeyer:** None. **S. Eddarkaoui:** None. **R. Caillierez:** None. **M. Schneider:** None. **S. Humez:** None. **N. Sergeant:** None. **Y. Chern:** None. **C. Mueller:** None. **L. Buée:** None. **A. Halle:** None. **L. Lopes:** None. **D. Blum:** None.

Poster

786. Pharmacology for Alzheimer's Disease Therapeutics

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 786.05/H1

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH R01 AG050518

Title: Intranasal orexin A (hypocretin 1) increases neuronal activation in cortical and basal forebrain regions implicated in memory and attention

Authors: C. B. CALVA, *J. R. FADEL;
Univ. of South Carolina Sch. of Med., Columbia, SC

Abstract: Hypothalamic orexin/hypocretin (OX) neurons are implicated as integrators of physiological function and have recently been proposed as a potential therapeutic target in the treatment of age-related cognitive disorders. OX neurons project to the medial prefrontal (mPFC) and agranular insular cortices (AIC), two areas implicated in attention and interoceptive awareness of physiological status, respectively. Additionally, OX neurons send projections directly to all parts of the basal forebrain cholinergic system, including the vertical limb of the diagonal band of Broca (vDBB) and the ventral pallidum/substantia inominata (VP/SI), two areas highly involved in emotional memory formation and attention, respectively. We have previously shown that orexins increase cortical acetylcholine release and that aged rats have reduced numbers of OX neurons, which suggests that orexins play a role in the cognitive and homeostatic dysfunction seen with age. A limited number of human and animal studies have suggested that intranasal OX may enhance cognition and wakefulness, but the brain regions and neurotransmitter systems underlying these effects are unknown. Here, young (3 months) male Fisher344/Brown Norway rats received intranasal administration of either vehicle (0.9% saline) or orexin A (OxA; 25 ul of a 5nM solution) into each nare. At two hours post-treatment, the animals were sacrificed and their brains were processed for immunohistochemical detection of the neuronal activity marker, c-Fos, and phenotypic markers of specific neuronal populations. Intranasal OxA significantly increased c-Fos expression in the prelimbic mPFC and AIC compared to vehicle treatment. Intranasal OxA treated animals also showed greater activation of

cholinergic neurons in the vDBB and VP/SI. Interestingly, c-Fos expression in parvalbumin positive (PV+) interneurons was decreased in the prelimbic mPFC, which could be mediated through inhibition by PV+ GABAergic projection neurons of the basal forebrain. OxA did not alter c-Fos expression in several other rostral cortical areas, including the horizontal DBB and infralimbic cortex, indicating that effects produced by intranasal OxA were not a global phenomenon. Overall, these data demonstrate that intranasal OxA activates brain regions that mediate attention to the external environment as well as attention to internal homeostatic cues, two functions that are dysregulated during age-related cognitive decline. Ongoing studies of neurochemical correlates of intranasal OxA will provide additional insight into the mechanisms underlying the putative cognitive effects of this manipulation.

Disclosures: C.B. Calva: None. **J.R. Fadel:** None.

Poster

786. Pharmacology for Alzheimer's Disease Therapeutics

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 786.06/H2

Topic: C.02. Alzheimer's Disease and Other Dementias

Title: Compound A, a selective and potent muscarinic acetylcholine M4 receptor positive allosteric modulator (PAM), is active in pre-clinical models sensitive to clinically-active antipsychotic drugs

Authors: *S. M. GRAUER[1], X. ZHOU[1], N. JOCHNOWITZ[1], L. A. HYDE[1], N. HASTINGS[1], G. VARTY[1], R. MAZZOLA[2], J. MORROW[3];
[1]In Vivo Pharmacology-Neuroscience, Merck Res. Labs, Kenilworth, NJ; [2]Chem., Merck Res. Labs, Rahway, NJ; [3]Neurosci., Merck Res. Labs, West Point, PA

Abstract: Current understanding of the pathophysiology of both Alzheimer's disease (AD) and schizophrenia suggests altered muscarinic cholinergic activity. Xanomeline, a M_1/M_4 preferring muscarinic acetylcholine receptor (mAChR) agonist, was evaluated in clinical studies and demonstrated efficacy in alleviating psychosis and behavioral disturbances in AD and schizophrenic patients, with a profile that matched or was superior to that of existing antipsychotics. Despite this, xanomeline's clinical development was halted due to adverse side effects, primarily gastrointestinal (GI) in nature, likely due to inadequate mAChR subtype selectivity. Targeting the less conserved and spatially distinct allosteric binding site was a strategy adopted to overcome selectivity issues with orthosteric agonists such as xanomeline. Arising out of this approach is Compound A, a selective and potent M_4 PAM, which has low nM binding affinity at the M_4 receptor, and exhibits $\geq$1200-fold functional selectivity over other

mAChRs. Compound A was tested in a series of preclinical assays designed to assess antipsychotic-like activity. These models included the attenuation of hyperactivity induced by either the indirect dopamine receptor agonist d-amphetamine or the selective D_1 dopamine receptor agonist SKF 82958 in both rats and mice, and the reversal of deficits in prepulse inhibition (PPI) in mice. Compound A (100 mg/kg PO) significantly attenuated both d-amphetamine and SKF 82958 hyperactivity in CD rats, while doses as low as 30 mg/kg were active in C57Bl/6 mice. On-target activity in the locomotor assay was confirmed by an absence of activity vs. SFK 82958 hyperactivity in M_4 knockout (KO) mice. Compound A (100 mg/kg PO) significantly potentiated PPI when administered alone, and significantly attenuated a d-amphetamine induced PPI deficit. The PPI effects were M_4 mediated, as Compound A (100 mg/kg PO) was without effect against a SKF 82958 induced PPI deficit in M_4 KO mice, but blocked the SKF 82958 gating deficit in wild type littermates. Compound A was also evaluated in a mouse GI transit model where activation or inhibition of M_2 or M_3 mAChRs accelerate or attenuate, respectively, intestinal motility. Compound A was without effect, whereas indirect activation of GI mAChRs by the acetyl cholinesterase inhibitor donepezil significantly increased transit, an effect blocked by a selective M_2 antagonist. The on-target effects of an M_4 PAM, in two well established preclinical assays related to the dopamine hyperfunction hypothesis of psychosis, support the viability of a therapeutic approach which will not be limited by side effects associated with non-selective activation of mAChRs.

Disclosures: **S.M. Grauer:** A. Employment/Salary (full or part-time): Merck Research Labs. **X. Zhou:** A. Employment/Salary (full or part-time): Merck Research Labs. **N. Jochnowitz:** A. Employment/Salary (full or part-time): Merck Research Labs. **L.A. Hyde:** A. Employment/Salary (full or part-time): Merck Research Labs. **N. Hastings:** A. Employment/Salary (full or part-time): Merck Research Labs. **G. Varty:** A. Employment/Salary (full or part-time): Merck Research Labs. **R. Mazzola:** A. Employment/Salary (full or part-time): Merck Research Labs. **J. Morrow:** A. Employment/Salary (full or part-time): Merck Research Labs.

Poster

786. Pharmacology for Alzheimer's Disease Therapeutics

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 786.07/H3

Topic: C.02. Alzheimer's Disease and Other Dementias

Title: Sesamol reverse memory deficit and restore phospho-GSK3beta decreased in hippocampus in intracerebroventricular streptozotocin induced Alzheimers disease model

Authors: *M. GOLECHHA[1,2], J. BHATIA[1], V. PARIHAR[4], D. SAXENA[3], D. ARYA[1]; [1]Pharmacol., All India Inst. of Med. Sci. (AIIMS), New Delhi, India; [2]Hlth. Policy, [3]Epidemiology, Indian Inst. of Publ. Hlth. Gandhinagar, Gandhinagar- Gujarat, India; [4]Dept. of Radiation Oncology, Univ. of California, Irvine, Irvine, CA

Abstract: Intracerebroventricular (ICV) streptozotocin (STZ) treated rat has been described as a suitable model for sporadic Alzheimer's disease (AD). Therefore, the present study was undertaken to investigate the effect of post-training administration of sesamol, a bioflavonoid with potent antioxidant and anti-inflammatory activities on memory functions, brain insulin receptors (IRs), acetylcholinesterase (AChE) activity and oxidative stress in intracerebroventricular (ICV) administered streptozotocin (STZ) induced dementia in rats. In these same animals the phosphorylated GSK3β (p-GSK3β) and total GSK3β levels were determined, and importantly GSK3β regulates the tau phosphorylation responsible for neurofibrillary tangle formation in AD. Wistar rats received ICV STZ application (3mg/kg twice) and 2 weeks later short- (STM) and long-term memories (LTM) were assessed in an autoshaping learning task. Animals were sacrificed immediately following the last autoshaping session, their brains removed and dissected. The enzymes and IR protein levels were measured in the hippocampus and prefrontal cortex (PFC) by western blotting. ICV STZ-treated rats showed a memory deficit and significantly decreased p-GSK3β levels and significant decrease in IR protein level in both hippocampus and PFC, while total GSK3β did not change, in both the hippocampus and PFC. Memory impairment was reversed by sesamol (5 and 10 mg/kg, i.p.). The p-GSK3β and IR protein levels were restored by sesamol in the hippocampus and PFC. Sesamol produced no changes in p-GSK3β levels in neither the hippocampus nor PFC. Total GSK3β levels did not change with either drug. Furthermore, STZ (ICV) resulted into enhanced AChE activity in hippocampus and PFC which was normalized by sesamol. An increase in MDA level and decrease in GSH level were obtained in both hippocampus and PFC in STZ treated group, indicating state of oxidative stress, which was also attenuated by sesamol. Altogether these results show the beneficial effects of sesamol due different mechanisms of actions on memory impairment induced by ICV STZ. The results suggest that besides the anticholinesterase and antioxidant activity, effect on brain IR, p-GSK3β levels, a kinase key of signaling cascade of insulin receptor may also be an important factor for protective effect of sesamol against STZ induced dementia model.

Disclosures: M. Golechha: None. **J. Bhatia:** None. **V. Parihar:** None. **D. Saxena:** None. **D. Arya:** None.

Poster

786. Pharmacology for Alzheimer's Disease Therapeutics

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 786.08/H4

Topic: C.02. Alzheimer's Disease and Other Dementias

Title: Systemic administration of IGF-II facilitates memory enhancement in rats with decreased TrkB receptor activity in the brain

Authors: *J. H. GRAHAM[1], T. CONNER[2], K. BARANOWSKY[2];
[1]DPT, Emory and Henry Col., Marion, VA; [2]Psychology, Emory and Henry Col., Emory, VA

Abstract: One of the most identifiable symptoms of Alzheimer's disease (AD) and other types of dementia is a decline in cognitive function with memory impairment. Brain derived-neurotropic factor (BDNF) and its receptor, tyrosine kinase B (trkB), have been shown to play a critical role in this process. Animals lacking BDNF show impairment in long term potentiation, learning, and memory formation. BDNF is correlated with synaptic plasticity, as well as cell genesis, growth, and survival, while AD patients have been shown to have a decrease in BDNF levels. Other studies have shown an injection of insulin-like growth factor 2 (IGF-II) into an AD mouse model improved memory and decreased the accumulation of amyloid plaques observed in the hippocampus. In this study, a novel object recognition task was used with female, Sprague-Dawley rats to study episodic memory, which is known to be affected and impaired in AD patients. The rats were tested when they were young (3 months) and older (9 months), at intervals 4-6 hrs. after injection, and 24 hrs. after injection A spontaneous alteration task was also used, to test working memory, which is impaired in AD patients. Again the rats were tested when they were young and older, at intervals 20-30 min. after injection, and 4-6 hrs. after injection. TrkB receptors were blocked with a BDNF-antagonist (ANA-12), and IGF-II was used to overcome the effects of that blockade. IGF-II rescued memory deficits created by lower BDNF levels during the novel object recognition task in young rats. IGF-II enhanced working memory in the spontaneous alternation task in young and middle-aged rats. This study showed that a systemic injection of IGF-II in rats rescues the episodic memory deficit created during a novel object recognition task and significantly enhances working memory in a spontaneous alternation task. Thus, IGF-II does indeed have the potential to be a clinical candidate for AD and dementia patients who have substantial memory decline.

Disclosures: J.H. Graham: None. **T. Conner:** None. **K. Baranowsky:** None.

Poster

786. Pharmacology for Alzheimer's Disease Therapeutics

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 786.09/H5

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: Hallym Univrsity Specialization Fund (HRF-S-51)

The Catholic University of Korea

Title: Protective effects of a dimeric derivative of ferulic acid in animal models of Alzheimer's disease

Authors: *D.-K. SONG[1], J. JUNG[2], J. YAN[2], H. LI[2], M. SULTAN[2], K. SHIN[3];
[1]Dept. Pharmacol., Col. of Medicine, Hallym Univ., Chuncheon, Korea, Republic of; [2]Hallym Univ., Chuncheon, Korea, Republic of; [3]The Catholic Univ. of Korea, Seoul, Korea, Republic of

Abstract: Ferulic acid is a compound with potent anti-oxidant and anti-inflammatory activities. We previously reported the protective effects of ferulic acid administration against two animal models of Alzheimer's disease (AD): intracerebroventricular (i.c.v.) injection of Aß1-42 in mice and APP/PS1 mutant transgenic mice. In this study using the same AD animal models, we examined the effect of KMS4001, one of dimeric derivatives of ferulic acid. Intragastric pretreatment of mice with KMS4001 (30mg/kg/day) for 5 days significantly attenuated the Aß1-42 (i.c.v.)-induced memory impairment both in passive avoidance test and in Y-maze test. APP/PS1 mutant transgenic mice at KMS4001 doses of 3 and 30mg/kg/day via drinking water showed the significantly enhanced novel-object recognition memory at both 1.5 and 3 months after the start of KMS4001 treatment. Treatment of APP/PS1 mutant transgenic mice with KMS4001 for 3 months at the doses of 3 and 30mg/kg/day markedly decreased Aβ1-40 and Aβ1-42 levels in the frontal cortex. The KMS4001 dose-response relationships for Aβ decrease and for improvement in novel-object recognition test corresponded to each other. Taken together, these results suggest that KMS4001 could be an effective drug candidate against AD.

Disclosures: **D. Song:** None. **J. Jung:** None. **J. Yan:** None. **H. Li:** None. **M. Sultan:** None. **K. Shin:** None.

Poster

786. Pharmacology for Alzheimer's Disease Therapeutics

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 786.10/H6

Topic: C.02. Alzheimer's Disease and Other Dementias

Title: Estimating receptor occupancy requirements for positive allosteric modulators of the M1 muscarinic acetylcholine receptor as cognitive enhancers

Authors: *D. BEHER, A. SAND, M. NÉNY, J. HANTSON, S. OUSSON, B. PERMANNE, A. QUATTROPANI, C. WIESSNER;
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Abstract: Clinical use of acetylcholinesterase inhibitors (AChEis) has established that the restoration of deficits in cholinergic transmission improves cognitive function in patients with Alzheimer's disease (AD) and Parkinson's disease dementia (PDD). Nonetheless, the use of AChEis is limited due to the dose-limiting side effects since these drugs non-selectively raise acetylcholine (ACh) neurotransmitter levels throughout the body. We have partially optimized novel, potent, and selective positive allosteric modulators (PAMs) of the M1 muscarinic acetylcholine receptor, which increase the affinity of the receptor for its natural ligand. Based on their mechanism of action M1 PAMs have the potential to maintain the cholinergic tone in AD and PDD patients at a physiological level. Since our PAMs do not display any intrinsic agonism, this approach will maintain the spatial and temporal pattern of neurotransmission whilst having a reduced likelihood of receptor desensitisation. Overall, this should lead to a wide therapeutic window with a reduced risk of overdosing. One of the challenges of PAM development is to understand receptor occupancy which is required to achieve a certain potentiation of the endogenous ligand response. To address this question, we have investigated the potentiation of M1 receptor response by M1 PAMs in a cellular assay system. In the absence of a radioligand, which correlates the affinity and cellular response, we have calculated cellular receptor occupancy by the following equation: relative occupancy = [PAM] / ([PAM] + EC_{50}) assuming that PAM binding is independent of acetylcholine binding. The corresponding results using this approximation suggest that a relatively high receptor occupancy (>80%) will be required to achieve a meaningful receptor potentiation in the brain.

Disclosures: D. Beher: A. Employment/Salary (full or part-time): Asceneuron SA. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Asceneuron SA. **A. Sand:** A. Employment/Salary (full or part-time): Asceneuron SA. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Asceneuron SA. **M. Nény:** A. Employment/Salary (full or part-time): Asceneuron SA. E. Ownership Interest

(stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Asceneuron SA. **J. Hantson:** A. Employment/Salary (full or part-time): Asceneuron SA. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Asceneuron SA. **S. Ousson:** A. Employment/Salary (full or part-time): Asceneuron SA. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Asceneuron SA. **B. Permanne:** A. Employment/Salary (full or part-time): Asceneuron SA. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Asceneuron SA. **A. Quattropani:** A. Employment/Salary (full or part-time): Asceneuron SA. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Asceneuron SA. **C. Wiessner:** A. Employment/Salary (full or part-time): Asceneuron SA. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Asceneuron SA.

Poster

786. Pharmacology for Alzheimer's Disease Therapeutics

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 786.11/H7

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIA AG044712

P01 AG014449

P30 AG028383

Title: The locus coeruleus: a potential link between cerebrovascular and neuronal pathology in Alzheimer’s disease

Authors: *S. C. KELLY[1,2], P. T. NELSON[4,5,5], S. E. COUNTS[1,3,2,6];
[1]Translational Sci. and Mol. Med., [2]Cell and Mol. Biol. Program, [3]Dept. Family Med., Michigan State Univ., Grand Rapids, MI; [4]Dept. Pathology & Lab. Med., [5]Dept. Anat. & Neuobiol, Univ. of Kentucky, Lexington, KY; [6]Hauenstein Neurosci. Ctr., Mercy Hlth. St. Mary’s, Grand Rapids, MI

Abstract: Noradrenergic locus coeruleus (LC) neuron loss is a major feature of Alzheimer’s disease (AD). The LC is the primary source of norepinephrine (NE) in the forebrain, where it modulates attention and memory in vulnerable cognitive regions such as prefrontal cortex and

hippocampus. Furthermore, LC-mediated NE signaling is thought to play a role in blood brain barrier maintenance and neurovascular coupling, suggesting that LC degeneration may impact the high comorbidity of cerebrovascular disease (CVD) and AD. However, the extent to which LC projection system degeneration occurs in the earliest stages of AD is not fully characterized to date. To address these issues, we analyzed LC tissue samples from University of Kentucky AD Center subjects who died with a premortem diagnosis of no cognitive impairment (NCI) and Braak stages 0-II at autopsy, NCI subjects with Braak stages III-V thought to be in a preclinical AD (PCAD) stage, and subjects with mild cognitive impairment (MCI) or mild AD (n = 5-6 cases/group). Paraffin-embedded pontine tissue blocks containing the LC were cut at 20µm, immunostained with tyrosine hydroxylase (TH, a marker for NE synthesis), and analyzed by stereology to estimate total LC neuron number (total number of neuromelanin-containing LC neurons) and the percentage of TH+ LC neurons. Preliminary analysis reveal a ~20% loss of both total and TH+ LC neurons in PCAD ($p = 0.08$), a ~30-35% loss of these neurons in MCI ($p < 0.05$), and a ~45-50% loss of total and TH+ neurons in AD ($p < 0.01$) compared to NCI. Studies were also performed to compare additional LC neuronal pathologies (phospho-tau, TDP-43, and 8dOHG) in the diagnostic groups. A substantial increase in 8dOHG and phospho-tau is observed in PCAD compared to NCI. The morphometric data will be correlated with postmortem neuropathologic and CVD variables (e.g., microinfarcts and cerebral amyloid angiopathy) to gauge the relationship between LC neurodegeneration and cerebral AD and vascular pathology. To model these relationships *in vivo*, we stereotactically lesioned LC projection neurons innervating the PFC, a major LC projection zone, in the TgF344-19 rat model of AD (6 months old) using the noradrenergic immunotoxin, dopamine-β-hydroxylase-saporin, or a control lesion (n = 8/group). Prior to sacrifice at 9 months, immunotoxin- and control-lesioned rats will be tested behaviorally on the Barnes maze task. Postmortem PFC will be analyzed for LC fiber innervation, NE and NE metabolite levels, CVD pathology and AD-like pathology. Taken together, these data will shed light on the multifactorial noradrenergic pathways contributing to neuronal and vascular pathologies during the onset of AD.

Disclosures: **S.C. Kelly:** None. **P.T. Nelson:** None. **S.E. Counts:** None.

Poster

786. Pharmacology for Alzheimer's Disease Therapeutics

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 786.12/H8

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: Department of Education Title III HBGI Grant No. P031B141010

National Science Foundation HRD-1238723 to HMF

Title: Investigating the effects of Chromobacterium violaceum violacein at the human serotonin 2C receptor

Authors: *L. FEARS[1], M. CURTIS[2], T. JOHNSON[2], H. FENTRESS[2];
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Abstract: The monoamine neurotransmitter serotonin (5-HT) plays a role in many physiological responses by binding to at least 14 receptor subtypes. The 5-HT_{2C} receptor subtype is a 7-transmembrane, G protein-coupled receptor (GPCR) that is involved in neuronal excitability, spatial learning, mood, and appetite. The microorganism *Chromobacterium violaceum* produces a purple pigment, violacein, which can be extracted. Violacein has antibiotic, antileishmanial, antifungal and antitumoral properties in various cancer cell lines. Violacein is derived from the amino acid tryptophan like 5-HT, and therefore they have similar chemical structures, however, no one has reported the activity of violacein at 5-HT receptors. To investigate the effect of violacein on receptor trafficking, Human Embryonic Kidney (HEK) 293 cells expressing fluorescently-tagged 5-HT_{2C}receptor were treated with 5-HT, violacein, water or vehicle then cells were fixed and visualized with fluorescent microscopy. Violacein treatment did not cause receptor internalization. Our recent studies suggest that the 5-HT_{2C} receptor can activate the JAK/STAT pathway. To see if violacein can effect this pathway, HEK 293 cells expressing 5-HT_{2C} receptor were treated with violacein or pretreated with violacein followed by incubation with 5-HT. Phosphorylation states of JAK2 and STAT3 were examined by immunoblotting. Preliminary data suggests that violacein may hinder activation of STAT3 but further study is required. Future studies will examine G protein-coupling by measuring phosphoinositide hydrolysis and affinity for violacein at the 5-HT_{2C}receptor via competition binding.

Disclosures: **L. Fears:** None. **M. Curtis:** None. **T. Johnson:** None. **H. Fentress:** None.

Poster

786. Pharmacology for Alzheimer's Disease Therapeutics

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 786.13/H9

Topic: C.02. Alzheimer's Disease and Other Dementias

Title: Cognitive deficits and impaired long-term potentiation in adiponectin knockout mice

Authors: *J. BLOEMER[1], W. SMITH[2], A. ALHOWAIL[2], D. BHATTACHARYA[2], S. BHATTACHARYA[2], P. DAS[2], R. JUDD[2], V. SUPPIRAMANIAM[2];
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Abstract: Adiponectin is a hormone produced by adipocytes which regulates numerous metabolic processes, and it has recently been implicated as a potential player in Alzheimer's Disease and other cognitive disorders. Plasma levels of adiponectin are inversely proportional to body fat percentage, and a number of animal studies show that absence of adiponectin decreases insulin sensitivity and impairs normal glucose metabolism leading to diabetes. Our laboratory has previously demonstrated that central insulin resistance results in hippocampal glutamatergic dysfunction leading to cognitive impairment. In addition, animals lacking adiponectin display higher levels of amyloid beta compared to age matched controls, and amyloid beta is a hallmark of Alzheimer's disease. It is known that adiponectin receptors (AdipoR1 and AdipoR2) are found in the hippocampus of the brain, but the central function of these receptors is unknown. Based on existing literature, adiponectin may play a major role in the shared pathophysiology between diabetes and cognitive impairment. We hypothesize that adiponectin plays a role in hippocampal synaptic plasticity, and lack of adiponectin leads to cognitive deficits. One-year-old Adiponectin KO and C57BL/6J mice were utilized. Behavioral analysis was done using novel-object recognition test. Long-term potentiation (LTP) theta-burst protocol was utilized to measure hippocampal field potentials in Schaffer collateral pathway. Our results indicate that adiponectin KO mice display cognitive deficits in novel-object recognition test. In addition these mice showed a decrease in LTP and decrease in PI3k expression. Our findings demonstrate that adiponectin is necessary for normal cognitive function and hippocampal synaptic plasticity.

Disclosures: J. Bloemer: None. **W. Smith:** None. **A. Alhowail:** None. **D. Bhattacharya:** None. **S. Bhattacharya:** None. **P. Das:** None. **R. Judd:** None. **V. Suppiramaniam:** None.

Poster

786. Pharmacology for Alzheimer's Disease Therapeutics

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 786.14/H10

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH / NINDS (NS085770)

NIH / NIA Alzheimer's Disease Cebter Grabt (AG013854)

Title: Significant and asymmetric depletion of basal forebrain cholinergic system in primary progressive aphasia with Alzheimer pathology

Authors: N. LALEHZARI, *D. T. OHM, G. KIM, S. WEINTRAUB, E. H. BIGIO, M.-M. MESULAM, C. GEULA;
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Abstract: Primary Progressive Aphasia (PPA) is a disorder that presents with progressive loss of language capabilities. Approximately 30-40% of PPA cases show Alzheimer's disease (PPA-AD) pathology, with asymmetric distribution favoring the cortical language network in the dominant hemisphere. The amnestic variant of AD is characterized by significant loss of basal forebrain cholinergic neurons (BFCN) and their cortical projections. However, the status of BFCN and their axons in PPA is unknown. The purpose of this study was to determine the presence and extent of hemispheric asymmetry of AD pathology, neuronal loss and axonal loss in the BFCN system in PPA-AD. Tissue from four PPA-AD and four normal controls, with frozen or paraffin sections, were used. Thioflavin-S stain, and immunohistochemistry with antibodies to phospho tau (AT8) and amyloid-β, revealed abundance of neurofibrillary tangles (NFT) / pre-NFT in BFCN, and moderate diffuse amyloid plaques (AP) in the BF region in PPA-AD, and sparse NFT / pre-NFT and diffuse AP in the normal controls. Neuritic plaques were rare in the area occupied by the BFCN. Nissl stains demonstrated substantial loss of BFCN in PPA-AD when compared with control brains. In one PPA-AD and one control case, stereological counting was conducted. BFCN in the left hemisphere of the PPA-AD case contained 19% more thioflavin-S-positive NFT when compared with the right. Immunohistochemistry for low affinity neurotrophin receptor, which is enriched in BFCN, revealed 14.1% fewer cholinergic neurons in the left hemisphere than the right. The PPA-AD brain contained 80.8% less cholinergic neurons in the left hemisphere than the control case. Acetylcholinesterase-positive cholinergic axons were also stereologically quantified in three language (superior temporal gyrus, inferior parietal lobule and inferior frontal gyrus) and two non-language (anterior cingulate and entorhinal cortices) cortical areas. Cholinergic axon length was 16.2-58.1% lower in the left hemisphere than the right in the PPA-AD case. The PPA-AD case also displayed 34-98% less cholinergic axon length when compared with the control case. This difference was more pronounced in language areas (92-98%) than in non-language regions (34-56%). These findings indicate that, like typical amnestic AD, PPA-AD is characterized by substantial degeneration of basal forebrain cholinergic system. Furthermore, the cholinergic pathology reveals a leftward asymmetry that has not been described in typical amnestic forms of AD. The results suggest that cholinesterase inhibitors used as therapeutic agents in AD are likely to also be effective in PPA-AD.

Disclosures: N. Lalehzari: None. **D.T. Ohm:** None. **G. Kim:** None. **S. Weintraub:** None. **E.H. Bigio:** None. **M. Mesulam:** None. **C. Geula:** None.

Poster

786. Pharmacology for Alzheimer's Disease Therapeutics

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 786.15/H11

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH Grant DA09082

Title: Amyloid beta co-localizes with tyrosine hydroxylase in the locus coeruleus and with dopamine beta hydroxylase in the infralimbic medial prefrontal cortex of mice with forebrain specific overexpression of corticotropin releasing factor: anatomical evidence for putative regulated co-secretion

Authors: *J. A. ROSS[1], B. A. S. REYES[1], V. RISBROUGH[2], R. J. VALENTINO[3], E. J. VAN BOCKSTAELE[1];
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Abstract: Over 5 million Americans are currently suffering from Alzheimer’s disease (AD), the most common cause of dementia. AD is a neurodegenerative disorder classically characterized by histological features including amyloid beta (Aβ) peptide aggregates known as senile plaques, and hyper-phosphorylated tau protein aggregates known as neurofibrillary tangles (NFT). One of the earliest regions to become dysregulated in AD is the locus coeruleus (LC), the dorsal pontine nucleus that provides the neurotransmitter norepinephrine (NE) to almost all levels of the neuraxis. In response to stress, the LC releases norepinephrine (NE) throughout the entire neuraxis via its broadly distributed efferent projections. Stress-induced activation of the LC is mediated by corticotropin releasing factor (CRF) and CRF receptors exhibit sex-biased stress signaling. Sex differences have been described in the neurochemical, morphological and molecular regulation of LC neurons by CRF, providing a compelling basis for vulnerability of females to stress-related disorders such as AD. In the present study, we examined the cellular substrates for interactions between Aβ and tyrosine hydroxylase (TH) a marker of noradrenergic somatodendritic processes in the LC in mice conditionally overexpressing CRF in the forebrain (CRF OE) under a Doxycycline (DOX) regulated tetO promoter. Preliminary immunofluorescence data shows co-localization of Aβ and TH in somatodendritic processes of the LC. Using high resolution immunoelectron microscopy semi-quantitative preliminary analysis revealed that 42.9% (51/119) of TH-containing somatodendritic processes also exhibited Aβ-immunogold silver particles in DOX treated males, compared to 32.4% (92/284) in male transgenic littermate untreated controls and 61.6% (151/245) TH-containing somatodendritic processes also exhibited Aβ-immunogold silver particles in DOX treated females compared to

34.4% (21/61) in female transgenic littermate untreated controls. Thus, the preliminary results of immunoelectron microscopy experiments in male and female CRF OE mice indicate a trend towards increased Aβ in TH labeled somatodendritic processes of the LC, and that these increases may be exaggerated in females. Preliminary immunofluorescence also shows Aβ immunoreactivity in noradrenergic terminals of the infralimbic medial prefrontal cortex (ILmPFC) labeled with Dopamine-β-hydroxylase (DβH). An ongoing study seeks to quantify alterations of Aβ levels and subcellular distribution under conditions of CRF overexpression.

Disclosures: J.A. Ross: None. **B.A.S. Reyes:** None. **V. Risbrough:** None. **R.J. Valentino:** None. **E.J. Van Bockstaele:** None.

Poster

786. Pharmacology for Alzheimer's Disease Therapeutics

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 786.16/H12

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: CNPQ

FAPERJ

CAPES

Human Frontier Science Program (HFSP)

John Simon Guggenheim Foundation

Title: Aβ oligomer-induced synapse loss in mature culture hippocampal neurons and brain's macaques: protection by an anti-diabetic agent

Authors: *A. F. BATISTA[1], L. FORNY-GERMANO[1], N. LYRA E SILVA[1], J. BRITO-MOREIRA[1], M. GRALLE[1], S. BOEHNKE[2], B. COE[2], A. LABLANS[2], C. HOLSCHER[3], S. MARQUES[1], A. MARTINEZ[1], W. KLEIN[4], J. HOUZEL[1], S. FERREIRA[1], D. MUNOZ[2], F. DE FELICE[1];
[1]Federal Univ. of Rio de Janeiro, Rio de Janeiro, Brazil; [2]Queen's Univ., Kingston, ON, Canada; [3]Lancaster Univ., Lancaster, United Kingdom; [4]Northwestern Univ., Evanston, IL

Abstract: Alzheimer's disease (AD) is a debilitating neurodegenerative disorder and a major health problem worldwide. The lack of effective drugs to treat AD stimulates an intense pursuit of disease-modifying therapeutics. However, a major impediment may lie in fundamental

differences between humans and animal models, largely based in rodents. Disruption of insulin signaling has been recently described in the brains of AD patients and animal models, and may further contribute to cognitive impairment in this disease. Therefore, drugs that restore normal insulin function in the central nervous system have been recently suggested as promising novel approaches to treat AD. The aim of this study is to test a possible beneficial effect of Liraglutide, an anti-diabetic agent that activates pathways common to insulin signaling through stimulation of glucagon-like peptide 1 (GLP-1) receptors, on Aβ oligomer-induced synapse loss in the macaque brain. We further investigated the possible protection by Liraglutide on the impact of Aβ oligomers in cultured hippocampal neurons.Nine female cynomolgus macaques (Macaca fascicularis) were used. Three were shamoperated and served as a control group. We performed intracerebroventricular (i.c.v.) injections of Aβ oligomers into six cynomolgus macaques. Two of these monkeys had been pre-treated for one week with daily intraperitoneal injections of Liraglutide. Liraglutide administration continued daily until the last injection of oligomers. Brain sections were used for immunohistochemistry to evaluate the levels of synaptic markers. Our results showed that i.c.v. injections of oligomers trigger loss of synaptic proteins in cynomolgus macaques. Synapse density and levels of NMDA, AMPA and insulin receptors were decreased in the brains of macaques that received i.c.v. injections of AβOs, and these effects were prevented in animals pre-treated with liraglutide. In addition we have shown that synapses and insulin receptors were decreased in hippocampal neurons in vitro and significantly Liraglutide protects against these effects. In conclusion, this study suggests that Aβ oligomers, important synaptotoxins that accumulate AD brains, induce loss of synaptic proteins when injected into the brains of non-human primates. Importantly, treating monkeys with the novel anti-diabetic drug Liraglutide prevented the impact of Aβ oligomers on synapses.

Disclosures: **A.F. Batista:** None. **L. Forny-Germano:** None. **N. Lyra e Silva:** None. **J. Brito-Moreira:** None. **M. Gralle:** None. **S. Boehnke:** None. **B. Coe:** None. **A. Lablans:** None. **C. Holscher:** None. **S. Marques:** None. **A. Martinez:** None. **W. Klein:** None. **J. Houzel:** None. **S. Ferreira:** None. **D. Munoz:** None. **F. De Felice:** None.

Poster

786. Pharmacology for Alzheimer's Disease Therapeutics

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 786.17/H13

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: MOP-102501

NARSAD Young Investigator Award

Title: Amyloid beta peptide induces Dserine dependent NMDAR dysfunction in the mouse hippocampus

Authors: B. WANG[1], P. KHACHO[1], E. HRISTOVA[1], M. J. LALANDE[2], *M. A. SNYDER[1], R. BERGERON[1,2];
[1]Ottawa Hosp. Res. Inst., Ottawa, ON, Canada; [2]Cell. and Mol. Med., Univ. of Ottawa, Ottawa, ON, Canada

Abstract: Background: The toxicity of amyloid-beta (Aβ) is strongly associated with Alzheimer's disease (AD), which has a high incidence in the elderly worldwide. Recent evidence shows that alteration in N-methyl-D-aspartate receptor (NMDAR) activity plays a key role in Aβ-induced neurotoxicity. NMDARs are glutamate-gated ion channels that require the co-agonists glycine or D-serine. It has been suggested that D-serine is the primary co-agonist at synaptic NMDARs while glycine plays this role at extrasynaptic sites. The activation of synaptic and extrasynaptic NMDARs has distinct consequences for plasticity, gene regulation, neuronal death, and Aβ production. It is also known that synaptic and extrasynaptic receptors are involved in Aβ-mediated effects. Activation of synaptic NMDARs is thought to be neuroprotective. In contrast, extrasynaptic NMDARs are activated under conditions that result in glutamate spillover and are linked to excitoxicity. Previous work suggests that Aβ-induced excitotoxicity is attenuated in serine racemase knockout (SRKO) mice, which have depleted D-serine levels. **Objective:** The main goal of this investigation was to determine the effects of Aβ on synaptic and extrasynaptic NMDAR function and how D-serine alters these Aβ-mediated effects. We used SRKO mice and Aβ secreted from CHO cells containing the V717F mutation in the APP gene. **Preliminary data:** In CA1 pyramidal neurons, Aβ significantly reduced the amplitude of evoked synaptic NMDAR excitatory postsynaptic currents (EPSCs) in wild type (WT) mice. Interestingly, this effect was significantly more pronounced in SRKO mice. A similar effect was observed on isolated evoked extrasynaptic NMDAR currents. In addition, ambient levels of D-serine and glutamate tonically activate extrasynaptic NMDARs in the absence of synaptic stimulation, and changes in this current were observed by monitoring the holding current. During recordings of synaptic NMDAR currents, Aβ potentiated the holding current only in WT mice, suggesting an increase in tonic extrasynaptic NMDAR activation in WT but not in SRKO mice. SRKO mice also showed lower levels of tonic NMDAR activation. Furthermore, these experiments were performed in parallel with behavioral tests. Having lower levels of extrasynaptic NMDAR activation could be a possible mechanism through which SRKO mice attenuate Aβ-induced toxicity. **Conclusion:** These data suggest that low levels of D-serine alter NMDAR function upon application of Aβ and provide insight for future experiments exploring the importance of D-serine in the pathophysiology of AD.

Disclosures: B. Wang: None. **P. Khacho:** None. **E. Hristova:** None. **M.J. Lalande:** None. **M.A. Snyder:** None. **R. Bergeron:** None.

Poster

786. Pharmacology for Alzheimer's Disease Therapeutics

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 786.18/H14

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: Major Research Program from the State Ministry of Science and Technology of China (2013CB530902).

Title: Efr3a regulates oligomeric amyloid-β induced disruption of excitatory transmitter release in hippocampus

Authors: *Y. HE[1], M. WEI[1], F. HUANG[2], Y.-D. ZHOU[1];
[1]Dept. of Neurobio., Zhejiang Univ. Sch. of Med., Zhejiang, China; [2]Ctr. for Stem Cell and NanoMedicine, Chinese Acad. of Sci., Shanghai, China

Abstract: Amyloid-β (Aβ) oligomer-inducedaberrant neurotransmitter release has been proposed to be a crucial early event leading to synapse dysfunctionin Alzheimer's disease (AD).In the present study, we found that knocking outthe membrane protein Efr3a, a key component in thephosphatidylinositol 4-kinase (PI4K) complex, in CA3 region of the hippocampus in mice strongly preventedexogenousoligomeric Aβ-induced suppression of the frequency of miniature excitatory postsynaptic currents (mEPSCs)recorded from CA1 pyramidal neurons.By contrast, overexpression of Efr3aaggravatedoligomeric Aβ-induced impairment in mEPSC frequency.By estimating the release probability at the synapse between the Schaffer collateral (SC) and CA1 pyramidal neurons (PNs), we found that oligomeric Aβ-induced decrease of mEPSC frequency was mainly due to a reduction in thepresynaptic release probability, whereas the readily releasable pool size did not change. Remarkably, knocking out Efr3a in CA3 area of the hippocampus in a mouse model of AD significantly rescued aberrant release probability at the SC-PN synapse in these mice. Our work demonstrates that Efr3a regulates oligomeric Aβ-induced impairment of synaptic transmission via a presynaptic mechanism, and implicates that the level of phosphatidylinositol-4,5-bisphosphate (PtdIns(4,5)P2)in the membrane of the presynaptic terminal, which is related to synaptic vesicle fusion,may be tightly regulated by Aβ-Efr3a interaction. Keywords: Efr3a, release probability, amyloid-β. Support: Major Research Program from the State Ministry of Science and Technology of China (2013CB530902).

Disclosures: Y. He: None. **M. Wei:** None. **F. Huang:** None. **Y. Zhou:** None.

Poster

787. Parkinson's Neuroprotection II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 787.01/H15

Topic: C.03. Parkinson's Disease

Support: 1R01 NS06338-01A2

Title: UCH-L1 in nigrostriatal dopaminergic neurodegeneration: neurotoxicant exposure and aging

Authors: *B. M. WINNER, M. M. FARTHING, H. ZHANG, K. J. LOOKINGLAND, J. L. GOUDREAU;
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Abstract: Deficits in protein degradation are a hallmark of neurodegenerative diseases. In Parkinson disease (PD), protein clearance mechanisms such as the ubiquitin proteasome system (UPS) and autophagy lysosome pathway are dysfunctional in post-mortem brain tissue. Not surprisingly, key players in the UPS are mutated in familial forms of PD, such as ubiquitin carboxy-terminal hydrolase L1 (UCH-L1). UCH-L1 is a neuron-specific, highly abundant deubiquitinating enzyme tasked with maintaining pools of monomeric ubiquitin. UCH-L1 function ensures that an adequate supply of monomeric ubiquitin is available so that targeted proteins may be tagged and degraded by the 26S proteasome. UCH-L1 is downregulated and oxidatively modified in post-mortem brain tissue from PD and Alzheimer disease patients, providing a clue that loss of UCH-L1 function could contribute to neurodegeneration. In mice, UCH-L1 and monomeric ubiquitin are decreased in the substantia nigra 24 h after acute neurotoxicant treatment. Similarly, UCH-L1 protein, activity, and monomeric ubiquitin are altered over time in striatal synaptosomes from mice treated with 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP). Decreased UCH-L1 protein was correlated with the decrease in monomeric ubiquitin, suggesting an integral relationship between the abundance of these two key UPS-related proteins. Loss of UCH-L1 and monomeric ubiquitin is hypothesized to contribute to loss of tyrosine hydroxylase (TH) expression in the striatum characteristic of acute neurotoxicant stress and contribute to increased susceptibility of aged mice to MPTP exposure. These experiments will yield insight into the ability of UCH-L1 to preserve TH phenotype by maintaining supply of monomeric ubiquitin and promote UPS-mediated protein degradation.

Disclosures: B.M. Winner: None. **M.M. Farthing:** None. **H. Zhang:** None. **K.J. Lookingland:** None. **J.L. Goudreau:** None.

Poster

787. Parkinson's Neuroprotection II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 787.02/H16

Topic: C.03. Parkinson's Disease

Support: NRF Grant 2011-0030049

NRF Grant 2010-0027945

NRF Grant 2015R1A2A2A01005226

Title: Matrix metalloproteinase-8 inhibitor ameliorates inflammatory responses and behavioral deficits in LRRK2 G2019S parkinson's disease model mice

Authors: *T. KIM[1], J. JEON[1], J.-S. PARK[2], J. KIM[1], H. NOH[1], H.-S. KIM*[2], H. SEO*[1]; [1]Hayang Univ., Ansan, Gyeonggi, Korea, Republic of; [2]Ewha Womans Univ., Seoul, Korea, Republic of

Abstract: Parkinson's disease (PD) is a neurodegenerative disorder that involves the loss of dopaminergic neurons in the substantia nigra (SN). Matrix metalloproteinases (MMPs) are known to be related to neuroinflammation and neurodegeneration in the nigro-striatal pathway in PD. MMP-8, also known as neutrophil collagenase, is a functional player in the progressive pathology of various inflammatory disorders. In this study, we administered an MMP-8 inhibitor (MMP-8i) in an *in vivo* PD model, LRRK2 G2019S transgenic mice, to determine the effects of MMP-8i on PD pathology. We observed a significant increase in inflammatory markers (CD45, CD11b and SRA) and the number of Iba1-positive activated microglia in the striatum (STR) of LRRK2 G2019S mice, indicating increased neuroinflammation. MMP-8i administration significantly decreased CD45 and SRA levels as well as the number of Iba1-positive activated microglia. In addition, MMP-8i increased the levels of phosphorylated alpha-tubulin, which is a cytoskeletal network protein, and cellular ATP, the product of oxidative phosphorylation from mitochondria. Although MMP-8i did not alter the number of tyrosine hydroxylase (TH)-positive dopaminergic neurons in the SN brain region, MMP-8i significantly increased the cell body area of TH-positive dopaminergic neurons in the SN region of LRRK2 G2019S mice indicating neuroprotective effects on cellular atrophy in PD model mice. Furthermore, MMP-8i markedly improved behavioral abnormalities in LRRK2 G2019S mice, as determined by the rota-rod and open field tests. These data suggest that MMP-8i administration attenuates the pathological symptoms of PD through anti-inflammatory processes in LRRK2 G2019S PD model mice

Disclosures: **T. Kim:** None. **J. Jeon:** None. **J. Park:** None. **J. Kim:** None. **H. Noh:** None. **H. Kim*:** None. **H. Seo*:** None.

Poster

787. Parkinson's Neuroprotection II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 787.03/H17

Topic: C.03. Parkinson's Disease

Support: Australian NHMRC project grant 1029401

NIH R01 grant 075046

CASS foundation grant SM/08/2053

Helen McPherson Smith Trust Project grant 5965

Monash University MBio Postgraduate Award

Victorian Government's Operational Infrastructure Support Program

NHMRC Senior Research Fellowship

Title: Regulation and function of the y-chromosome gene sry in acute and chronic animal models of parkinson's disease

Authors: *P. PINARES-GARCIA[1,2], H. LOKE[1], D. THYAGARAJAN[3], V. HARLEY[1,2], J. LEE[1,2];
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Abstract: Whilst the cause of dopamine cell loss in Parkinson's disease (PD) is unknown, it is clear that the male-sex is a strong risk factor. The incidence of PD is 2-fold higher in males, and disease progression more rapid in males than females. Aside from the protective actions of sex hormones, growing evidence suggests that sex-specific genes contribute to this male-bias in PD. We previously showed that the Y-chromosome gene, SRY, co-localises with dopamine neurons, where it regulates dopamine biosynthesis and motor function in males. Here, we investigated the regulation and function of nigral SRY in i) acute toxin-induced hemiparkinsonian and ii) chronic systemic rotenone rat models of PD. We assessed the effect of reducing nigral SRY levels, via repeated infusions of SRY antisense oligonucleotide into the rat substantia nigra (SNc), on motor and dopaminergic function. In normal male rats, reducing SRY expression, via repeated intranigral SRY antisense oligonucleotide (ASO) infusion, transiently reduced motor function in the cylinder and rotarod tests, compared to the sense oligonucleotide (SO) treated control group. In contrast, ASO treatment in female rats did not affect motor function. In the acute 6-hydroxydopamine (6-OHDA) or rotenone-lesioned rat models of PD, nigral *SRY mRNA* was

significantly up-regulated at 7 days post 6-OHDA (+330%) or rotenone (+250%) injection. Remarkably, repeated ASO infusion significantly attenuated motor deficits and nigrostriatal degeneration in both 6-OHDA and rotenone-induced models of PD in male rats. In contrast, female rats showed no differences in 6-OHDA-induced motor deficits or nigrostriatal degeneration between the ASO- and SO-infused groups. In the chronic systemic rotenone rat model of PD (Cannon et al., 2009), we assessed the effect of daily intraperitoneal (IP) injections of rotenone on motor function and nigral gene expression.
Daily IP injections of rotenone (3mg/kg/day) for 14 days led to a time-dependent reduction in rearing behaviour (-59%,-69%,-77%,-79% on days 3, 7, 10 and 14 respectively compared to day 0). Similarly, in the open-field test we showed a time-dependent reduction in distance travelled (-67%, -73%, -75%, -66%), velocity (-68%, -74%, -76%, -67%), and increased duration inactive (+169%, +288%, +279%, +147%). Reduction in motor function was associated with a reduction in nigral *TH* mRNA expression (-55%) and increased nigral *SRY* mRNA expression (+160%) at day 7 compared to day 0. These data indicate that dysregulation of SRY directs a novel genetic mechanism of nigral cell death in males, and that inhibition of nigral SRY may be a novel therapeutic target to slow the progression of PD in males.

Disclosures: P. Pinares-Garcia: None. **H. Loke:** None. **D. Thyagarajan:** None. **V. Harley:** None. **J. Lee:** None.

Poster

787. Parkinson's Neuroprotection II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 787.04/H18

Topic: C.03. Parkinson’s Disease

Title: Analysis of PKCγ substrates in the nigro-striatum system: The role of CSPα phosphorylation in the neuronal survival

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Abstract: We found that PKCγ knockout (KO) mice showed Parkinsonian symptoms such as dopaminergic neuronal loss in the substantia nigra and dopamine release impairment in the striatum. However, the PKCγ substrates responsible for the neuronal cell survival *in vivo* have not yet been elucidated. To identify the PKCγ substrates, we employed phospho-proteome analysis. In the striatum of PKCγ KO mice, we found 10 candidate proteins with PKC

phosphorylation motif that exhibited decreased phosphorylation levels. Among them, we focused on csyteine string protein alpha (CSPα), which is a chaperone on the synaptic vesicle, and found that PKCγ directly phosphorylates CSPα at Serine 10 in the cell culture. Classical PKC inhibitors and CSPα knockdown (KD) significantly suppressed the neuronal survival in PC12 cells. The decreased level of neuronal survival in CSPα KD cells was rescued by wild-type CSPα, but not CSPα mutants whose serine 10 was substituted by alanine. These findings indicate that the phosphorylation of CSPα at serine 10 plays pivotal roles in neuronal survival in the substantia nigra. Thus, we propose that PKCγ positively modulates neuronal survival through CSPα phosphorylation. The PKCγ- CSPα phosphorylation axis may provide a new therapeutic target for the treatment of Parkinsonian syndrome.

Disclosures: **T. Shirafuji:** None. **T. Ueyama:** None. **K. Yoshino:** None. **N. Adachi:** None. **S. Tanaka:** None. **I. Hide:** None. **N. Saito:** None. **N. Sakai:** None.

Poster

787. Parkinson's Neuroprotection II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 787.05/H19

Topic: C.03. Parkinson’s Disease

Title: Nicotine-afforded neuroprotection of dopaminergic neurons is mediated by the alpha 4 subunit of nicotinic acetylcholine receptors

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Abstract: The cause and mechanisms underlying the loss of dopaminergic (DA) neurons in Parkinson’s disease (PD) are poorly understood. A major barrier to the development of new and effective therapies for PD is the current limitation in our understanding of the molecular and cellular events that lead to degeneration of the nigrostriatal DA system. Currently, there are two clinical trials underway to determine whether nicotine might be a useful therapeutic for the treatment of PD. Here, we evaluated the effect of nicotine pretreatment (0.5 or 1.0 μM 2 h prior to MPP+ exposure) in 1-methyl-4-phenylpyridinium (MPP+)-treated (1.0 mM) SHSY-5Y neuroblastoma cells, as an *in vitro* model of PD-related neuronal damage. Assessments were made 24 h after MPP+ exposure. Treatment with MPP+ significantly reduced the number of active mitochondria in neuronal cells, where pretreatment with nicotine prevented this effect. Additionally, nicotine significantly prevented MPP+ induced loss of cellular proliferation. A significant concentration-dependent neuroprotection afforded by nicotine against MPP+ induced

loss of DA was also observed. In a separate set of experiments, in which SH-SY5Y were transfected with 27-mer primer specific siRNA towards nicotinic acetylcholine receptor (nAChR) α4 subunits prior to MPP+ treatment, nicotine was no longer able to protect cells from the loss of DA caused by treatment with MPP+; this suggests that the neuroprotection afforded by nicotine is likely mediated via nAChRα4 subunits. These data suggest a role for nicotine in protecting mitochondria and facilitating neuronal proliferation via nAChRα4 subunits. Further research of this pathway might lead to critical insight into therapeutic approaches for neuroprotection in PD.

Disclosures: E. Cuevas: None. **S. Lantz:** None. **S. Sarkar:** None. **S. Ali:** None. **S. Ali:** None. **W. Slikker:** None. **M.G. Paule:** None. **S. Imam:** None.

Poster

787. Parkinson's Neuroprotection II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 787.06/H20

Topic: C.03. Parkinson's Disease

Title: Neuroprotector role of URB597 over inhibition of microglial activation in MTPT neuronal damage induce in adult C57BL6J mice.

Authors: *G. LOPEZ-ARMAS[1], A. TEJEDA- MARTÍNEZ[2], J. JURADO-TRIANA[3], M. FLORES-SOTO[4];
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Abstract: URB597 is fatty acid amide hydrolase (FAAH) enzymatic inhibitor; this enzyme is responsible of the degradation of endocannabinoids in special Anandamide or *N*-arachidonoylethanolamine (AEA) mediated by CB1 and CB2 receptor. AEA is involved in biological activities in central nervous system like synaptic communication, neurogenesis and neuroinflammation besides acting in pain perception because of neuroprotective response on demand after damage. The aim of this study was to determine how URB597 molecule is involved in behavior and microglia cells of mice C57BL/6J intraperitoneal injected (I.P) with MPTP (1-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine) that has been widely used as a model of PD. So in this work we investigate if prophylactic use URB597 administered 1 month at doses 0.2mg/kg I.P every 48 hours for 30 days before MPTP (30mg/kg/day for 5 days I.P) damage can

modify behavioral test like pole test, gait test and beam test and also if has any change in microglial activation stained with IBA-1 antibody. We use 10 mice for each one group: control, URB597, MPTP and URB597+MPTP. After 3 days of MPTP injection we performance behavioral test in 5 animals and for immunohistochemistry experiments resting mice were submitted to intracardiac perfusion with 4% paraformaldehyde and light immunohistochemistry technique was performed. Statistical analyses of the data were performed using the Kruskas-Wallis non parametric test and pos-hoc Mann-Whitney U test. The level of significance was set at $p<0.05$.Our result suggest that mice treated with URB597 + MPTP were significant different compared to the group with MPTP in pole, gait and beam tests ($p <0.05$). Finally IBA immunohistochemistry shows major microglial activation in MPTP group vs Control and URB597+MPTP groups respectively ($p <0.05$).

Disclosures: G. Lopez-Armas: None. **A. Tejeda- Martínez:** None. **J. Jurado-Triana:** None. **M. Flores-Soto:** None.

Poster

787. Parkinson's Neuroprotection II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 787.07/H21

Topic: C.03. Parkinson’s Disease

Support: KBRI Basic Research Program through Korea Brain Research Institute funded by the Ministry of Science, ICT & Future Planning #2231-415

Title: Inhibition of PTP1B increases a lysosomal degradation of α-synuclein in SH-SY5Y cells.

Authors: *H. CHOI, J. KIM, K. PARK, H.-H. LIM;
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Abstract: The ubiquitin-proteasome system (UPS) and lysosomal degradation pathway (autophagy) are two major pathways to degrade undesired proteins in the cells including α-synuclein. Since that, both systems are often called protein quality control systems in the cell. α-Synuclein can be removed by passing through the autophagy and the proteasomes. The failure in either of those two can lead accumulation of α-synuclein and cause neurodegeneration such as Parkinson’s disease. Previously, we demonstrated that PTP1B inhibitor increases phosphorylation of α-synuclein and the binding of α-synuclein to HSC70 for chaperone mediated autophagy. Also, the treatment of PTP1B inhibitor enhanced neuronal survivability and motor performance in the paraquat-induced PD mouse model. Here, we confirmed that PTP1B inhibitor

can increase the translocation of α-synuclein into lysosome, which results in a protective effect of PTP1B inhibitor against cellular toxicity of α-synuclein accumulation caused by the UPS impairment or other risk factors. Thus, the augmentation of lysosomal degradation pathway by PTP1B inhibitor could be a possible way to decrease α-synuclein aggregates from varied environmental stresses and to protect neuronal cells against cytotoxicity.

Disclosures: H. Choi: None. **J. Kim:** None. **K. Park:** None. **H. Lim:** None.

Poster

787. Parkinson's Neuroprotection II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 787.08/H22

Topic: C.03. Parkinson's Disease

Support: NRF-2014R1A2A1A11052042

NRF-2015M3A9B4067068

Title: Elucidation of extracellular matrix-related gene expression pattern in patients with Parkinson's disease

Authors: *M. KIM[1,2], M.-Y. LEE[1], J. YU[1,2], J.-H. SEO[1,2], Y. SHIN[1,2], S. WI[1,2], S.-R. CHO[1,2]; [1]Dept. & Res. Inst. of Rehabil., Yonsei Univ. Col. of Med., Seoul, Korea, Republic of; [2]Brain Korea 21 PLUS Project for Med. Science, Yonsei Univ., Seoul, Korea, Republic of

Abstract: Introduction: Parkinson's disease (PD) is common neurodegenerative disorder affecting the motor and cognitive functions. Pathologically, PD patients show a loss of dopaminergic neuron in substantia nigra pars compacta and are frequently present with Lewy bodies, eosinophilic intracellular inclusions composed of amyloid-like fibers and α-synuclein. However, the underlying mechanism causing pathogenesis of PD has not been elucidated so far. To elucidate differential gene expression associated with pathogenesis of PD, this study compared expression levels of genes, especially extracellular matrix (ECM) related genes, via transcriptome analysis in PD and normal control.
Methods: Human lipoaspirate was obtained from a volunteer with informed consent. Fat tissue was treated with 0.075% collagenase. After the isolation, adipose-derived mesenchymal stem cells (MSCs) were seeded in a specific medium. MSCs were subcultured from passage 1 to 8, and when they reached passage 8, transcriptome analysis was conducted. Differentially expressed genes (DEG), the result of transcriptome study, was then analyzed by a program DAVID, which yielded Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway. DEG

was validated by RT-PCR.
Results: KEGG pathway, the result of DAVID program, showed several pathways that explained the role of genes in the pathogenesis of PD. Among DEG, since the 12 down-regulated genes in PD were affected ECM, this study focused on the genes that related to ECM, and compared genes between PD and normal control. The result of RT-PCR showed that, among 12 genes, 6 genes—Collagen 5 alpha 3, Collagen 6 alpha 3, Collagen 6 alpha 2, Dystroglycan 1, Reelin, and Fibronectin 1—represented the same pattern as KEGG pathway.
Conclusion: The expression of collagen group, Dystroglycan 1, Reelin, and Fibronectin 1 showed down-regulated pattern in both KEGG pathway and RT-PCR. We have focused on ECM and suggest that ECM molecules such as Collagen 5 alpha 3, Reelin, and Fibronectin1 have neuroprotective effects in extra synaptic transmission, and might be associated with progression of PD.
Acknowledgements: This study was supported by grants from the National Research Foundation (NRF-2014R1A2A1A11052042, NRF-2015M3A9B4067068), the Ministry of Science and Technology, Republic of Korea.

Disclosures: **M. Kim:** None. **M. Lee:** None. **J. Yu:** None. **J. Seo:** None. **Y. Shin:** None. **S. Wi:** None. **S. Cho:** None.

Poster

787. Parkinson's Neuroprotection II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 787.09/H23

Topic: C.03. Parkinson’s Disease

Support: FinMIT cluster of excellence

Title: The therapeutic potential of alternative respiratory enzymes in neurodegeneration

Authors: *K. M. HOLMSTROEM, P. K. DHANDAPANI, M. SZIBOR, H. T. JACOBS; Inst. of Biotech., Univ. of Helsinki, Helsinki, Finland

Abstract: Neurodegenerative disorders encompass a large number of diseases that all stem from the progressive loss of brain cells. The two most common outcomes of aging associated neurodegenerative diseases are either dementia such as Alzheimer’s disease (AD) or a movement disorder such as Parkinson’s disease (PD). Despite intensive efforts, no cure exists for most neurodegenerative diseases, however, with an aging population the number of people suffering from the condition is growing. Mitochondrial dysfunction is a well-known characteristic of neurodegeneration, often due to failing oxidative phosphorylation and increased free radical

production. Our research demonstrates that the mammalian respiratory chain can be supplemented with respiratory proteins from other species not normally found in the vertebrate lineage. We have shown that this unique approach can alleviate some of the damage caused by the failing respiratory chain in various disease models including AD and PD, in mammalian cells and flies. We recently generated rat and mouse models that express the *Ciona instestinalis* alternative oxidase (AOX), an alternative oxidase capable of compensating for complex III and IV dysfunction, or the alternative NADH dehydrogenase (NDX), an alternative enzyme for complex I. These animals show no overt phenotype from the expression of the alternative enzymes, however, they confer resistance to toxic insults on the respiratory chain. They provide a unique opportunity to examine the potential of this exploratory approach in mammalian neurodegenerative models such as AD, PD and Huntington's disease.

Disclosures: K.M. Holmstroem: None. **P.K. Dhandapani:** None. **M. Szibor:** None. **H.T. Jacobs:** None.

Poster

787. Parkinson's Neuroprotection II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 787.10/H24

Topic: C.03. Parkinson’s Disease

Support: Multipark

Crafoord Foundation

Title: The vra1 locus plays a neuroprotective role in a 6ohda model of parkinson’s disease.

Authors: *M. JEWETT, I. JIMENEZ FERRER, E. N. LINDAU, M. SWANBERG; LUND UNIVERSITY, Lund, Sweden

Abstract: Parkinson’s disease (PD), like other major neurodegenerative disorders, is a complex disease: of the idiopathic cases (about 90%), an estimated 40% of the variation in disease risk is caused by unidentified genetic factors, while another 40% is caused by environmental factors. More work is needed to identify the unknown genetic risk factors for PD.
Thanks to linkage analysis, the Vra1 genetic locus, which includes Glutathione S-Transferase alpha 4 (GSTA4), has been identified in the PVG rat strain as being associated to neurodegeneration after nerve injury. Our goal is to determine whether this locus, isolated in a DA-congenic rat strain, is neuroprotective in a toxin model of PD: unilateral 6-hydroxydopamine (6-OHDA) injections in the striatum. Optical density and stereology data show 55% more

survival of midbrain dopaminergic neurons (mDNs) in DA-Vra1 rats compared to DA rats, indicating that the Vra1 alleles are somehow involved in mDN protection. These results allow us to continue investigating the role of Vra1 and study genes like GSTA4 that may be responsible for increased cell survival, first in rats, then in humans.

Disclosures: **M. Jewett:** None. **I. Jimenez Ferrer:** None. **E.N. Lindau:** None. **M. Swanberg:** None.

Poster

787. Parkinson's Neuroprotection II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 787.11/H25

Topic: C.03. Parkinson's Disease

Support: 2014R1A6A1029617

2014R1A1A1037655

2014R1A2A1A11051231

Title: Astrocytic High mobility group box 1 upregulates TH exprssion to maintain dopaminergic neurons in MPTP induced PD like model

Authors: ***S. KIM**, M. RYU, J. HAN, Y. JANG, J. KIM, M. LEE, I. RYU, G. KWEON, J. HEO;
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Abstract: Parkinson's disease (PD) is a progressive neurodegenerative disease that involves the loss of dopaminergic neurons from the substantia nigra (SN) and striatum. The inflammatory process with activated glial cells has been confused with dual functions as pathogenic and protective factor of PD development. Furthermore, we do not understand the molecular pathway through which dopaminergic neurons are lost via the actions of activated astrocytes and cytokines. High mobility group box 1 (HMGB1) can be actively secreted from inflammatory cells and is known to both promote inflammation and protect against disease propagation. Here we showed that the staining intensities of HMGB1 and Receptor for glycation end product (RAGE) are higher in the nigral area of methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-treated mice, a toxin-induced PD-like model, compared to those of saline-treated controls. HMGB1 was found to principally localize to astrocytes, and could affect the neighboring dopaminergic neurons, due to co-localization of RAGE with TH-positive cells. Treatment of a dopaminergic neuronal cell line with HMGB1 simultaneously induced JNK phosphorylation and

TH expression. A JNK inhibitor was found to block the HMGB1-induced upregulation of TH expression. Collectively, our results suggest that increased HMGB1 in astrocytes upregulates TH expression to maintain dopaminergic neurons in the progressive neurodegenerative disease, PD. (2014R1A6A1029617), (2014R1A1A1037655), (2014R1A2A1A11051231)

Disclosures: **S. Kim:** None. **M. Ryu:** None. **J. Han:** None. **Y. Jang:** None. **J. Kim:** None. **M. Lee:** None. **I. Ryu:** None. **G. Kweon:** None. **J. Heo:** None.

Poster

787. Parkinson's Neuroprotection II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 787.12/H26

Topic: C.03. Parkinson's Disease

Title: Neuroprotective effect of FTY720 in a mouse model of Parkinson's disease

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Abstract: Parkinson's disease (PD) is a progressive neurodegenerative disorder characterized by rigidity, tremor and an overall lack of smooth motor control. These symptoms are triggered by the loss of dopamine (DA) neurons of the substantia nigra that projects rostrally to the striatum. The cause of this debilitating disease remains unknown. For this reason, current PD medications involve symptoms management as opposed to halting disease progression and DA neuronal degeneration. Fingolimod (FTY720) is a known sphingosine-1-phosphate receptor modulator, which has been shown to promote endogenous neuroprotective mechanisms. Whether FTY720 could prevent DA neuronal death in PD has never been investigated. We studied the effects of FTY720 treatment on the nigrostriatal loss and motor deficits induced by the administration of 1-methyl-4-phenyl-1,2,3,6-tretrahydropyridine (MPTP) in mice, a well-recognized animal model of PD. Mice were divided into four groups: vehicle (saline), FTY720, MPTP + vehicle (MPTP) and MPTP + FTY720 (MPTP/FTY720). Chronic FTY720 treatments (1 mg/kg, once a day for 14 days) were administered orally and began two days before the acute MPTP treatments (4 injections of 20 mg/kg, i.p, every 2 hours). Seven days after MPTP administration, behavioral tests were performed to evaluate motor ability. Mice performances at the beam, wire suspension, pole and rotarod tests were similar in all groups. At the biochemical level, Western blot analyses were performed to evaluate tyrosine hydroxylase (TH) levels as a marker of DA neuronal integrity. FTY720 treatments did not affect striatal TH levels whereas a reduction of 29% ($p < 0.05$) was observed in MPTP-treated mice compared to control. Disappointingly, TH levels in the MPTP/FTY720-treated mice were also reduced by 37% ($p < 0.05$) compared to control.

Striatal brain-derived neurotrophic factor (BDNF) levels were measured by Western blot and an increase of 20% ($p > 0.05$) was noticed following the FTY720 treatment. In the MPTP-treated mice, BDNF levels were decreased by 27% ($p < 0.01$) whereas the MPTP/FTY720 treatment increased these levels by 60% relative to MPTP ($p < 0.001$). Altogether, these preliminary data indicates that even with an enrichment of BDNF in the striatum, chronic FTY720 treatment was not able to prevent the DA depletion induced by MPTP. Despite that further investigations will be needed in order to reach stronger conclusion, we still established the interesting possibility that FTY720 could exhibit neuroprotective effects through the modulation of neurotrophic factors.

Disclosures: **E. Pepin:** None. **G. L.Lemieux:** None. **G. Bureau:** None. **G. Massicotte:** None. **M. Cyr:** None.

Poster

787. Parkinson's Neuroprotection II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 787.13/I1

Topic: C.03. Parkinson's Disease

Support: HKGRF grants (14106914, 14111815)

General Grant of NSFC (31371092)

Key Project Grant of NSFC (31330035)

Title: GSK J4 protects neurons from oxidative stress via a catalase-like mechanism in Parkinson's disease model

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Abstract: Parkinson's disease (PD) is the second most common neurodegenerative disease, which affects millions of people worldwide. Iron accumulation in the substantia nigra (SN) is one of the most invariable pathological hallmarks, which is believed to drive oxidative stress that leads to selective destruction of dopaminergic (DA) neurons. Therefore, to remove accumulated iron and reduce oxidative stress provide a new therapeutic strategy for PD. GSK J4, a novel histone demethylases inhibitor, has been found to cross blood-brain barrier and possess anti-brain tumor function. Recently, we found that only a trace amount of GSK J4 was sufficient to

reduce cellular labile iron in SH-SY5Y neuronal cells. Here the effects of GSK J4 on 6-OHDA-induced PD model were investigated. MTT assay and TUNEL staining showed that GSK J4 prevented 6-OHDA-induced cell death and apoptosis via a mechanism independent of KDM6, its known target. Although Calcein-AM assay showed that GSK J4 suppressed free labile iron accompanied by decreased ferritin, an iron storage protein, the neuroprotective action of GSK J4 could not be blocked by iron supplement. Interestingly, we found that GSK J4 displayed an anti-oxidant ability via catalase-like mechanism in the presence of iron in cell-free assay. Consistently, it was found that GSK J4 suppressed H_2O_2-induced cell death in SH-SY5Y. In addition, cells treated with GSK J4 showed lower levels of reactive oxygen species and malondialdehyde. In parallel, GSK J4 rescued the DA neurons loss and motor defects in 6-OHDA-induced PD rat. Taken together, we demonstrate that the iron-binding ability of GSK J4 is necessary, but not sufficient, to explain their capacity to protect neurons from oxidative stress. Instead, our data suggest that GSK J4 might act as a catalase mimetic after binding iron, then catalyzes the dissociation of H_2O_2 into water oxygen.

Disclosures: **M. Mu:** None. **T. Liang:** None. **Z. Qian:** None. **W. Yung:** None. **Y. Ke:** None.

Poster

787. Parkinson's Neuroprotection II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 787.14/I2

Topic: C.03. Parkinson’s Disease

Support: Trinity University Biology Summer Undergraduate Fellowship 2016

Murchison Summer Undergraduate Fellowship 2015

Ruth C. and Andrew G. Cowles Endowed Professorship

Title: Age effects on astrocyte-mediated neuroprotection against a Parkinson’s Disease model

Authors: ***B. YARBERRY**[1], A. NGUYEN[2], M. BAINS[3], J. L. ROBERTS[1];
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Abstract: A major function of astrocytes is to provide neurons with reparative cholesterol in times of oxidative stress by way of a transport molecule known as Apolipoprotein E (ApoE). This function is especially relevant in neurodegenerative diseases, such as Parkinson's disease (PD), that target mitochondria, damage their functional integrity, and lead to the production of reactive oxygen species. Previously, our lab has shown that astrocytes produce less ApoE as they

age and we hypothesize that this will manifest as a decreased ability to provide neuroprotection against a toxic drug that models PD, MPP+ (1-methyl-4-phenylpyridinium), which results in enhanced oxidative stress in the dopaminergic neuron. To examine this hypothesis, N27 dopaminergic cells were treated with 10 μM retinoic acid for 48 hours to induce differentiation and to upregulate the dopamine transporter, the dopaminergic protein required for toxin intake. Thirty minutes prior to toxin treatment, N27s were incubated in astrocyte-conditioned media from different aged mouse astrocytes (4-28mo). Cells were then treated with 500 μM MPP+ for 24 hours and cell viability was analyzed by Western Blot for tyrosine hydroxylase, a marker for dopaminergic cells. We expect that neurons pre-treated with conditioned media from younger astrocytes will have increased levels of tyrosine hydroxylase compared to neurons given conditioned media from older astrocytes and this will be verified through the use of co-cultures. We are currently trying to identify the age-related changes of the factor(s) in astrocyte secretions and these findings will help explain why many neurodegenerative diseases are exacerbated by age.

Disclosures: **B. Yarberry:** None. **A. Nguyen:** None. **M. Bains:** None. **J.L. Roberts:** None.

Poster

787. Parkinson's Neuroprotection II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 787.15/I3

Topic: C.03. Parkinson’s Disease

Title: Neuroprotective and anxiolytic effect of weak static magnetic field in the rat.

Authors: ***R. UZAN**, Y. LOBODA, L. SCHACHTER, J. FINBERG;
Technion-Israel Inst. of Technol., Haifa, Israel

Abstract: Objectives: There is an increasing evidence of interaction between static magnetic fields (SMF) and biological systems. In the study of Ben Yakir-Blumkin et al, 2014, SMF was found to protect against etoposide-induced apoptosis in primary neuronal cultures. The aims of the present study were to investigate whether SMF can protect against 6-hydroxydopamine (6-OHDA) induced neuronal degeneration in rat substantia nigra (SN) and to explore the effect of SMF on rat behavior as a function of age *in vivo*. Methods: Male SD rats were injected intracerebroventricularly (i.c.v) with 6-OHDA (125μg) \saline. Immediately after, a small (3 mm diameter, 0.5 mm thick) disc-shaped magnet was fixed to the rat's skull (or control- non-magnetic metal disc). The magnet was positioned above bregma causing a magnetic field strength of 10 Gauss in the SN area. Five weeks later the rat’s tissues were perfusion-fixed and numbers of tyrosine hydroxylase positive (TH+) cells in SN were counted. In the behavioral

experiment, male SD rats aged 3 months (Young, Y), 12 months (Middle-Aged, MA) and 24 months (Old, O) were implanted with a magnet or control implant as above. After 7 days of SMF exposure rats were subjected to the open field (OF) and the elevated-plus maze (EPM) tests, for behavioral assessment. At the end of the experiment hippocampi were taken for mRNA and protein expression using RT- PCR and western blot analysis, respectively. Results: In the 6-OHDA-control implant group, SN TH+ cell number was reduced by 41±0.06 % (SEM, n=5) in relation to sham-operated controls .However, in the 6-OHDA- SMF-exposed rats, TH+ cell number maintained at normal levels. In the behavioural tests, O and MA rats showed decreased anxiety-like behavior in the EPM test. Increased levels of hippocampal ERK and PKCε proteins were found in MA rats and increased mRNA levels of Neurotrophin-4 (Ntf-4) were found in Y rats exposed to 7 days of SMF. Conclusion: The results demonstrate a neuroprotective effect of SMF in rats exposed to 6-OHDA. Moreover, SMF had an anxiolytic effect in MA and O rats accompanied by alteration in expression of key proteins involved in neuroprotection and plasticity in MA rats. The results indicate a possibility of using weak SMF in treatment of neurodegenerative disorders as well as anxiety conditions in man. Reference: Ben Yakir-Blumkin M., et al (2014) *Neuroscience* 278:313-26.

Disclosures: **R. Uzan:** None. **Y. Loboda:** None. **L. Schachter:** None. **J. Finberg:** None.

Poster

787. Parkinson's Neuroprotection II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 787.16/I4

Topic: C.03. Parkinson’s Disease

Support: NCTR Protocol: E746601

Title: Nicotine as a therapeutic candidate in a pre-clinical model of progressive PD: regulation of parkin function

Authors: ***S. M. LANTZ**, E. CUEVAS, S. SARKAR, S. FERGUSON, D. LAW, S. F. ALI, W. SLIKKER, Jr, M. G. PAULE, S. Z. IMAM;
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Abstract: Loss of dopaminergic (DA) neurons from the substantia nigra due to toxic protein aggregation is the primary pathological hallmark of Parkinson’s disease (PD). We have recently identified that the regulation of parkin--a major player in protein clearance--by stress-activated, c-Abl-mediated, tyrosine phosphorylation plays a significant role in PD pathogenesis. Numerous studies have shown that nicotine protects DA neurons and smoking reduces the risk of PD. Here,

we evaluated the possible molecular mechanism of nicotine-mediated protective pathways in an animal model of PD. Adult male C57BLJ6 mice were treated with an ip MPTP regimen as follows: 15 mg/kg free base on day 1, 25 mg/kg on day 2, and 30 mg/kg on days 3-7. Nicotine therapy was administered ip at 0.025, 0.05 or 0.1 mg/kg free base under two conditions, either A) given daily for 1 week before the first dose of MPTP and also 1 hr before each dose of MPTP (pre-MPTP nicotine therapy) or B) given daily for 1 week after the last MPTP dose (post-MPTP nicotine therapy). Behavioral changes, DA status and c-Abl/Parkin pathways were evaluated to see if nicotine therapy would prevent the progressive DA damage seen in this PD model. As revealed by HPLC analysis, MPTP-treatment alone resulted in a significant loss of DA (~80%) in the striatum. Nicotine therapy prevented the loss of dopamine in a dose-dependent manner with approximately 75% restoration seen at the 0.1mg/kg dose. Given this finding, to evaluate clinical applicability, post-MPTP nicotine therapy was employed to investigate whether parkin function was affected. Nicotine therapy significantly prevented c-Abl mediated tyrosine phosphorylation and reduced aggregation of the toxic parkin substrate, aminoacyl-tRNA synthetase (ARS) interacting multifunctional protein type 2 (AIMP2). For the first time, these data provide clear evidence that in a pre-clinical model of progressive PD, nicotine has the potential to serve as a viable therapeutic candidate by maintaining the protein clearance machinery, specifically diminishing the aggregation of AIMP2, in the DA system *after* the onset of PD. Additional studies are underway to further elucidate these mechanisms and to better understand the therapeutic potential of nicotine in PD.

Disclosures: **S.M. Lantz:** None. **E. Cuevas:** None. **S. Sarkar:** None. **S. Ferguson:** None. **D. Law:** None. **S.F. Ali:** None. **W. Slikker:** None. **M.G. Paule:** None. **S.Z. Imam:** None.

Poster

787. Parkinson's Neuroprotection II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 787.17/I5

Topic: C.03. Parkinson’s Disease

Support: Deutsche Forschungsgemeinschaft (DFG) grant

Deutscher Akademischer Austauschdienst (DAAD) support

Title: Environmental enrichment protects from transcriptional disturbances in a predisposition PD model.

Authors: Z. WASSOUF, T. HENTRICH, N. CASADEI, S. SAMER, M. CELKOVA, *O. RIESS, J. M. SCHULZE-HENTRICH;
Univ. of Tuebingen, Tuebingen, Germany

Abstract: Parkinson's disease (PD) is a progressive neurodegenerative disorder, characterized by accumulation of misfolded alpha-synuclein protein (aSYN) in intracellular structures called Lewy bodies and loss of dopaminergic neurons. In addition to the resulting motoric impairments, PD patients exhibit a variety of non-motor symptoms including neuropsychiatric disturbances and cognitive impairments. While genomic mutations and multiplications have been linked to rare familial forms of PD, the preponderance of PD cases cannot be explained by genetics alone and seems to occur sporadically. Moreover, disease characteristics often vary considerably despite identical gene defects in patients, and age as well as environmental factors correlate with onset and progression. This multi-factorial interplay suggests a highly complex pathomechanism that has remained largely enigmatic. Using a transgenic mouse model, which was generated in our lab and carries a Bacterial Artificial Chromosome (BAC) construct with the human wildtype full length *SNCA* gene, we measured genome-wide changes in gene expression induced by exposing animals to either an enriched environment -a combination of increased physical and cognitive stimulation- or a Chronic Unpredictable Mild Stress (CUMS) paradigm. Our data revealed features of the mouse genome that show intriguing changes in gene activity accompanied by distinctive epigenetic pattern. Age-dependent transcriptional disturbances were evident in disease background, while exposure to environmental enrichment exhibited protective effects on these disturbances. Further, bioinformatic analysis pointed towards several pathways and signaling cascades linked to aspects of the disease such as membrane potential, synaptic vesicle clustering, neurotransmitter transport, and regulation of cytoskeleton. Tracing down the key molecular regulators driving the observed effects, we suggest a mechanism involving interplay between transcription factors with a role in neuronal plasticity and homeostatic synaptic scaling, promoter methylation, and modulation of synaptic structures that, in concert, could explain the protective impacts of the EE. Utilizing identified features as anchor points, additional (epi-)genome-wide studies are already under way. We consider these efforts to be essential in assessing whether changes in life style can delay or ameliorate PD symptoms in human and whether the epigenome offers novel opportunities for better diagnosis and much-needed therapies of Parkinson's disease.

Disclosures: Z. Wassouf: None. **T. Hentrich:** None. **N. Casadei:** None. **S. Samer:** None. **M. Celkova:** None. **O. Riess:** None. **J.M. Schulze-Hentrich:** None.

Poster

787. Parkinson's Neuroprotection II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 787.18/I6

Topic: C.03. Parkinson's Disease

Support: NIH NS065338-01A2

T32 GM092715

Title: Parkin modulates proteasome activity in dopamine axon terminals following neurotoxic insult

Authors: *T. LANSDELL[1], K. J. LOOKINGLAND[1], J. L. GOUDREAU[2];
[1]Pharmacol. and Toxicology, [2]Pharmacol. and Toxicology, Neurol. and Ophthalmology, Inst. for Integrative Toxicology, Michigan State Univ., East Lansing, MI

Abstract: The motor symptoms of Parkinson disease result from the chronic degeneration of nigrostriatal dopamine (NSDA) neurons. While NSDA neurons are susceptible, tuberoinfundibular dopamine (TIDA) neurons are spared. This pattern of DA neuronal susceptibility can be recapitulated with exposure to the selective DA neurotoxicant MPTP. Following exposure to MPTP, the recovery of DA neurons is dependent upon the induction of parkin expression, which occurs in TIDA, but not NSDA neurons following MPTP exposure. Parkin, an E3 ligase, is part of the ubiquitin proteasome system that targets proteins for degradation by the 26S proteasome. In cellular assays, parkin directly binds to the 26S proteasome and enhances its activity through an E3 ligase independent mechanism, suggesting that it maintains proteasome activity following neurotoxic insult. To test this hypothesis, chymotryptic-like activity of the proteasome was assessed *in vitro* and *in vivo* following exposure to MPTP or its active metabolite, MPP^+. In cell free proteasome assays MPP+, but not MPTP decreased proteasome activity and this effect was attenuated in the presence of purified parkin. Proteasome activity was decreased in striatal (ST) tissue and synaptosomes derived from $Park2^{-/-}$ mice compared to those from WT mice. MPTP caused a decrease in ST parkin expression as well as proteasome activity in both WT and $Park2^{-/-}$ mice. In contrast, proteasome activity was impaired in the median eminence (ME) of $Park2^{-/-}$ mice, but not in WT mice where parkin expression was increased. The role of parkin in promoting proteasome activity was further assessed *in vivo* with rAAV2/5 mediated over expression of parkin in $Park2^{-/-}$ mice. Unilateral over expression of parkin resulted in increased proteasome activity in ST synaptosomes compared to the contralateral side. Further studies mediating the overexpression of parkin in the substantia nigra will determine if parkin over expression in NSDA neurons will protect axon terminals from loss of proteasome activity. rAAV2/5 mediated over expression of parkin in the arcuate nucleus will determine if parkin expression is sufficient to restore proteasome activity in

the ME of Park2$^{-/-}$ mice. Collectively, these results indicate that parkin plays a role in maintaining proteasome activity following acute neurotoxicant injury in DA neurons.

Disclosures: **T. Lansdell:** None. **K.J. Lookingland:** None. **J.L. Goudreau:** None.

Poster

787. Parkinson's Neuroprotection II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 787.19/I7

Topic: C.03. Parkinson's Disease

Support: FAPESP

CNPq

NAPNA

Title: [^{11}C]PBR28 PET imaging of the exercise-induced reduction in neuroinflammation and behavior improvement in a rat model of Parkinson´s Disease

Authors: ***C. C. REAL**[1], P. KOPSCHINA FELTES[2], D. VÁLLEZ GARCÍA[2], J. DOORDUIN[2], L. R. G. BRITTO[1], E. F. J. DE VRIES[2];
[1]ICB - Univ. of São Paulo (USP), SAO PAULO, Brazil; [2]Dept. of Nuclear Med. and Mol. Imaging, Univ. Med. Ctr. Groningen, Groningen, Netherlands

Abstract: Previous human and animal studies have shown a link between microglial activation and dopaminergic neurons loss in Parkinson's Disease (PD). Moreover, it has been suggested that neuroinflammation contributes to the cascade of events that leads to neurodegeneration, and exercise can reduce the microglial activation. This study aims to evaluate exercise-induced reduction in the neuroinflammatory response by [^{11}C]PBR28 PET scan (a second generation of 18 kDa translocator protein PET tracers) and the behavior improvement in animals submitted to the PD model induced by unilateral striatal 6-hydroxydopamine and to a protocol of wheel running exercise (3 times per week during 40 minutes). 44 male Wistar rats were divided into 4 groups (sedentary - SED; exercised - EX; SED+PD; and EX+PD). A baseline, 10 and 30 day post surgery PET scan with [^{11}C]PBR28 was conducted to quantify neuroinflammation. Behavior was evaluated by novel object recognition (NOR) and the cylinder test. The scans were automatically registered to a tracer-specific PET template and the right/left striatum ratio was analyzed. Post mortem microglial activation was evaluated with Iba-1 on day 10 and 30. Statistical analyses were performed using Generalized Estimating Equations model.
The NOR data revealed that the animals from SED+PD group had a decreased discrimination

index for short memory when compared to the other groups (SED - 27%, $p<0.001$; EX - 24%, $p<0.05$; EX+PD - 29%, $p<0.0001$), and for long memory when compared to the SED group (9%, $p<0.05$). The cylinder test revealed that there was a increase in the asymmetry forelimb use for SED+PD (37%, $p<0.0001$). Iba-1 revealed that at 10 days there was an intense microglial activation in the SED+PD group (SED - 86%, $p<0.0001$; EX - 43%, $p<0.05$; EX+PD - 50%, $p<0.01$), which did not happen in the exercised rats. On day 30, no between groups difference was found. A higher [^{11}C]PBR28 uptake was observed in SED+PD rats on day 10 (62%, $p<0.01$), whereas the EX+PD rats increased 14% ($p<0.01$) when compared to baseline levels. On day 30, an increased uptake was only observed in the SED+PD animals (10%, $p<0.01$). The [^{11}C]PBR28 SUV was as sensitive as the staining with Iba-1, as the correlation of data was significant (R^2 linear:0.239; $p=0.0208$).
The present study suggests that exercise decreases the activation of microglia, measured by Iba-1 and [^{11}C]PBR28 PET. The exercise-induced attenuation of neuroinflammation seems to have a beneficial effect on behavioral symptoms in this PD rat model. The imaging data suggest that [^{11}C]-PBR28 PET can be a good marker for investigating pathophysiological aspects of neurodegenerative diseases.
Financial support: FAPESP, CNPq, NAPNA

Disclosures: **C.C. Real:** None. **P. Kopschina Feltes:** None. **D. Vállez García:** None. **J. Doorduin:** None. **L.R.G. Britto:** None. **E.F.J. de Vries:** None.

Poster

787. Parkinson's Neuroprotection II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 787.20/I8

Topic: C.03. Parkinson’s Disease

Support: NIH P01 DA028555

NIH R01 NS36126

NIH P01 NS31492

NIH 2R01 NS034239

NIH R01 NS070190

Title: Manganese-enhanced magnetic resonance imaging for detection of vasoactive intestinal peptide receptor 2-agonist therapy in a model of Parkinson’s disease

Authors: *K. OLSON[1], A. BADE[2], C. SCHUTT[2], J. DONG[2], S. SHANDLER[3], M. BOSKA[2], R. MOSLEY[2], H. GENDELMAN[2], Y. LIU[2];
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Abstract: Neuroprotective immunity is defined by transformation of T cell polarity for therapeutic gain. For neurodegenerative disorders and specifically, for Parkinson's disease (PD), vasoactive intestinal peptide receptor 2 (VIPR2)-agonists (referred to as LBT-3627) elicit robust anti-inflammatory responses leading to neuronal sparing in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-intoxicated mice. While the neurotherapeutic potential has previously been demonstrated for PD, there remains inherent limitation in translating these inventions clinically. One obstacle for clinical translation centers on the availability of suitable noninvasive methods to track disease progression and therapeutic efficacy. To this end, we developed manganese-enhanced magnetic resonance imaging (MEMRI) assays as a method to assess glial activation and LBT-3627-induced neuroprotective immunity for MPTP-induced nigrostriatal degeneration. Following either PBS or LBT-3627 treatment, mice were intoxicated with MPTP. At two and seven days post MPTP intoxication, mice were scanned using MEMRI, and images were registered to an MEMRI-based brain atlas for comparison. Manganese-induced MRI signal enhancement was calculated. MEMRI revealed MPTP-induced inflammation as well as a coincident reduction in signal with LBT-3627 treatment. MPTP-treated mice showed a significantly higher signal enhancement within the hippocampus, the substantia nigra, and the striatum when compared to saline controls. LBT-3627 treatment reversed the signal enhancement indicating the ability of MEMRI to detect both an inflammatory state and the neurotherapeutic potential of LBT-3627, supporting MEMRI as a method to assess changes in nigrostriatal lesions following anti-inflammatory therapy use. Signal enhancement changes were associated with changes in both neuron numbers and astrocyte activation. Dopaminergic neurons were lost following MPTP intoxication. LBT-3627 treatment significantly spared dopaminergic neurons, resulting in a 62% and 64% survival when compared to PBS alone. Likewise, MPTP intoxication noticeably increased GFAP reactivity by nearly 6-fold, and LBT-3627 pretreatment attenuated astroglial response by significantly decreasing GFAP reactivity by ~50% when compared to MPTP treatment. Correlation analysis revealed a positive relationship between signal intensity and TH+ neuron number as well ($r = 0.3600$, $p = 0.0208$). Taken together, the data suggest that MEMRI can be developed as a biomarker tool to monitor neurotherapeutic responses that are relevant to common neurodegenerative disorders used to improve disease outcomes.

Disclosures: K. Olson: None. **A. Bade:** None. **C. Schutt:** None. **J. Dong:** None. **S. Shandler:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Longevity Biotech, Inc. **M. Boska:** None. **R. Mosley:** None. **H. Gendelman:** Other; Longevity Biotech, Inc. **Y. Liu:** None.

Poster

787. Parkinson's Neuroprotection II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 787.21/I9

Topic: C.03. Parkinson's Disease

Support: The Michael J. Fox Foundation

National Parkinson Foundation

Par fore Parkinson's

Title: Preclinical validation of Bach1 inhibition for the development of Parkinson's disease therapy

Authors: ***M. AHUJA**[1], N. AMMAL KAIDERY[1], J. MORGAN[2], K. IGARASHI[3], O. C. ATTUCKS[4], B. THOMAS[1];
[2]Neurol., [1]Augusta Univ., Augusta, GA; [3]Dept. of Biochem., Tohoku Univ. Grad. Sch. of Med., Sendai, Japan; [4]vTv Therapeut. LLC, High Point, NC

Abstract: Parkinson's disease (PD) is a progressive and debilitating neurodegenerative movement disorder that is characterized by marked dopaminergic cell loss in the brain. Except for the palliative treatment, no preventive therapy or cure is yet available for PD. Based on recent pathophysiological findings, aberrant oxidative stress and inflammation are extensively targeted for developing novel PD therapies. The most promising target is the nuclear-factor-E2-related factor 2 (Nrf2)/antioxidant response element (ARE) signaling pathway which regulates the expression of a battery of genes encoding anti-oxidative, anti-inflammatory, and cytoprotective genes. However, all known Nrf2 activators are electrophilic and thus, may potentially result in oxidative stress. Transcription factor Bach1 [BTB (broad-complex, tramtrack and bric-a-brac) and CNC (cap'n'collar protein) homology 1] binds to ARE-like sequences, functioning as a transcriptional repressor, thus antagonizing the activator function of Nrf2 and hence, potentially be aimed to develop better non-elcetrophillic ARE activators. In our current target validation study, we employed genetic as well as pharmacological inhibition of Bach1. We investigated the effects of Bach1 inhibition on Nrf2/ARE signaling both *in vitro* and *in vivo* and the ability to block 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) induced neurotoxicity, associated oxidative damage, and inflammation in mice. Assessment of mRNA levels exhibited induction of several antioxidant, anti-inflammatory and cytoprotective genes in Bach1 null mouse and also with Bach1 inhibitors. In case of Bach1 null mouse, subacute MPTP induced dopaminergic neurotoxicity was found to be significantly blocked that was accompanied with decrease in the 3-nitrotyrosine (oxidative stress marker) and CD68 immunoreactivity (inflammatory marker) in the substantia nigra. Interestingly, activation of the Nrf2 ARE signaling pathway by oral

administration of a novel non-electrophilic Bach1 inhibitor at 10mg/kg showed good penetration in the brain that significantly blocked against MPTP neurotoxicity without affecting the MPP+ levels. Thus taken together, our results suggests that Bach1 inhibition is a very effective target against dopaminergic neurodegeneration by virtue of its ability to activate neuroprotective Nrf2/ARE genetic program. Hence, we validate, for the first time, Bach1 as a novel therapeutic target for PD.

Disclosures: **M. Ahuja:** None. **N. Ammal Kaidery:** None. **J. Morgan:** None. **K. Igarashi:** None. **O.C. Attucks:** A. Employment/Salary (full or part-time): vTv Therapeutics LLC. **B. Thomas:** None.

Poster

787. Parkinson's Neuroprotection II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 787.22/I10

Topic: C.03. Parkinson's Disease

Title: Simvastatin-loaded PEG-PLA polymersomes confers neuroprotection through inhibition of inflammation in parkinson's disease.

Authors: *D. MANICKAVASAGAM[1,2], K. NOVAK[2], J. R. RICHARDSON[2], M. O. OYEWUMI[2,1];
[1]Biomed. Sci. - Neurosciences, Kent State Univ., Kent, OH; [2]Pharmaceut. Sci., Northeast Ohio Med. university, Rootstown, OH

Abstract: Simvastatin, a cholesterol lowering drug has recently been studied in neurodegenerative conditions due to its potential protective properties. Despite being an attractive drug both for immune and survival mediated responses in glial and neuronal cells, the efficiency of simvastatin is hindered by its poor water solubility, low permeability and adverse side effects. In this regard, the objective of the present work is to develop a polymersome delivery system using PEG: PLA (methoxy polyethylene glycol: poly (D,L) lactic acid) diblock copolymer to improve simvastatin's delivery, solubility, bioavailability and assess their suitability as a neuroprotective agent in Parkinson's disease. Simvastatin-loaded polymersomes were prepared using a modified nanoprecipitation method at concentrations 5, 10 and 20 µg/mL. The preparation resulted in polymersomes of approximately 200 nm in size with a narrow size distribution. The resulting polymersomes also exhibited high drug entrapment efficiency of >97%. In addition, both blank and simvastatin-loaded polymersomes remained stable when stored as aqueous suspensions for up to 30 days after preparation with no evidence of agglomeration or pH change in dissolving medium. The *in-vitro* biocompatibility study

conducted using macrophage cell line did not show any signs of toxicity at all treated concentrations (0, 25, 50, 75 and 100 µg/ml). In cultured BV-2 microglia challenged with hydrogen peroxide or LPS, we observed that simvastatin-loaded polymersomes was superior to simvastatin alone in protecting cell death at drug concentrations ranging from 1-100 ng/mL. Additional mechanistic studies are being conducted in neuronal PC12 cells with the aim of delineating the basis of neuroprotective effects of simvastatin-loaded polymersomes. These results suggest that therapeutic efficacy of simvastatin-loaded polymersomes can be used as a strategy for attenuating inflammation which may be relevant in stopping the degeneration of dopaminergic neurons in Parkinson's disease.

Disclosures: D. Manickavasagam: None. **K. Novak:** None. **J.R. Richardson:** None. **M.O. Oyewumi:** None.

Poster

787. Parkinson's Neuroprotection II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 787.23/I11

Topic: C.03. Parkinson's Disease

Support: IRSC MOP-82692

Title: Inhibition of the enzyme 5alpha-reductase by dutasteride induces neuroprotection of dopaminergic neurons of male mice when administered before but not after MPTP

Authors: *N. LITIM[1,2], M. MORISSETTE[1], D. CARUSO[3], R. MELCANGI[3], T. DI PAOLO[1,2]; [1]Neurosci. Res. Unit, CHU De Quebec, Quebec, QC, Canada; [2]Laval University, Fac. of Pharm., Quebec City, QC, Canada; [3]Dept. of Pharmacol. and Biomolecular Sciences, Ctr. of Excellence on Neurodegenerative D, Univ. degli Studi di Milano, Milan, Italy

Abstract: Dutasteride and finasteride are inhibitors of the enzyme 5alpha-reductase used in humans to treat various endocrine conditions. We recently reported that dutasteride but not finasteride exhibited neuroprotective activity in the mouse model of Parkinson's disease (PD) intoxicated with 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP). The present study further investigated the neuroprotective effects of dutasteride in intact as well as MPTP-lesioned mice. C57Bl6 male mice were treated with dutasteride (5 or 12.5 mg/kg) once daily for 10 days. Mice received 4 injections of MPTP (5.5 mg/kg) or saline on the 5th day. Analysis of the motor behavior of these mice showed that treatment with MPTP or MPTP + dutasteride did not affect their motor performance as planned using a low dose of MPTP to induce a moderate lesion modeling early stages of the disease. In these mice dutasteride prevented the depletion of striatal

DA as well as its metabolite DOPAC measured by HPLC while serotonin concentrations remained unchanged. DA and its metabolite levels were unchanged by dutasteride treatment in intact mice. Autoradiography of striatal dopamine transporter (DAT) and vesicular monoamine transporter 2 (VMAT2) specific binding showed that treatment with dutasteride decreased the effect of the toxin while it enhanced DAT specific binding in intact mice. MPTP-treated mice had levels of plasma and brain dihydrotestosterone (DHT) significantly lower than control mice. Dutasteride treatment elevated plasma and brain concentrations of testosterone when compared to control and MPTP mice while as expected from an inhibitor of the enzyme 5alpha-reductase decreased the levels of DHT. The plasma and brain levels of 17beta-estradiol remained low at/or under detection levels in the controls and treated mice of all experimental groups. Striatal glial fibrillary acidic protein (GFAP) levels measured by Western blots were found to be markedly elevated in MPTP mice compared to control mice and dutasteride at both doses significantly reduced the GFAP protein levels in MPTP mice supporting the hypothesis of an anti-inflammatory effect of dutasteride. Taken together these results suggest that dutasteride exhibited neuroprotective effects on DA neurons. A second experiment investigated dutasteride administered for 5 days starting 1 hour after MPTP administration. Analysis of DA contents showed that there was no significant change in the DA levels and metabolism in the striatum of mice post-treated with dutasteride compared with MPTP-lesioned mice. The above results propose dutasteride as promising therapeutic molecule for PD neuroprotection.

Disclosures: **N. Litim:** None. **M. Morissette:** None. **D. Caruso:** None. **R. Melcangi:** None. **T. Di Paolo:** None.

Poster

787. Parkinson's Neuroprotection II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 787.24/I12

Topic: C.03. Parkinson’s Disease

Support: Research Grants Council of Hong Kong

Title: A study on the relationship of pick1 and parkin

Authors: ***J. HE**[1], P. K. YEUNG[2], K. K. CHUNG[1], S. K. CHUNG[2], J. XIA[1];
[1]Life Sci. division, The Hong Kong Univ. of Sci. and Technol., Hong Kong, Hong Kong; [2]Li Ka Shing Fac. of Med., The Univ. of Hong Kong, Hong Kong, Hong Kong

Abstract: Parkinson’s disease (PD) is a prevalent neurodegenerative disease, clinically characterized by resting tremor, rigidity, bradykinesia, and postural instability. Degeneration of

dopaminergic neurons in substantia nigra pars compacta and presence of Lewy bodies are the two pathologic hallmarks of PD. PD is primarily a sporadic disease, but 5-10% of PD cases are inherited. Loss-of-function mutations in Parkin are associated with familial PD, especially early-onset PD. Parkin is an E3 ligase, which preserves cell functions against various toxic paradigms. Parkin binds to PICK1 (protein interacting with C-kinase 1), which is a peripheral membrane protein important for protein trafficking. PICK1 regulates the trafficking of receptors, channels, and transporters in neurons and other types of cells. PICK1 is also involved in proacrosomal vesicle trafficking during spermiogenesis in testes, insulin granule trafficking in pancreatic beta-cells, and growth hormone secretion in brain. Here we demonstrate that PICK1 is a potential inhibitor of Parkin. PICK1 compromised Parkin-mediated prevention of cell death and mitophagy in neurons. Our data suggested that reducing PICK1 could reduce neuronal death by enhancing the protective effect of Parkin.

Disclosures: J. He: None. **P.K. Yeung:** None. **K.K. Chung:** None. **S.K. Chung:** None. **J. Xia:** None.

Poster

787. Parkinson's Neuroprotection II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 787.25/J1

Topic: C.03. Parkinson’s Disease

Support: Austrian Science Fund F4402

Austrian Science Fund P27809

Austrian Science Fund W1101-B12

DFG LI 1754/1

Title: Splice-variant and isoform-dependent isradipine-inhibition of recombinant L-type Ca^{2+} currents evoked by substantia nigra dopamine neuron-like activity patterns

Authors: *N. J. ORTNER[1], G. BOCK[1], A. DOUGALIS[2], M. KHARITONOVA[1], J. DUDA[2], P. TULUC[1], T. POMBERGER[1], N. STEFANOVA[3], F. PITTERL[4], T. CIOSSEK[5], H. OBERACHER[4], H. J. DRAHEIM[5], B. LISS[2], J. STRIESSNIG[1];
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Abstract: Inhibition of brain L-type Ca^{2+} channel (LTCC) subtypes, in particular Cav1.3, by the dihydropyridine isradipine (ISR), is currently tested in a phase 3 clinical trial (NCT02168842) for neuroprotection in Parkinson's disease (PD) to prevent loss of *Substantia nigra* dopamine (SN DA) neurons.
We found that neither knockout of Cav1.3 nor in vivo pretreatment with therapeutic plasma levels of ISR was neuroprotective in a 6-OHDA PD mouse model. Compensatory upregulation of other voltage-gated Ca^{2+} channels may explain this finding in knockouts (Poetschke *et al.*, 2015). Instead, the absence of ISR neuroprotection could be due to weaker voltage-dependent inhibition of LTCCs in SN DA neurons compared to arterial smooth muscle (aSM) Cav1.2 channels, responsible for dose-limiting hypotensive effects in humans.
We confirmed robust transcript expression of both Cav1.3 variants and of Cav1.2 in micro-dissected mouse SN DA neurons, and established HEK293 cell lines stably expressing human long ($hCav1.3_L$) or short ($hCav1.3_S$) Cav1.3 splice variants or hCav1.2 (+β3, α2δ1). I_{Ca} characteristics and ISR sensitivity were quantified using whole-cell patch-clamp recordings during command voltages corresponding to SN DA- and aSM-like activity patterns. During sustained SN DA-like pacemaking (2.5 Hz) only 15–24 % of maximal LTCC current remained and only Cav1.3 splice variants conducted currents during the interspike interval. During a simulated 3-spike burst, integrated I_{Ca} increased significantly ($hCav1.3_S$: 2.0-fold, $hCav1.3_L$: 1.8-fold, hCav1.2: 2.9-fold). Integrated I_{Ca} of Cav1.3 isoforms but not of Cav1.2 was 1.5-fold higher during the first spike that followed the post-burst afterhyperpolarization (1.5 s). ISR sensitivity of Cav1.3 currents evoked by SN DA-like activity was splice variant-specific (IC_{50} $hCav1.3_L$: 7.7 (6.3-9.6) nM; $hCav1.3_S$: 17.0 (13.8-20.9) nM; mean (95% CI)) and significantly lower than those of hCav1.2 (3.1 (2.3-4.3) nM, n≥23). ISR inhibited hCav1.2 currents, evoked by aSM-like activity at 2-fold lower concentrations (IC_{50}=1.6 (1.3-1.9) nM, n=31).
We show that LTCC Ca^{2+} load increases significantly during and after SN DA-like bursts. The absence of neuroprotective effects of ISR can be explained by its weaker state-dependent inhibition of LTCCs in SN DA neurons as compared to aSM Cav1.2 channels. Cav1.3 channels which are considered the main target for ISR-mediated neuroprotection require 5-10-fold higher ISR concentrations for inhibition than aSM Cav1.2. Our data predict that only supratherapeutic doses of ISR, unlikely to be tolerated during long term treatment, could mediate Cav1.3-mediated neuroprotection in PD.

Disclosures: **N.J. Ortner:** None. **G. Bock:** None. **A. Dougalis:** None. **M. Kharitonova:** None. **J. Duda:** None. **P. Tuluc:** None. **T. Pomberger:** None. **N. Stefanova:** None. **F. Pitterl:** None. **T. Ciossek:** A. Employment/Salary (full or part-time): Boehringer Ingelheim Pharma GmbH & Co KG. **H. Oberacher:** None. **H.J. Draheim:** A. Employment/Salary (full or part-time): Boehringer Ingelheim Pharma GmbH & Co KG. **B. Liss:** None. **J. Striessnig:** None.

Poster

788. Immune Responses and Glial Functions in Neurodegenerative Disease

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 788.01/J2

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH Grant R41AG044897

The Saban Family Foundation

The Marciano Family Foundation

Title: Local inflammation associated with amyloid-beta deposition in postmortem retinas of AD and MCI patients

Authors: *Y. KORONYO[1], D.-T. FUCHS[1], E. BARRON[2], J. SHEYN[1], A. RENTSENDORJ[1], N. J. HART[1], C. A. MILLER[3], D. R. HINTON[2], K. L. BLACK[1], M. KORONYO-HAMAOUI[1,4]; [1]NeuroSurgery Dept., Cedar-Sinai Med. Ctr., Los Angeles, CA; [2]The Doheny Eye Institute, Pathology, Neurosurgery, Ophthalmology, [3]Dept. of Pathology and Neurol., Keck Sch. of Medicine, Univ. of Southern California, Los Angeles, CA; [4]Dept. of Biomed. Sci., Cedars-Sinai Med. Ctr., Los Angeles, CA

Abstract: Background Until recently Alzheimer's disease (AD) was assumed to present only in the brain. We have shown that amyloid-β protein (Aβ) plaques, a pathological hallmark of AD, exist in postmortem retinas of AD patients and form at early stages. Subsequent studies have found the characteristic brain pathology pTau, Aβ-like deposits, and $A\beta_{42}$ peptide accumulation, in postmortem AD retinas. Furthermore, studies have shown nerve fiber layer thinning in live AD patients, retinal ganglion cell (RGC) degeneration in postmortem AD retinas, and most recently, a link between melanopsin-RGC degeneration and retinal Aβ accumulation. We hypothesize that retinal cell degeneration and Aβ plaques in AD patients similar to those observed in the brain will be accompanied by a surrounding inflammatory response.
Methods We studied postmortem retinal and brain Aβ plaques from the same AD patients. The geographical distribution, layer location, and ultrastructure morphology of Aβ deposits were analyzed using retina whole mounts and cross sections from neuro-pathologically confirmed MCI, AD patients, and age-matched controls. Retinas were examined for the phenotype of resident and infiltrating immune cells as well as astrocytes. The overall amount and morphological changes in RGCs were also studied.
Results In MCI and AD patients, retinal Aβ deposits manifested in distinct layers, mostly in the peripheral regions of the superior quadrant. They presented as extracellular and intracellular accumulation, and often associated with blood vessels. We identified a variety of retinal Aβ deposits and used electron microscopy to analyze their ultrastructure. These Aβ deposits were

associated with surrounding inflammation, including activated microglia as well as infiltrating lymphocytes and monocytes. The microglia, engulfing Aβ aggregates, exhibit a full-blown phagocytic amoeboid phenotype. Age-matched controls showed scarce retinal Aβ deposition with no inflammation. Moreover, we detected marked reactive astrocytosis in the vicinity of Aβ in the RGC layer. These changes along with degeneration of RGCs were detected in AD and at early-disease stages.
Conclusions We demonstrates accumulation of Aβ in AD and MCI retinas, abundant in certain retinal layers and geometric regions. Retinal Aβ deposition is associated with activated microglia, reactive astrocytes, infiltrating immune cells, and specific cell loss. Since the retinal pathologies observed in AD and MCI patients mimic those seen in the brain, the retina, which can be imaged noninvasively and repeatedly at high-resolution, may be targeted to assess disease progression and monitor response to therapies.

Disclosures: **Y. Koronyo:** None. **D. Fuchs:** None. **E. Barron:** None. **J. Sheyn:** None. **A. Rentsendorj:** None. **N.J. Hart:** None. **C.A. Miller:** None. **D.R. Hinton:** None. **K.L. Black:** None. **M. Koronyo-Hamaoui:** None.

Poster

788. Immune Responses and Glial Functions in Neurodegenerative Disease

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 788.02/J3

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: the Research Grants Council of Hong Kong SAR (C6003-14G)

the National Basic Research Program of China (973 program; 2013CB530900)

Hong Kong Research Grants Council Theme-based Research Scheme (T13-607/12R)

the Innovation and Technology Fund for State Key Laboratory (ITCPT/17-9)

the Shenzhen Peacock Plan

the SH Ho Foundation

Title: IL-33 modulates the inflammatory response in the brains of alzheimer’s disease mouse model

Authors: ***W.-Y. FU**[1,2,3], A. K. FU[1,2,3], K.-W. HUNG[1,2,3], M. Y. YUEN[1,2,3], X. ZHOU[1,2,3], D. S. MAK[1,2,3], I. C. CHAN[1,2,3], F. Y. LIEW[4,5], T. H. CHEUNG[1,2,3], N. Y. IP[1,2,3];

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Abstract: Dysfunction of the innate immune system is believed to play a significant role in the pathogenesis of Alzheimer's disease (AD). However, the pathophysiological mechanisms underlying these dysfunctions are unclear. Microglia is the major effector and regulator for coordination of the immune response in the central nervous system. Studies using transgenic AD mouse models suggest that impairment of microglial function contributes to AD pathological progression and disease severity. Our laboratory previously reported that interleukin (IL)-33 ameliorates the amyloid pathology, suggesting a potential therapeutic role for this interleukin in AD. Here, we show that the attenuation of β-amyloid (Aβ) accumulation in APP/PS1 mice (transgenic mice with AD-like pathologies) by IL-33 is accompanied with the modulation of innate immune response in the brain. IL-33 skews microglia and macrophages towards an alternative activation state with enhanced Aβ phagocytic capacity and elevated anti-inflammatory gene expression such as Fizz-1 and Arg1. Furthermore, IL-33 administration significantly suppressed the increased gene expression of pro-inflammatory proteins such as IL-1β, IL-6, and NLRP3 in the cerebral cortex of APP/PS1 mice. Collectively, IL-33 modulates the inflammatory responses in the brain to ameliorate the AD-like disease pathogenesis of APP/PS1 mice. These results suggest a potential therapeutic role of IL-33 in AD.

Disclosures: W. Fu: None. **A.K. Fu:** None. **K. Hung:** None. **M.Y. Yuen:** None. **X. Zhou:** None. **D.S. Mak:** None. **I.C. Chan:** None. **F.Y. Liew:** None. **T.H. Cheung:** None. **N.Y. Ip:** None.

Poster

788. Immune Responses and Glial Functions in Neurodegenerative Disease

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 788.03/J4

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: the Research Grants Council of Hong Kong SAR (C6003-14G)

the National Basic Research Program of China (973 program; 2013CB530900)

the Hong Kong Research Grants Council Theme-based Research Scheme (T13-607/12R)

the Innovation and Technology Fund for State Key Laboratory (ITCPT/17-9)

the Shenzhen Knowledge Innovation Program (JCYJ20151030154629774)

the Shenzhen Peacock Plan

the SH Ho Foundation

Title: IL-33 ameliorates Alzheimer's disease-like pathology and cognitive decline

Authors: ***A.-Y. FU**[1,2,3,4], K.-W. HUNG[1,2,3,4], M. Y. YUEN[1,2,3], X. ZHOU[1,2,3,4], D. S. MAK[1,2,3], I. C. CHAN[1,2,3], T. H. CHEUNG[1,2,3], B. ZHANG[5], W.-Y. FU[1,2,3,4], F. Y. LIEW[6,7], N. Y. IP[1,2,3,4]; [1]Div. of Life Sci., [2]Mol. Neurosci. Ctr., [3]State Key Lab. of Mol. Neurosci., The Hong Kong Univ. of Sci. and Technol., Hong Kong, China; [4]Guangdong Key Lab. of Brain Science, Dis. and Drug Develop., HKUST Shenzhen Res. Inst., Shenzhen, China; [5]Dept. of Neurol., Zhejiang Univ., Hangzhou, China; [6]Inst. of Infection, Immunity and Inflammation, Col. of Medical, Vet. and Life Sci., Univ. of Glasgow, Glasgow, United Kingdom; [7]Sch. of Biol. and Basic Med. Sci., Soochow Univ., Suzhou, China

Abstract: Alzheimer's disease (AD) is a devastating and currently incurable neurological condition characterized by cognitive decline as well as impaired locomotor ability, reasoning, and judgment. The accumulation of β-amyloid (Aβ) in the brain is believed to be a major cause of the synaptic and neuronal dysfunction, microglial activation, and neuronal loss in AD. Emerging evidence suggests that the innate immune response plays a major role in the pathogenesis of AD. Here, we show that interleukin (IL)-33, a crucial mediator of the innate immune response, contributes to the pathogenesis of AD. Serum levels of soluble ST2 (sST2), a decoy receptor of IL-33, were elevated in patients with mild cognitive impairment. Moreover, administration of IL-33 reversed hippocampal synaptic plasticity impairment and cognitive deficits in APP/PS1 mice, a mouse model with AD-like pathologies. Furthermore, IL-33 administration exerted a beneficial effect on the pathological conditions of AD by reducing soluble Aβ levels and amyloid plaque deposition in these mice. The results collectively demonstrate that the deregulation of IL-33/ST2 signaling contributes to the pathogenesis of AD.

Disclosures: **A. Fu:** None. **K. Hung:** None. **M.Y. Yuen:** None. **X. Zhou:** None. **D.S. Mak:** None. **I.C. Chan:** None. **T.H. Cheung:** None. **B. Zhang:** None. **W. Fu:** None. **F.Y. Liew:** None. **N.Y. Ip:** None.

Poster

788. Immune Responses and Glial Functions in Neurodegenerative Disease

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 788.04/J5

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: Multipark

Title: The role of extracellular vesicles in the neuroinflammation in Alzheimer's disease

Authors: *Y. YANG;
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Abstract: Microglia are the immune cells in the central nervous system (CNS) and have an important function in brain pathologies. Under neurodegenerative conditions, activated microglia is a typical feature in the neuroinflammatory processes. Inflammatory activated microglia leads to neuronal dysfunction, and accelerates progression of neurodegenerative diseases, such as Alzheimer's disease (AD). AD is the most common cause of dementia and is characterized by amyloid plaques and neurofibrillary tangles (NFT) formation. Previous research has implicated both beneficial and detrimental roles of microglia in plaque degradation related to the neuropathology. A better understanding of the interaction between microglia and other cells in the brain will be crucial to eliminate detrimental effects of immune response as a strategy to intervene the progression of the disease.
Extracellular vesicles (EVs) are considered as one of the main participants in cell-cell interaction as well as post-modification of extracellularly neuropathogenical protein, for example beta-amyloid (Aß) and tau. They are able to carry pathogen-associated and damage-associated molecular patterns, cytokines, enzymes and nucleic acids. According to size, origin and functions, EVs are classified into different groups. We are specifically interested in exosomes (50-200nm) and microvesicles (100-1000nm). EVs are likely involved in propagation of inflammatory signals and act as mediators in the regulation of cell-cell communication.
In this study, we will investigate the dynamics of EVs released from microglia under inflammatory conditions. A murine microglia cell line, BV2, will be treated with lipopolysaccharide (LPS) to obtain fully activated microglial features, which could be verified with inducible nitric oxide synthase (iNOS) expression in the cells by western blot. EVs are collected from conditional medium by sequential ultracentrifugation. The size distribution of EVs will be assessed with Nanosight as well. The origins of EVs will be indicated by western blot using plasma membrane marker and endosomal marker, flotillin-1 and Alix, respectively. Importantly, inflammatory cytokines from EVs, pre-and post-ultracentrifugation conditional medium will be measured by multiplex ELISA. In order to understand potential roles of EVs in AD pathogenesis, EVs will be harvested from BV2 triggered with recombinant Aß.

We found size changes in the EVs upon Aß stimulus and presence of inflammatory markers, galectin3 and NLRP3, in LPS-EVs. These findings will shed light on the important roles of EVs for the neuroinflammation and pathogenesis of AD.

Disclosures: Y. Yang: None.

Poster

788. Immune Responses and Glial Functions in Neurodegenerative Disease

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 788.05/J6

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH Grant AG08487

NIH Grant P50-AG05134

NINDS Grant R25

Title: Glial responses in the cerebral cortex of Lewy body diseases

Authors: *A. SERRANO-POZO[1], G. ALDRIDGE[1], Q. ZHANG[1], M. P. FROSCH[2], N. NARAYANAN[1], B. T. HYMAN[2];
[1]Dept. of Neurol. of the Univ. of Iowa, Iowa City, IA; [2]Massachusetts Gen. Hosp., Boston, MA

Abstract: Background: Diffuse cortical Lewy bodies are a pathological signature of Parkinson disease dementia (PDD) and dementia with Lewy bodies (DLB). However, there is considerable pathological overlap with pathological features of Alzheimer's disease (AD), especially amyloid plaques and, to a lesser extent, neurofibrillary tangles (NFTs). We have previously shown that glial responses - reactive astrocytes and activated microglia - associate not only with amyloid plaques but also with NFTs in AD. Here we focused on Lewy body diseases and hypothesized that glial responses in these disorders associate with the concurrent AD neuropathological changes rather than with alpha-synuclein aggregates (Lewy bodies and neurites). **Methods:** We conducted a quantitative neuropathological study in a cohort of consecutive patients who had an *antemortem* clinical diagnosis of PD, PDD, or DLB, and donated their brain to the Massachusetts General Hospital Alzheimer Disease Research Center Brain Bank. We applied peroxidase-DAB immunohistochemistry and measured the load of alpha-synuclein (LB509-immunoreactive), amyloid-beta (10D5 or 6F/3D-immunoreactive), and phospho-tau (PHF1-immunoreactive) pathology in paraffin-embedded sections from the frontal association cortex (BA8,9). We conducted an unbiased stereology-based quantitation of reactive astrocytes (GFAP-immunoreactive) and activated microglia (CD68 or MHC2-immunoreactive). We also performed

double fluorescence immunohistochemistry in selected cases. **Results:** Median (interquartile range) pathological burden was 0.0045% (0.001-0.017) for aggregated alpha-synuclein (LB509+ Lewy bodies and neurites); 0.02% (0.004-0.069) for hyperphosphorylated tau (PHF1+ NFTs, neuropil threads, and plaque-associated dystrophic neurites), and 0.96% (0.21-1.44) for amyloid beta (10D5+ or 6F/3D+ amyloid deposits). We performed correlations between the number of reactive astrocytes and activated microglia and the load of Lewy bodies/neurites, amyloid deposits, and tau pathology. Double fluorescence immunohistochemistry in selected cases enabled the study of the spatial relationships between reactive glia and these pathological protein deposits. **Discussion:** These results could have important implications in the pathophysiology of alpha-synucleinopathies.

Disclosures: A. Serrano-Pozo: None. **G. Aldridge:** None. **Q. Zhang:** None. **M.P. Frosch:** None. **N. Narayanan:** None. **B.T. Hyman:** None.

Poster

788. Immune Responses and Glial Functions in Neurodegenerative Disease

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 788.06/J7

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: Joseph Drown Foundation

Maxine Dunitz Neurosurgical Institute

Title: Aberrant T cells enter brain and induce Alzheimer’s-like neurodegeneration

Authors: *C. J. WHEELER;
Neurosurg., Cedars-Sinai Med. Ctr., Los Angeles, CA

Abstract: Sporadic Alzheimer’s disease (AD) is characterized by progressive neurodegeneration with amyloid-beta (Aβ) plaque and neurofibrillary deposits in brain. Rare familial AD is guaranteed by gene mutations that increase Aβ deposition, but aging is the only known cause of sporadic AD. Immune processes such as neuroinflammation contribute to AD pathophysiology, but whether human-specific features of immune aging do so remains unknown. We induced human-like age-related changes in CD8 T cells by homeostatic expansion in nude mice. The resulting homeostatically-induced CD8 T cells (“hiT cells”) precipitated human-specific features of AD not seen in current animal models, including neurodegeneration and neurofibrillary deposition. Neurodegeneration, but not proteinopathy, was dependent on both lytic (Perforin1) and proinflammatory (IFNγ) T effector functions. Transfer of hiT cells into wild-type mice

decreased neuronal metrics even more quickly, and synergized with brain injury to confer human-specific amyloidosis. Gene expression, effector protein, and immune receptor specificity associated with hiT cells in mice were all significantly elevated in AD brain. These findings introduce a pre-clinical model of AD-like neurodegeneration uniquely based on age-associated physiology. Further dissection of this model should increase our understanding of sporadic AD pathophysiology, identify novel targets for disease intervention, and elucidate physiological mechanisms of age-related tissue destruction.

Disclosures: C.J. Wheeler: Other; author of provisional patent application titled, 'NOVEL BLOOD CELL BIOMARKER FOR LATE ONSET ALZHEIMER'S DISEASE'. This application was assigned U.S. Serial No. 62/212,070..

Poster

788. Immune Responses and Glial Functions in Neurodegenerative Disease

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 788.07/J8

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: KAKENHI

Title: Microglial SOCS3 prevents IL6 production in Alzheimer's disease model mice

Authors: *N. IWAHARA;
Sapporo Med. Univ., Hokkaido, Japan

Abstract: [Objective] Inflammatory responses to Aβ increase expression of cytokines and production of reactive oxygen species (ROS) along with activation of microglia (MG). Suppressor of cytokine signaling (SOCS) family is a key regulator of JAK/STAT pathways, and SOCS3 is reported to regulate inflammatory processes. Recently, Waller D.G. et al. reported that SOCS3 expression was increased in brain of Alzheimer's disease (AD) patients. Here, we show that *SOCS3* expression was induced in AD model mice and SOCS3 prevented IL6 production of Aβ stimulated primary cultured microglia (pMG). [Methods] 3-18 month-old APPswe/PS1dE9 transgenic (APdE9) mice were used in this study. pMG were isolated from one brain hemisphere of APdE9 mice. pMG were treated with control or *SOCS3* specific siRNA then stimulated by oligomeric Aβ (oAβ) for 6h. Gene expression of *SOCS3* and pro-inflammatory cytokines (*TNFα, IL1β, IL6*) were measured by qRT-PCR. [Results] *SOCS3* mRNA expression level of MG derived from APdEd9 mice were increased in 9 months of age. Compared to up-regulation of *TNFα* and *IL1β* gene expression coinciding with *SOCS3*, induction of *IL6* was not significant. Up-regulation of *IL6* was observed only with knocking down of *SOCS3* expression in pMG.

[Conclusions] Increase of *SOCS3* and pro-inflammatory cytokines such as *TNFα* and *IL1β* were observed in APdE9 mice. However, induction of *IL6* was not observed in APdE9 mice, and gene expression of IL6 was suppressed by SOCS3 in pMG. Microglial SOCS3 might restrain the progress of AD through the suppression of IL6 production.

Disclosures: **N. Iwahara:** A. Employment/Salary (full or part-time): part-time. B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution; KAKENHI.

Poster

788. Immune Responses and Glial Functions in Neurodegenerative Disease

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 788.08/J9

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIA PO1AG14449

RO1AG043375

P30AG010161

Title: TREM2 levels are preserved in the Frontal Cortex and Hippocampus in prodromal Alzheimer's disease

Authors: ***M. NADEEM**[1], S. PEREZ[2], B. HE[3], J. C. MIGUEL[4], M. M. AHMADI[7], L. MAHADY[5], E. MUFSON[6];
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Abstract: Loss of function of the mutations encoding for the triggering receptor expressed on myeloid cells 2 (TREM2), a transmembrane glycoprotein expressed selectively on the cell surface of microglia and macrophages, is associated with increased risk of Alzheimer's disease (AD). Studies in cases carrying TREM2 variants showed that altered TREM2 levels translate to functional and morphological dysfunction of the microglia and phagocytosis that may lead to accelerated plaque and neurofibrillary tangle formation. Recently, it has been shown that TREM2 levels are also altered in brains of sporadic AD, suggesting a role for TREM2 in the pathogenesis of AD. However, whether TREM2 levels are altered in prodromal AD is unknown. In this study, TREM2 levels were measured in the frontal cortex (n=49) and hippocampus (n=46) of people who died with an ante-mortem clinical diagnosis of non-cognitive impairment (n=18,

mini-mental state examination score (MMSE) ≥ 28), mild cognitive impairment (n=18, MMSE ≥ 27), mild AD (n=16, MMSE ≥ 20) from the Rush Religious Orders Study and severe AD (n=13, MMSE < 15) from the Rush Brain Bank using quantitative immunoblotting. Our findings revealed that TREM2 levels in the frontal cortex were significantly increased in severe AD compared to NCI, MCI and mild AD ($p = 0.002$), while hippocampal TREM2 levels were unchanged across the clinical groups examined. Interestingly, cortical TREM2 levels were significantly higher compared to hippocampus in each of the clinical groups examined ($p < 0.05$). In addition, there was no association between cortical and hippocampal TREM2 levels across clinical groups or with Aβ load, neuritic and diffuse plaques neuropathological criteria (CERAD, NIA-Reagan and Braak stage) or cognitive test scores (episodic memory and global cognitive score) during AD progression These findings indicate that TREM2 levels within the frontal cortex and hippocampus are not dysregulated during the early stages of AD

Disclosures: **M. Nadeem:** None. **S. Perez:** None. **B. He:** None. **J.C. Miguel:** None. **M.M. Ahmadi:** None. **L. Mahady:** None. **E. Mufson:** None.

Poster

788. Immune Responses and Glial Functions in Neurodegenerative Disease

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 788.09/J10

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: Fapesp

CNPq

Title: Effect of granulocyte and macrophages colonie stimulating factor (GM-CSF) in the hippocampus of transgenic animals for Alzheimer's disease

Authors: *D. S. PAIVA, Y. L. GIULIO, S. A. A. ROMARIZ, P. M. MARTIM, M. L. QUINTELLA, S. W. HAN, B. O. MONTEIRO;
Unifesp, São Paulo, Brazil

Abstract: Progressive cognitive impairment and emotional disorders are the major characteristics of Alzheimer´s disease (AD). Neuropathological signs of AD are mainly described as amyloid-β protein (Aβ) deposit forming Aβ plaques, neurofibrillary tangles and disseminated state of inflammation in the CNS. *The Granulocyte-Macrophage Colony-Stimulating Factor* (GM-CSF) is a hematopoietic cytokine that stimulates bone marrow stem cells and neural progenitors, but has showed ambiguous activities upon inflammation. Here, we

questioned whether the hippocampal transduction with a lentiviral vector expressing GM-CSF could reduce inflammation, amyloid plaques and ameliorate cognitive deficits. Double transgenic male adult mice with APPswe/PS1dE9 mutation between 4-5months old were used as Alzheimer's disease model, and the respective wild type mice (WT) used as controls forming the following groups: AD; AD-GM-CSF; WT; WT-GM-CSF. Saline or lentivector carrying GM-CSF gene were infused into the hippocampus at 5 months of age. After 2 months from recovery, animals were subjected to the Open Field (OF) and Morris Water Maze (MWM) tests for exploratory behaviour and learning and memory evaluation. After the last day of the MWM, animals were euthanasied for quantification by ELISA or perfused for brain histology. The slices were processed for immunohistochemistry to stain amyloid plaques and microglia in the hippocampus. There was an increase in the expression of GM-CSF in the CNS of GM-CSF transduced animals ($p< 0.05$). The GM-CSF was detected by immunohistochemistry for GFP that was highly expressed in the hippocampusof AD-GM-CSF mice. Also, GM-CSF increased the number of microglial cells and reduced the quantity of Aβ plaques in the hippocampus,when compared with non-infected AD ($p< 0.05$). No improvement in learning and memory was observed in Morris Water Maze test of GM-CSF transduced AD animals compared with AD non-transduced mice, although the AD-GM-CSF group improved the exploratory behavior in OF ($p< 0.05$). We suggest that, despite not having important behavioral changes, GM-CSF overexpression in the hippocampus of AD mice modified the pattern ofinflammatory response,which have a direct effectin amyloid plaques involved in Alzheimer´s disease.

Disclosures: D.S. Paiva: None. **Y.L. Giulio:** None. **S.A.A. Romariz:** None. **P.M. Martim:** None. **M.L. Quintella:** None. **S.W. Han:** None. **B.O. Monteiro:** None.

Poster

788. Immune Responses and Glial Functions in Neurodegenerative Disease

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 788.10/J11

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: ISAO

Alzheimer Nederland

Title: Amyloid pathology and microglial cells are affected life-long after stress exposure in early-life.

Authors: *L. HOEIJMAKERS[1], A. AMELIANCHIK[1], D. IVAN[1], A.-M. VAN DAM[2], P. J. LUCASSEN[1], A. KOROSI[1];

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Abstract: Alzheimer's disease (AD) is characterized by accelerated cognitive decline, neuroinflammation and abundant neuropathology. The risk to develop AD is, next to genetic causes, modified by environmental factors that might affect the onset and gravity of AD symptoms. Early-life stress (ES) exposure is hypothesized to be a modulator of AD development. However this hypothesis has not yet been tested. Interestingly stress in adulthood is well known to modulate the neuroimmune system. We here tested whether exposure to ES 1) aggravates amyloid (Aβ) pathology and if 2) ES primes neuroimmune functions (i.e. microglia) in wildtype (WT) mice 3) as well as in an AD transgenic mouse model to test if such priming might mediate ES-induced alterations in amyloid pathology. 4) Finally we tested in vitro whether glucocorticoids are the key element in the priming of microglial cells.
We used WT and APPswe/PS1dE9 overexpressing mice. The APP/PS1 transgenic mouse line exhibits Aβ plaque accumulation from ±4 months onwards and cognitive impairments after 6 months. Both WT and APP/PS1 mice were subjected to a chronic ES mouse model consisting of exposing dams to limited nesting/bedding material from postnatal day (P)2-P9, that results in cognitive impairments in 4 month old WT mice. Thus to test for ES-induced acceleration and/or aggravation of AD hallmarks, including cognitive functioning, Aβ load and microglial activity were studied at ages 3 to 4 months and 8 to 10 months. To further explore the role of glucocorticoids in the ES-induced priming of microglia we exposed primary glia cultures to ex vivo lipopolysaccharide following dexamethasone.
Although ES exposure did not accelerate or aggravate cognitive decline in APP/PS1, ES affected Aβ load in an age dependent manner. ES exposed APP/PS1 showed less cell-associated amyloid at 4 months, but elevated Aβ plaque load at 10 months. In addition to this pathological change, ES increased microglial CD68 expression in WT. This increase was further exacerbated under APP/PS1 overexpression in the hippocampus at 4 months, indicating possible increased phagocytic activity. Further characterization of microglial activity and the inflammatory profile following ES and/or APP/PS1 overexpression is currently ongoing.
Our results so far suggest that ES exposure modulates microglial functioning in adulthood both in WT and under pathological conditions, with possible implications for the progression of AD related neuropathology. Insights into the effects of ES on neuroimmune functions and AD pathology may not only lead to new mechanistic insights but also to the identification of vulnerable populations for neurodegenerative diseases.

Disclosures: L. Hoeijmakers: None. **A. Amelianchik:** None. **D. Ivan:** None. **A. van Dam:** None. **P.J. Lucassen:** None. **A. Korosi:** None.

Poster

788. Immune Responses and Glial Functions in Neurodegenerative Disease

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 788.11/J12

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH Grant U01AG-046170

Title: TYROBP/DAP12 and its role in Alzheimer's disease

Authors: *J.-V. HAURE-MIRANDE[1], S. KIM[1], M. WANG[2], B. ZHANG[2], E. SCHADT[2], S. GANDY[1], M. EHRLICH[1];
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Abstract: Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterized by amyloid beta (Aß) peptide accumulation which is believed to be a major pathophysiologic factor of the disease. An inflammatory component in AD has long been recognized, and it was first assumed that the chronic neuroinflammation associated with AD may be a secondary or even protective event in response to Aß deposition and may occur only in late stages of AD. Recent genetic studies, however, identified an association between AD and mutations in genes encoding important immune mediators, e.g. *CD33* and *TREM2*, highlighting the role of a dysregulated immune response and neuroinflammation in AD and suggesting an earlier, and perhaps causative, role in pathogenesis. In addition, integrative genomic analyses of human AD brain transcriptomes have provided convincing data regarding the role of microglia in the pathogenesis of AD. Microglial activation may therefore be causative, reactive, and/or protective, perhaps varying with disease stage. For example, phagocytosis of Aß peptides may prevent their deposition into plaques. Alternatively, microglial activation leads to the release of proinflammatory cytokines that can contribute to synaptic dysfunction and neuronal death. *TYROBP* (aka *DAP12*) was identified by members of our team as a hub gene mediating microglial activation, and its expression is increased in human AD and mouse AD model brains. Naturally occurring mutations of *TYROBP* cause Nasu-Hakola disease. *TYROBP* encodes a transmembrane signaling polypeptide which contains an immunoreceptor tyrosine-based activation motif (ITAM) in its cytoplasmic domain and is a downstream adaptor of immune receptors associated with AD risk factor such as *TREM2, CR3* and *SIRPβ1*. However, the role of *TYROBP* in the pathogenesis of AD and microglial function clearance remains unclear.
We sought to determine the *in vivo* effect of loss of function of *Tyrobp* in an AD mouse model. We crossed *Tyrobp*-deficient mice and the *APP/PSEN1*$^{\Delta exon9}$ AD mouse model. The *Tyrobp*-null mouse was developed via deletion of exons 3 and 4 of *Tyrobp* gene, including the transmembrane region, part of the cytoplasmic region, and the first tyrosine of the ITAM motif. We will present phenotypic assays in male and female mice of *APP/PSEN1*$^{\Delta exon9}$ and

APP/PSEN1$^{\Delta exon9}$*xTyrobp*-null genotypes, including behavior, Aβ and Aβ oligomer levels, microglial phagocytic ability, cytokine expression, and plaque deposition accumulation. This study should advance our understanding of the normal function of *TYROBP* and its role in AD, including its role as a potential therapeutic target.

Disclosures: J. Haure-Mirande: None. **S. Kim:** None. **M. Wang:** None. **B. Zhang:** None. **E. Schadt:** None. **S. Gandy:** None. **M. Ehrlich:** None.

Poster

788. Immune Responses and Glial Functions in Neurodegenerative Disease

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 788.12/J13

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: National Center for Research Resources & National Center for Advancing Translational Sciences: UL1 TR001414

National Institute on Aging: P50 AG16573

Program Project Grant AG00538

Title: Pathological tau impairs anti-inflammatory interleukin-37 on Alzheimer's disease

Authors: *A. C. MARTINI[1,2], W. W. POON[2], D. CHENG[2], R. A. AGER[2], R. C. BOHANNAN[2], D. BAGLIETTO-VARGAS[2], M. I. DIAMOND[3], A. J. RAJIC[2], R. C. KIM[2], D. H. CRIBBS[2], J. BUSCIGLIO[2,4], F. M. LAFERLA[2,4], R. MEDEIROS[5,2,4];
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Abstract: The microtubule-associated protein tau has been implicated in Alzheimer's disease (AD) pathogenesis. Although inflammation is positively correlated with tau hyperphosphorylation and aggregation, the impact of tau pathology on the immune response remains elusive. Here, we provide evidence that tau aggregation drives the failure of critical molecular events that limit and resolve inflammation. Specifically, pathological tau impairs interleukin-37 (IL-37), a unique cytokine that belongs to the IL-1 family and possesses potent anti-inflammatory properties, inhibiting both innate and adaptive responses. Brains from AD subjects show lower soluble IL-37 levels compared with the brains of non-demented subjects. Mechanistically, IL-37 is sequestered by tau into neurofibrillary tangles, and tau pathology

progressively impairs neuronal IL-37 release. Notably, IL-37 overexpression in aged AD transgenic mice with robust amyloid plaques and neurofibrillary tangles mitigates the critical pathological features of AD, including inflammation, synaptic toxicity and cognitive decline. Our findings provide clear evidence that targeting the IL-37 anti-inflammatory network will provide a new approach for the treatment of AD. Likewise, therapies that ameliorate tau-mediated neurodegeneration and further accumulation of pathological tau species could be validated with the development of an IL-37 biomarker assay.

Disclosures: **A.C. Martini:** None. **W.W. Poon:** None. **D. Cheng:** None. **R.A. Ager:** None. **R.C. Bohannan:** None. **D. Baglietto-Vargas:** None. **M.I. Diamond:** None. **A.J. Rajic:** None. **R.C. Kim:** None. **D.H. Cribbs:** None. **J. Busciglio:** None. **F.M. LaFerla:** None. **R. Medeiros:** None.

Poster

788. Immune Responses and Glial Functions in Neurodegenerative Disease

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 788.13/J14

Topic: C.02. Alzheimer's Disease and Other Dementias

Title: Innate immune cell circadian rhythms in aging and Alzheimer’s disease

Authors: *C. TSAI, K. I. ANDREASSON;
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Abstract: Recent systems biology approaches have identified innate immune cell dysfunction as a dominant risk factor for developing Alzheimer’s disease, underscoring the importance of understanding basic innate immune cell biology. On important aspect of innate immune biology is circadian regulation of gene expression and cellular function in microglia and macrophages. Young macrophages exhibit circadian rhythms in cytokine release, cell trafficking, phagocytosis capacity, and gene expression. How these myeloid circadian rhythms change with aging or Alzheimer’s disease remains unclear. Using unbiased transcriptomic approaches and in vitro assays, we tested the hypothesis that aged microglia and macrophages exhibit less robust circadian rhythms and lead to an increased risk for developing Alzheimer’s disease. Our results suggest that aging impairs circadian regulation of microglial clearance activity and increases accumulation of amyloid beta.

Disclosures: **C. Tsai:** None. **K.I. Andreasson:** None.

Poster

788. Immune Responses and Glial Functions in Neurodegenerative Disease

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 788.14/J15

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH Grant AG051495

NIH Grant AG050597

NIH Grant AG051495

Title: Trem2 deficiency reduces proliferation, increases cell death and exacerbates inflammation in a mouse model of Alzheimer's disease

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Abstract: Alzheimer's disease (AD) is a neurodegenerative disorder characterized pathologically by amyloid-beta plaques. Myeloid cells, which are comprised of microglia and peripherally derived macrophages, can alter AD pathology through inflammation or plaque clearance. Variants in the Trem2 (Triggering Receptor Expressed on Myeloid Cells 2) gene confer increased risk for developing AD. It was previously found in a study of Trem2 WT and KO AD mouse models that Trem2 is expressed on plaque-associated myeloid cells, and that Trem2 is necessary for the recruitment of myeloid cells to plaques. We explored several mechanisms as potential explanations for reduced myeloid cell number around plaques in Trem2 deficient APPPS1-21 AD mice including changes in cell proliferation and cell death. Cell proliferation was examined by measuring incorporation of bromodeoxyuridine (BrdU) in myeloid cells in APPPS1-21;Trem2+/+ and APPPS1-21;Trem2-/- mice. Using immunohistochemistry (IHC), brain tissue of these mice was co-stained for BrdU and the myeloid cell marker Iba1. The number of cells with colocalization between the two stains was measured in the cortex and the hippocampus, brain regions where amyloid pathology is prevalent. The number of BrdU+Iba1+ cells was significantly reduced in both the hippocampus ($p<0.01$) and cortex ($p<0.001$). Myeloid cell apoptosis was quantified with IHC by counting the number of cells expressing cleaved-caspase 3, an apoptotic cell marker, and Iba1. There was a strong trend towards increased cell death in the Trem2 KO mice. These findings suggest that the reduction in cell number in the Trem2 KO mice is at least partially explained by both a reduction in proliferation of those cells and possibly increased myeloid cell death. Next, we wanted to assess if a change in myeloid cell number affected general myeloid cell functions related to AD. First, phagocytosis between the two models was examined using an *ex vivo* slice phagocytosis assay, which measures phagocytosis of florescent beads in myeloid cells within a brain slice.

However, there was no significant change in phagocytosis between the Trem2 KO and WTs. Second, we measured the general inflammatory response by means of qPCR with pro-inflammatory markers (IL1β, IL6, iNOS, TLR4, and TNFα) and anti-inflammatory markers (Fizz1, Arg1, TGFβ, and Arg1). We found that Trem2 KOs expressed significantly reduced levels of pro-inflammatory markers and increased levels of anti-inflammatory markers. Understanding how Trem2 affects myeloid cell number, phagocytosis, and inflammation may help to elucidate Trem2's role as a risk factor for AD.

Disclosures: T.R. Jay: None. **M. Broihier:** None. **G. Landreth:** None. **B. Lamb:** None.

Poster

788. Immune Responses and Glial Functions in Neurodegenerative Disease

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 788.15/J16

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NSC102-2320-B-400-010

MOST104-2320-B-400 -001

NHRI NP-104-PP03

Title: Soluble epoxide hydrolase regulates astrocyte immune responses and GFAP expression through suppression of STAT3 phosphorylation

Authors: *F.-S. SHIE[1], S. SHEN[1,2], Y.-T. HSU[1], P.-C. HSU[2], Y.-H. LEE[2];
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Abstract: Astrocyte activation is a common pathological feature in many brain diseases and plays an important role in the pathogenesis of Alzheimer's disease (AD). Here, we demonstrate that soluble epoxide hydrolase (sEH) immunoreactivity was escalated in activated astrocytes in the vicinity of β-amyloid (Aβ) aggregates in parallel with the progression of AD-like pathology in APP/PS1 transgenic mice. Importantly, our results show that silence against sEH mRNA enhanced, but overexpression of sEH ameliorated the LPS-induced expression of pro-inflammatory markers, such as inducible nitric oxide (iNOS), cyclooxygenase 2 (COX-2), and pro-inflammatory cytokines. These findings suggest that sEH negatively regulates astrocyte immune responses. Data from primary astrocytes with sEH knockout (sEH-/-) background also support the notion that sEH functions to suppress astrocyte activation. Similarly, sEH-/- mice received intraperitoneal injection of LPS displaced an exacerbated astrocyte activation in the

brain as evidenced by the elevated expressions of glial fibrillary acidic protein (GFAP) and pro-inflammatory markers at both levels of protein and mRNA. We further demonstrate that phosphorylation of signal transducer and activator of transcription 3 (STAT3) was up-regulated in activated astrocytes of sEH-/- mouse brain and pharmacological blockade of STAT3 activity alleviated the pro-inflammatory effects of sEH deletion in LPS-activated primary astrocytes. In conclusion, our results provide evidence for the first time showing that sEH negatively regulates astrocytic immune responses and GFAP expression, while the underlying mechanism is at least partly involved in the down-regulation of STAT3 phosphorylation. The discovery of the novel function of sEH in the negative control of STAT3-mediated astrocyte activation confers further insights into the regulatory machinery of astrocyte activation in the diseased brain.

Disclosures: **F. Shie:** None. **S. Shen:** None. **Y. Hsu:** None. **P. Hsu:** None. **Y. Lee:** None.

Poster

788. Immune Responses and Glial Functions in Neurodegenerative Disease

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 788.16/J17

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: R01AG027924

R01AG035355

R01AG046205

81370459

31400914

20720150051

Title: Soluble TREM2 (sTREM2) inhibits cellular apoptosis and induces pro-inflammatory response in microglia

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Abstract: Triggering receptor expressed on myeloid cells 2 (TREM2) is an innate immune receptor expressed on the surface of myeloid cells including microglia. Loss-of-function mutations of TREM2 are associated with increased risk for a spectrum of neurodegenerative disorders including Alzheimer’s disease (AD). A soluble form of TREM2 (sTREM2) derived

from proteolytic cleavage of the cell surface receptor is abundantly detected in the cerebrospinal fluid (CSF) and plasma. The CSF sTREM2 levels are elevated in AD and associated with the onset of cognitive decline. Moreover, sTREM2 levels are correlated with those of total and phosphorylated tau in the CSF. However, the physiological and pathological functions of sTREM2 remain unknown. To dissect the roles of sTREM2 in microglia, we investigated the functions of purified sTREM2 protein in primary microglial cultures from wild-type (WT) and Trem2-knockout (KO) mice. We found that sTREM2 triggers robust pro-inflammatory cytokine expression but inhibits apoptosis induced by GM-CSF withdrawal in both WT and Trem2-KO microglia. The presence of NF-κB inhibitor, Bay 11-7082, completely abrogated the pro-inflammatory response induced by sTREM2. Importantly, sTREM2 exposure led to the activation of Akt/GSK3β/β-catenin signaling pathway. Interestingly, sTREM2 that carried AD-associated mutations (R47H and R62H) partially lost their ability in suppressing apoptosis and triggering pro-inflammatory response. Taken together, the presence of sTREM2 but not the AD-associated mutants triggers pro-inflammatory responses in microglia via the NF-κB signaling pathway, yet prevents microglial apoptosis by modulating the activity of Akt/GSK3β/β-catenin signaling pathway. Thus, sTREM2 exhibits opposing effects on microglia-mediated neuro-inflammation and their survival.

Disclosures: **X. Chen:** None. **L. Zhong:** None. **T. Wang:** None. **Z. Wang:** None. **G. Bu:** None.

Poster

788. Immune Responses and Glial Functions in Neurodegenerative Disease

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 788.17/J18

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: AG034214

Title: Soluble TREM2 levels in neurodegenerative disorders.

Authors: ***L. BEKRIS**[1], M. KHRESTIAN[2], Y. SHAO[2], J. LEVERENZ[2];
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Abstract: Alzheimer’s disease (AD) has been both genetically and pathologically associated with neuroinflammation. Genetic variants of triggering receptor expressed on myeloid cells 2 (*TREM2*) have been linked to late-onset AD and other neurodegenerative diseases including Parkinson’s disease (PD). *TREM2* rare coding variants are associated with increased late-onset AD risk, while loss of function mutations in the gene lead to Nasu-Hakola disease an autosomal

recessive early-onset degenerative disorder. Genome-wide association study (GWAS) analyses have found associations between a genetic variants at the *TREM2* locus and sTREM2 levels in biofluids from neurodegenerative disease patients and with C-reactive protein (CRP) levels in healthy African American and Hispanic American women. TREM2 is a microglial receptor involved in innate immunity. Soluble TREM2 (sTREM2) is a cleavage product of TREM2 present in cerebrospinal fluid (CSF) and plasma. CSF levels of sTREM2 have been reported as changed during the clinical course of AD. In addition, CSF sTREM2 levels have been described as higher in mild cognitive impairment due to AD compared to AD and cognitively normal controls. Furthermore, increased CSF sTREM2 levels have been associated with higher CSF total tau and phosphorylated-tau, which are markers of neuronal degeneration and tau pathology. These reports suggest that a change in this inflammatory marker may occur in response to neuronal degeneration, or perhaps participates in driving neurodegeneration. Therefore, the hypothesis of this investigation is that not only are markers of neuronal degeneration associated with sTREM2 in neurodegenerative disorders, but also markers of inflammation are associated with sTREM2 in neurodegenerative disorders. The aim was to demonstrate a correlation between sTREM2 and CRP as well as other inflammation markers in multiple neurodegenerative disorders. We found that inflammation markers are indeed associated with sTREM2 levels in certain neurodegenerative disease disorders, but not others. These results suggest that TREM2 is linked to the inflammatory processes related to neurodegeneration. Furthermore, CSF sTREM2 may be an important biomarker for inflammatory activity in neurodegenerative disease.

Disclosures: **L. Bekris:** None. **M. Khrestian:** None. **Y. Shao:** None. **J. Leverenz:** A. Employment/Salary (full or part-time): Cleveland Clinic. B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution; Alzheimer's Association, Alzheimer's Drug Discovery Foundation, Genzyme/Sanofi, Lundbeck, Michael J Fox Foundation, NIH. F. Consulting Fees (e.g., advisory boards); Axovant, GE Healthcare, Navidea, Piramal, Teva.

Poster

788. Immune Responses and Glial Functions in Neurodegenerative Disease

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 788.18/K1

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH R21AG039596 (X.X.)

NIH HL107466 (M-X. C.)

Alz 11RG-05-14584 (X.X.)

UTK,COE

Title: Determine the mechanism of lysophosphatidic acid (LPA)-induced apoptosis

Authors: Y. DONG[1], Y. WU[2], H. CHEN[3], M.-Z. CUI[4], *X. XU[4];
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Abstract: Oxidative stress is now at the forefront of Alzheimer's disease (AD) research. Evidence suggests that oxidized lipids in the central nervous system (CNS) function as risk factors in AD. The human brain is composed of approximately 60-70% lipids by dry weight. Most of the lipids are actively synthesized in the CNS itself. In addition, lipids are taken up by brain cells throughout life. These various forms of brain lipids serve not only as structural components but also as essential signaling molecules. Among them, lysophosphatidic acid (LPA) is the most potent bioactive lipid species that can be produced within brain tissues under pathological conditions such as oxidation of low-density lipoprotein (LDL). LPA is involved in many cellular processes, including cell survival and apoptosis. LPA has been shown to induce apoptosis in different cell types including neuronal, vascular, and cancer cells. Thus, LPA, at pathophysiological levels, can induce neuronal apoptosis and thereby participate in neurodegenerative disorders, such as AD. However, the molecular mechanism by which LPA induces apoptotic cell death remain unknown. In this study, we investigated this issue using cultured cell model. Our data showed that treatment of cells with LPA induced apoptosis and a dramatic increase in the level of death receptor 6 (DR6). More interestingly, our data also revealed that knockdown of DR6 blocked LPA-induced apoptosis. Thus, our results strongly suggest LPA-induced apoptosis is mediated by upregulation of DR6 expression. In this study, we have also determined the intracellular signaling cascades that are involved in LPA-induced DR6 expression.

Disclosures: **Y. Dong:** None. **Y. Wu:** None. **H. Chen:** None. **M. Cui:** None. **X. Xu:** None.

Poster

788. Immune Responses and Glial Functions in Neurodegenerative Disease

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 788.19/K2

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: Consejo Superior de Investigaciones Científicas

Title: ^{3}H-PK11195 binding reflects astrogliosis and reduces pathological neuroinflammation in TgAPP Alzheimer's disease mice

Authors: *S. SEDDIGHI[1], B. BRERA[2], M. L. DE CEBALLOS[2];
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Abstract: Glial cell activation is an invariant feature of Alzheimer's disease (AD) neuropathology and is largely responsible for the ongoing, deleterious inflammation in patients suffering from this condition. A large body of literature suggests that increased binding of ^{3}H-PK11195, a translocator protein (TSPO 18kD) receptor ligand, reflects microglial activation. However, astrocytes may also be involved. The objectives of this project were first, to investigate whether ^{3}H-PK11195 binding is coupled to astrogliosis and second, to assess the impact of long-term treatment with PK11195 on AD-like neuroinflammatory responses. For the first experiment, rats received either a single or 7 daily intracerebroventricular injections of β-Amyloid (Aβ, 20 μg/day/rat, ICV). Control rats received a peptide with identical amino acids in a scrambled sequence. Animals were sacrificed at 3 weeks after initiation of treatment, and ^{3}H-PK11195 binding was assessed via a membrane filtration assay. Results indicated a 3-fold increase in ^{3}H-PK11195 binding in the hippocampus of rats receiving the 7-day treatment with Aβ. A significant increase in binding of ^{3}H-PK11195 was also observed in cultured astrocytes treated with Aβ (1μM) for 24 or 48 h. Finally, prolonged oral treatment with PK11195 (1mg/kg/day, 5 months, administered in drinking water) diminished the increased astrocyte hippocampal density (GFAP immunostaining) in TgAPP 2576 AD mice, while microglial cell counts (Iba1 immunostaining) were unaltered. Taken together, these results suggest that astrogliosis contributes to enhanced ^{3}H-PK11195 binding, as observed in PET studies of AD patients, and that astrocytes are a target for the anti-inflammatory effects of this TSPO ligand. Our studies thereby reveal a potential dual-role nature of this synthetic ligand in both the diagnosis and treatment of Alzheimer's disease neuropathology.

Disclosures: **S. Seddighi:** None. **B. Brera:** None. **M.L. de Ceballos:** None.

Poster

788. Immune Responses and Glial Functions in Neurodegenerative Disease

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 788.20/K3

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: BrightFocus Foundation Grant A2013328S00

The Cheryl and Haim Saban Foundation

The Marciano Family Foundation

Title: Effects of IL-34 on macrophage immunological profile in response to Alzheimer's-related amyloid-beta$_{42}$ assemblies

Authors: *N. J. HART[1], L. R. ZUROFF[1], T. TORBATI[1,3], D.-T. FUCHS[1], J. SHEYN[1], A. RENTSENDORJ[1], Y. KORONYO[1], E. Y. HAYDEN[3], D. B. TEPLOW[3], K. L. BLACK[1], M. KORONYO-HAMAOUI[1,2];
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Abstract: Background. Interleukin-34 (IL-34) is a newly-discovered cytokine that acts as a second ligand of the colony stimulating factor 1 (CSF1; also called macrophage colony-stimulating factor) receptor. Similar to CSF1, but with lower binding affinity, IL-34 stimulates viability of bone marrow (BM)-derived monocytes (Mo) and formation of macrophage (MΦ) progenitors. The expression of IL-34 in the brain shows a pattern distinct from that of CSF1, particularly in the hippocampus and cerebral cortex. Increasing evidence indicates a key role for peripheral Mo/MΦ in the physiological clearance of cerebral amyloid-β protein (Aβ), especially neurotoxic Aβ_{42} which is tightly associated with Alzheimer's disease (AD). As a second ligand of the CSF1 receptor, IL-34 may be relevant to the innate immune responses in AD.
Methods. To investigate how IL-34 affects macrophage phenotype in response to structurally-defined and stabilized Aβ_{42} oligomers and preformed fibrils, we characterized murine BM-derived Mo/MΦ (BMM) primary cultures supplemented with media containing CSF1, IL-34, or a regimen involving both cytokines.
Results. Immunological profile and activation phenotype of IL-34-stimulated BMM were altered in comparison to those of cells cultured with CSF1 alone. Surface expression of type B scavenger receptor CD36, known to facilitate Aβ recognition and uptake, was modified following treatment with IL-34. Uptake of fibrillar or oligomeric Aβ_{42} differed between groups stimulated by IL-34 versus CSF1. Intracellular compartmentalization of Aβ visualized by staining of early endosome antigen 1 (EEA1) was also distinct in IL-34-treated BMM. Expression of triggering receptor expressed on myeloid cells 2 (TREM2), which is implicated in Aβ uptake and clearance, as well as matrix metallopeptidase 9 (MMP-9), an Aβ-degrading enzyme, decreased dramatically in IL-34 groups when compared with CSF1 controls. Elongated cell morphology associated with a pro-healing MΦ phenotype was also quantified, yielding an elongation factor (EF). The BMM group initially stimulated with CSF1 and then with IL-34 showed a significant increase in EF compared to BMM treated with CSF1 alone. Further, monocytes treated with IL-34 alone yielded fewer mature MΦ in comparison to CSF1 controls. This reduction was attenuated in BMM treated with a combination of CSF1 and IL-34.
Conclusion. Our data may indicate that IL-34 affects monocyte differentiation into MΦ and their ability to resist pathological forms of Aβ. Future experimentation should investigate how IL-34 may differentially stimulate Mo/MΦ and brain-resident microglia, which may in turn contribute to neuronal protection in AD.

Disclosures: **N.J. Hart:** None. **L.R. Zuroff:** None. **T. Torbati:** None. **D. Fuchs:** None. **J. Sheyn:** None. **A. Rentsendorj:** None. **Y. Koronyo:** None. **E.Y. Hayden:** None. **D.B. Teplow:** None. **K.L. Black:** None. **M. Koronyo-Hamaoui:** None.

Poster

788. Immune Responses and Glial Functions in Neurodegenerative Disease

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 788.21/K4

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: Grant FONDECYT 1131025

Fellowship CONICYT 21120013

Title: Class a scavenger receptor deficiency impairs immune response of microglia and astrocytes in app/ps1 transgenic mice

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Abstract: Neuroinflammation has become an attractive mechanism for understanding progression of Alzheimer's disease (AD), because of the increasing evidence showing a central role for glial cells in AD development. We have focused on alterations of glial cell activation that could participate in AD pathophysiology. Class A Scavenger Receptor (SR-A) has emerged as a key modulator of microglia and astrocytes inflammatory response. Scavenger receptors appear to be crucial for microglia Aβ uptake. However, little is known about how SR-A regulates glial activation in response to Aβ. Here, we used a triple congenic mice strain developed in our laboratory, which accumulates Aβ and is knockout for SR-A (APP/PS1/SR-A$^{-/-}$) to address the inflammatory role of SR-A in an AD animal model. Our results show that glial cells from triple transgenic mice had an impaired oxidative response and nitric oxide induction, produce up to 7-fold more pro-inflammatory cytokines with a 12-fold reduction in anti-inflammatory cytokines basal release. Moreover, we observed significant impairments in the glial inflammatory response after LPS stimulation, and a reduced phagocytic activity in microglia isolated from young and adult mice, both *in vitro* and *ex vivo*. Our *in vivo* results show that lifespan was greatly reduced in triple transgenic mice, accompanied by a 3-fold increase in plasmatic pro-inflammatory cytokines levels, with increased IL-1β and reduced TGF-β levels in the hippocampus as mice ages. We conclude that dysfunction of glial inflammatory response induced by impaired SR-A

contributes to AD progression. Key words: scavenger receptor, APP/PS1, microglia, astrocytes, neuroinflammation.

Disclosures: **F.A. Cornejo:** None. **M. Vruwink:** None. **P. Muñoz:** None. **M. Andres:** None. **R. von Bernhardi:** None.

Poster

788. Immune Responses and Glial Functions in Neurodegenerative Disease

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 788.22/K5

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: CNPq

FAPERJ

Title: Brain immune imbalance underlies depressive-like behavior induced by Alzheimer's amyloid-β oligomers in mice

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Abstract: Despite substantial clinical and epidemiological evidence supporting an intriguing connection between Alzheimer's disease (AD) and depression, the molecular and cellular mechanisms underlying this association are still largely unknown. We recently found that soluble amyloid-β oligomers (AβOs), toxins that accumulate in AD brain and are thought to be responsible for synapse failure and memory loss,induce depressive-like behavior in mice, a process associated with gliosis. Here, we report that AβOs directly activate microglia, leading to increased production and secretion of TNF-α. Intracerebroventricular (i.c.v.) injection of AβOs causedsignificant increases in brain levels of TNF-α mice. Consistent with a role of microglia in brain inflammation and mood alterations, pharmacological inactivation or ablation of microglia blocked the elevation in brain TNF-α and depressive-like behavior in AβO-injected mice. These findings establish that aberrant activation of microglia by AβOs may be a key trigger of mood alterations in AD.

Disclosures: **F. Campos Ribeiro:** None. **J. Ledo:** None. **E. Azevedo:** None. **D. Beckman:** None. **D. Razolli:** None. **L. Santos:** None. **H. Melo:** None. **M. Bellio:** None. **A. Teixeira:** None. **L. Velloso:** None. **D. Foguel:** None. **F. De Felice:** None. **S. Ferreira:** None.

Poster

788. Immune Responses and Glial Functions in Neurodegenerative Disease

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 788.23/K6

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH Grant RF1AG048099

Alzheimer's Association Grant BFG-14-317000

NIH Grant P50 AG016573

NIA Grant T32 AG00096-30

NINDS Grant T32 NS082174-01

Title: Examining the role of adaptive immunity and peripheral immune cell infiltration in Alzheimer's disease pathogenesis

Authors: ***S. E. MARSH**[1], E. M. ABUD[1], L. L. MCINTYRE[2], A. KARIMZADEH[2], A. LAKATOS[3], S. T. YEUNG[3], L. LAU[3], M. A. INLAY[2], C. M. WALSH[2], W. W. POON[3], M. BLURTON-JONES[1];
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Abstract: Alzheimer's disease is complex neurodegenerative disorder characterized pathologically by amyloid and tau accumulation, synaptic and neuronal loss, and widespread inflammation. Research over the last few decades has enumerated many of the complexities of the inflammatory state in the AD brain. However, almost all of these studies have focused on the role of the innate immune system in disease pathogenesis. However, the adaptive immune system often interacts closely with the innate immune system to modulate the peripheral immune response to bacteria and other pathogens, but the impact of the adaptive immune system has largely been ignored in AD and other neurodegenerative disorders.
To examine the role of adaptive immunity in AD pathogenesis, we generated an immune-deficient AD mouse model by backcrossing the 5xfAD mouse onto a Rag2-/- il2rg-/- immune-deficient background, that lacks T-, B-, and NK-cells. Investigation of the resulting 'Rag-5xfAD'

mice revealed significantly accelerated disease pathogenesis, including a more than 2-fold elevation in Aβ. Significant changes were also observed in Rag-5xfAD neuroinflammation indicated by shifts in microglial gene expression, morphology, and phagocytosis. Interestingly, we find non-amyloid reactive IgG associated with microglia in the brains of immune-intact 5xfAD mice and demonstrate that the addition of preimmune IgG to Rag-5xfAD mice can reduce pathology.
Furthermore, analysis of GFP-bone marrow chimeras established without radiation or chemotherapeutic myeloablation, has revealed significant peripheral infiltration into the brain parenchyma of 6-month-old Rag-5xfAD mice. Additional analyses of these infiltrating cells including their phenotype and association with disease pathology will yield valuable data not only on the mechanisms of infiltration but also the interactions between these peripheral immune cells, resident CNS microglia, and AD-associated pathology.

Disclosures: **S.E. Marsh:** None. **E.M. Abud:** None. **L.L. McIntyre:** None. **A. Karimzadeh:** None. **A. Lakatos:** None. **S.T. Yeung:** None. **L. Lau:** None. **M.A. Inlay:** None. **C.M. Walsh:** None. **W.W. Poon:** None. **M. Blurton-Jones:** None.

Poster

788. Immune Responses and Glial Functions in Neurodegenerative Disease

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 788.24/K7

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: Canadian Institutes of Health Research grant MOP-97776

Title: Inflammasome activation in the pre clinical and clinical stages of alzheimers disease pathology in down syndrome

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Abstract: Before clinical presentation, Alzheimer’s disease (AD) develops silently for decades. The identification of this AD silent stage is an unmet need. We have reported the occurrence of an early disease-aggravating pro-inflammatory process in transgenic rat and mouse models of AD-like amyloid pathology (1-3). While the neuroinflammation in AD has been well-characterized at late stages of the pathology, little is known about the CNS inflammatory process at the silent stages of AD.Given the triplication of the amyloid precursor protein, Down

Syndrome (DS) individuals show a gradual intraneuronal amyloid beta (AB) accumulation before the development of a full-blown AD pathology and dementia (4). In order to study the AD pre-clinical stage, we are studying the early AB-driven inflammatory process occurring at the silent stages of AD in DS. We hypothesize that the early intraneuronal accumulation of AB, unleashes a toxic pro-inflammatory process which differs from the late, and well-established amyloid-plaque-associated overt inflammatory reaction. We are interested in defining the characteristics of this pro-inflammatory process at early stages of AD pathology in DS. We are currently investigating the possible activation of the inflammasome, a molecular complex that contributes to the onset of the inflammatory response and, whenever possible, correlating it to the ongoing, silent, AD pathology in post-mortem brain samples of individuals with DS. Towards the above objective, we have analyzed the expression of several pro-inflammatory and inflammasome-related genes via qPCR and a qPCR array (Qiagen, CA) in postmortem frozen frontal cortex tissue of DS infants (3 weeks-13 months old) and DS adults with AD (44-66 years old) from the UCI and NYU brain banks. Gene expression analysis in DS infants revealed an upregulation of several classical pro-inflammatory mediators such as IL-1B, IL-6, IL-12b, and the monocyte recruitment-chemokines MCP-1 and RANTES. Furthermore, inflammasome receptors (NLRP3, NLRP4, and NLRP6) and pro-inflammatory caspases (1 and 5) were found upregulated. While DS adults with AD also show an inflammatory profile, it is more attenuated when compared to the DS infants. Thus, preliminary results would indicate a differential expression in silent and preclinical AD stages in DS. We propose that the early AD inflammatory process is linked to the abnormal intraneuronal accumulation of AB (1). References: (1) C. E. Hanzel et al. *Neurobiology of aging,* 2014; (2) M. T. Ferretti et al. *Neurobiology of aging,* 2012; (3) M. T. Ferretti et al. *Journal of neuroinflammation,* 2012. (4) Busciglio et al. *Neuron*, 2002.

Disclosures: L. Flores Aguilar: None. **M. Iulita:** None. **T. Wisniewski:** None. **J. Busciglio:** None. **A. Cuello:** None.

Poster

788. Immune Responses and Glial Functions in Neurodegenerative Disease

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 788.25/K8

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: The BrightFocus Foundation

The Coins for Alzheimer’s Research Trust

The Cheryl and Haim Saban Foundation

The Marciano Family Foundation

Title: Synaptic effect of glatiramer acetate immunomodulation in a mouse AD model

Authors: ***S. LI**[1,2], Y. KORONYO[2], D.-T. FUCHS[2], D. DALEY[2], J. SHEYN[2], T. TORBATI[2], A. RENTSENDORJ[2], E. HAYDEN[3], K. BLACK[2], D. TEPLOW[3], M. KORONYO[2];
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Abstract: Synaptic changes in multiple brain regions play a crucial role in Alzheimer's disease (AD). The loss of synapses may contribute directly to the profound cognitive impairment in this disease. Our previous studies showed that glatiramer acetate (GA) immunomodulation improved the cognitive function of AD mice. We now further investigated the synaptic protection by GA immunotherapy using a mouse AD model. The brain tissues were stained with the presynaptic marker (anti-VGluT1) and postsynaptic marker (anti-PSD95). Synaptic puncta areas were precisely quantified with Puncta Analyzer. Our comprehensive analysis of entorhinal cortex (ENT) and hippocampal substructures in symptomatic $APP_{SWE}/PS1_{\Delta E9}$ transgenic mice indicated significant 50-68% pre- and 38-51% post-synaptic loss ($P < 0.001$-0.05) as compared to non-transgenic littermate onces (6 mice/group). This loss of synapses was strikingly preserved by immunomodulation with GA ($P < 0.001$-0.05; 6 mice/group). Specifically, following GA immunization of ADtg mice a remarkable synaptic preservation was found in the ENT, molecular layer (ML) of dentate gyrus, stratum lacunosum-moleculare (SLM), stratum oriens (SO), and stratum radium (SR) of the CA1 region. Also, peripheral blood enrichment with $CD115^{+}$-monocytes in ADtg mice produced a significant increase of synapses in ENT, ML and SLM. In addition, increased synapses following GA treatment was noted to correlate positively with reduced neuropathology and retained cognition ($P < 0.01$-0.05). Our data suggest that GA immunization protects specific brain areas from synaptic loss and holds great promise for AD therapy, the mechanism by which is currently being studied.

Disclosures: S. Li: None. **Y. Koronyo:** None. **D. Fuchs:** None. **D. Daley:** None. **J. Sheyn:** None. **T. Torbati:** None. **A. Rentsendorj:** None. **E. Hayden:** None. **K. Black:** None. **D. Teplow:** None. **M. Koronyo:** None.

Poster

788. Immune Responses and Glial Functions in Neurodegenerative Disease

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 788.26/K9

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH PO1AG014449

AG05133 (University of Pittsburgh ADRC)

NIH PO1AG025204

NIH RO1AG43775

Barrow Neurological Institute Barrow and Beyond

Title: Tenascin-C is associated with cored amyloid-β plaques in pathology burdened cognitively normal elderly and in Alzheimer's disease

Authors: *Z. MI[1,5], W. HALFTER[2], E. E. ABRAHAMSON[1,5], W. E. KLUNK[3], C. A. MATHIS[4], E. J. MUFSON[6], M. D. IKONOMOVIC[1,3,5];
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Abstract: Tenascin-C (TN-C) is an extracellular matrix glycoprotein implicated in inflammatory reactions in the CNS and in peripheral organs, and may play a role in the pathogenesis of Alzheimer's disease (AD). This study examined the localization and distribution of TN-C immunoreactivity in autopsy brains from Rush Religious Order study subjects with clinically and neuropathologically diagnosed AD compared to aged-matched non-demented controls with amyloid-β (Aβ) pathology (NC+Aβ) or free of pathology (NC-Aβ). In all cases TN-C immunoreactivity was detected in the white matter and in the pia/cortical layer 1, and occasionally in blood vessels. In NCI+Aβ controls and AD cases, but not in NC-Aβ cases, TN-C immunoreaction was also prominent in large (~100 microns) extracellular deposits which co-localized with and completely surrounded classic cored Aβ-immunoreactive (-ir) plaques in the cortex and hippocampus. TN-C deposits also encapsulated GFAP-ir astrocytes and processes, Iba-1-ir microglia, phosphorylated tau-ir neurites, and amyloid cores which were prominently fluorescent for 6-CN-PiB, a highly fluorescent derivative of the amyloid PET ligand Pittsburgh Compound-B (PiB). TN-C deposits were absent from diffuse Aβ plaques in the cortex, caudate nucleus and cerebellum, and Aβ-ir blood vessels were only weakly TN-C-ir. These results demonstrate that extracellular deposits of TN-C are associated primarily with classic Aβ plaques characterized by fibrillar cores of amyloid and presence of inflammatory and tau phosphorylation markers. TN-C may play a role in the formation or removal of amyloid plaques, and has potential value as a target for therapy in AD.

Disclosures: Z. Mi: None. **W. Halfter:** None. **E.E. Abrahamson:** None. **W.E. Klunk:** None. **C.A. Mathis:** None. **E.J. Mufson:** None. **M.D. Ikonomovic:** None.

Poster

788. Immune Responses and Glial Functions in Neurodegenerative Disease

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 788.27/K10

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH grant AG042292 (FRS, CD, XZ)

Coins for Alzheimer's Research Trust (CART) (FRS, XZ)

Title: Lipopolysaccharide (LPS) associates with amyloid in Alzheimer's brain

Authors: X. ZHAN[1], B. STAMOVA[1], L.-W. JIN[2], C. DECARLI[1], B. PHINNEY[3], *F. R. SHARP[1];
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Abstract: We have demonstrated that administration of gram negative bacteria (*E. coli)* derived LPS followed by ischemia/hypoxia (IS-H) produces amyloid β (Aβ) aggregates in rat brain. This LPS-IS-H model produces foci of damaged axons and myelin in cortex and hippocampus over several weeks. By 3 months aggregates of myelin basic protein and other myelin proteins occur in the deep layers of ischemic cortex which are associated with deposition of Aβ and APP. By 5 to 7 months Aβ decreased in the deep cortical layers and appeared in the superficial cortical layers and in periventricular ependymal cells. The appearance and distribution of these myelin aggregates that associate with Aβ and APP at 3 months is similar to that seen in mouse genetic AD models. In addition to this neuropathology following the LPS-IS-H, there was a progressive increase of IL1β, Granzyme B and LPS in cortex that occurred over a period of 3 months (Zhan et al., JAD, 2015; 46(2): 507-523).
These results in the rat led us to ask whether LPS and other molecules from *E. coli* bacteria are detectable in sporadic late onset Alzheimer's disease (LOAD) human brain. Western blots for LPS showed much more LPS in cortex of LOAD (n=3) compared to control brains (n=3). Immunocytochemistry for LPS showed that LPS co-localized with $A\beta_{1\text{-}40/42}$ in amyloid plaques and with $A\beta_{1\text{-}40/42}$ around vessels in AD brains. Assessment of *E coli* K99 pili protein levels by Western blots were greater in AD compared to control brains ($p < 0.01$) and K99 was localized to neurons in AD but not control brains. *E. coli* DNA or the E. coli K99 pili protein were detected in 9/10 control and 13/13 AD brains.
These results suggest that LPS associates with AD pathology in human brain. The rat LPS-IS-H model and human AD brain data support the hypothesis that LPS could be involved in the formation of amyloid plaques in human AD brain.
Support: NIH grant AG042292 (FRS, CD, XZ) and a grant from the Coins for Alzheimer's Research Trust (CART) (FRS, XZ).

Keywords: Alzheimer's disease, animal model, *E coli* bacteria, infection, inflammation, lipopolysaccharide

Disclosures: **X. Zhan:** None. **B. Stamova:** None. **L. Jin:** None. **C. DeCarli:** None. **B. Phinney:** None. **F.R. Sharp:** None.

Poster

788. Immune Responses and Glial Functions in Neurodegenerative Disease

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 788.28/K11

Topic: C.02. Alzheimer's Disease and Other Dementias

Title: CCL4 and CXCL10, two chemokines in neurovascular unit controlled by blood mononuclear cells from patients with Alzheimer's disease.

Authors: ***J. VERITE**[1], G. PAGE[1], A. JULIAN[1], D. CHASSAING[1], P.-O. COURAUD[2], M. PACCALIN[1], T. JANET[1];
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Abstract: Alzheimer's disease (AD) is the most common cause of dementia worldwide. Senile plaques, neurofibrillary tangles and neuron loss are the classical neuropathological hallmarks of AD. For the past three decades, it has been demonstrated that AD is accompanied by a neuroinflammation. Even if its beneficial or deleterious role is still a matter of debate in the scientific community, we cannot exclude its involvement in the progression of the disease. To go further, this situation of central nervous system distress could be helped by peripheral blood mononuclear cells (PBMCs), which after transmigration through the Blood Brain Barrier (BBB) could reduce amyloid plaques in the brain of patients with AD. To this purpose, we tested production and release of five chemokines (CCL2, CCL4, CCL5, CXCL10 and CX3CL1), already known to be implicated in the progression of AD, in three experimental conditions: in isolated cells constituting the BBB model, in a free PBMCs BBB model (H4 and hCMEC/D3 cells), and in a complete BBB model with PBMCs from AD patients (n=14 at a moderate state), hCMEC/D3 and H4 cells treated or not with 20μM Aβ42 for 48 hours. Results showed that CCL2 production was significantly increased in hCMEC/D3 cells in complete BBB model, compared to the other two conditions. CCL5 and CXCL10 had the same pattern of expression, with a reduced level in PBMCs in the complete BBB model, and an increase in hCMEC/D3, compared to isolated cells. For CCL4, the presence of PBMCs induced a robust and significant increase in H4 and hCMEC/D3. Furthermore, PBMCs triggered a significant increase of CX3CL1 in hCMEC/D3. No significant effect of Aβ42 treatment has been shown in the

complete BBB model in all cases. These findings also showed the interest of having the most accurate BBB model in order to explore chemokine production; each cellular actor forming the neurovascular unit and PBMCs from patients with AD influenced each other in a bi-directional manner. Here, PBMCs from patients with AD controlled production of CCL4 and CXCL10 in healthy BBB model. Further investigations will be needed to assess the role of PBMCs of patients with AD in the chemotactic environment and the functionality of BBB.

Disclosures: J. Verite: None. **G. Page:** None. **A. Julian:** None. **D. Chassaing:** None. **P. Couraud:** None. **M. Paccalin:** None. **T. Janet:** None.

Poster

788. Immune Responses and Glial Functions in Neurodegenerative Disease

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 788.29/K12

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: Cure Alzheimer's Fund (CAF)

NIH-NIDDK Grant DK42086

Title: Antibiotic-induced perturbations in gut microbial diversity influences neuro-inflammation and amyloidosis in a murine model of Alzheimer's disease.

Authors: *M. R. MINTER[1], C. ZHANG[3], V. LEONE[2], D. L. RINGUS[2], X. ZHANG[1], P. OYLER-CASTRILLO[1], M. W. MUSCH[2], R. E. TANZI[3], E. B. CHANG[2], S. S. SISODIA[1]; [1]Neurobio., [2]Med., The Univ. of Chicago, Chicago, IL; [3]Neurol., Massachusetts Gen. Hosp., Charlestown, MA

Abstract: Background: Severe amyloidosis and plaque-localized neuro-inflammation are key pathological features of Alzheimer's disease (AD). In addition to astrocyte and microglial reactivity, emerging evidence suggests a role of gut microbiota in regulating innate immunity that in turn leads to CNS dysfunction. Considering neuro-inflammation, proposed to be regulated in part by the host microbiome, is closely linked to amyloid pathology and cognitive decline in AD, we hypothesize that composition of the intestinal microbiome plays a key role in modulating neuro-inflammation and influences Aβ deposition.
Materials and Methods: 2 week old male $APP_{swe}/PS1_{\Delta E9}$ mice were gavaged daily with combinatorial antibiotics (ABX; gentamicin (1mg/ml), vancomycin (0.5mg/ml), metronidazole (2mg/ml), neomycin (0.5mg/ml), ampicillin (1mg/ml), kanamycin (3mg/ml), colistin (6000U/ml) and cefaperazone (1mg/ml)) for 1 week and then supplemented with ABX (1/50 concentration)

in drinking water until cull at 6 months of age and subsequent tissue harvesting.
Results: Illumina® Miseq amplicon sequencing, terminal restriction fragment length polymorphism analysis and Q-PCR of the bacterial 16s rRNA gene from fecal and cecal contents of ABX and vehicle control $APP_{swe}/PS1_{\Delta E9}$ mice revealed distinct changes in microbial community diversity, but not total abundance, at the time of cull (n=10, $p<0.001$). Elevated circulating levels of CCL11, CXCL16, TIMP1 and sTNFαR1 were confirmed by cytokine array in the sera of ABX-treated $APP_{swe}/PS1_{\Delta E9}$ mice (n=10, pooled sera). Significantly, serial sectioning and subsequent immunohistochemistry (using α-Aβ mAb 3D6) revealed decreased Aβ plaque size and total burden in brains of ABX-treated $APP_{swe}/PS1_{\Delta E9}$ mice (n=9, $p=0.0175$). These results were confirmed by MSD bioassay of TBS-insoluble Aβ1:40 and Aβ1:42 levels in these same mice. Intriguingly, this ELISA-based assay identified significant elevations in TBS-soluble Aβ1:40 and Aβ1:42 levels in ABX-treated $APP_{swe}/PS1_{\Delta E9}$ mice (n=9, $p<0.05$). IBA-1 and GFAP immunohistochemistry revealed significant decreases in the number of plaque-localized microglia and astrocytes in ABX-treated $APP_{swe}/PS1_{\Delta E9}$ mice (n=8, $0.001<p<0.01$) and 3D-IMARIS-based reconstruction of these cells confirmed altered branching morphology (n=4, $0.001<p<0.01$). Immunohistochemistry of plaque-localized microglia in ABX-treated $APP_{swe}/PS1_{\Delta E9}$ mice identified altered CD14, CD206 and CD86 cell surface expression indicative of a mixed M1/M2 inflammatory phenotype.
Conclusions: Our findings suggest gut microbiome composition regulates host innate immunity mechanisms that impact Aβ amyloidosis.

Disclosures: **M.R. Minter:** None. **C. Zhang:** None. **V. Leone:** None. **D.L. Ringus:** None. **X. Zhang:** None. **P. Oyler-Castrillo:** None. **M.W. Musch:** None. **R.E. Tanzi:** None. **E.B. Chang:** None. **S.S. Sisodia:** None.

Poster

788. Immune Responses and Glial Functions in Neurodegenerative Disease

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 788.30/K13

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: University of Oslo,

Anders Jahres stiftelse

Helse Sør-Øst

Civitan Foundation

APGeM, JNPD

Norsk Farmasøytisk Selskap

Title: Cerebrospinal fluid soluble triggering receptor expressed on myeloid cells 2 (TREM2) in aging and Alzheimer's disease

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Abstract: Alzheimer's disease (AD) neuropathology is associated with neuroinflammation, but there are few useful biomarkers. Such markers may complement the existing biomarkers and may also be used for monitoring the effect of future therapies. Variants of triggering receptor expressed on myeloid cells 2 *(TREM2)* have been linked to late-onset AD and other neurodegenerative disorders. TREM2 is a microglial receptor involved in innate immunity. It is known to mediate phagocytosis and anti-inflammatory reactions, but there is limited data of its function in brain health. A cleaved fragment of the TREM2 receptor, soluble TREM2 (sTREM2), is present in the cerebrospinal fluid (CSF). We therefore investigated the potential of sTREM2 as an AD biomarker, how it relates to the established AD core markers and to aging, the main risk factor of AD. To determine sTREM2 levels in CSF we developed a novel TREM2 ELISA with high sensitivity and low variability. We then assayed the level of sTREM2 in CSF in two independent patient/control cohorts. CSF sTREM2 did not discriminate between controls and patients with AD or mild cognitive impairment. However among cognitively healthy control subjects CSF sTREM2 correlated positively with T-tau (Spearman Rho 0.57; $p<0.001$; n=50), P-tau (Spearman Rho 0.63; $p<0.001$; n=50) and amyloid-β1-42 (Aβ42) (Spearman Rho 0.35; p=0.01; n=50). When applying a higher CSF Aβ42 cut-off (700pg/ml) in this cohort to ensure absence of amyloid deposits the positive correlation between sTREM2 and Aβ42 was stronger (Spearman Rho=0.44; p=0.002; n=46). We also found a positive correlation between sTREM2 and age, the main AD risk factor (Spearman Rho=0.50; $p<0.001$; n=75) among all controls. Our findings indicate that sTREM2 in CSF is a marker of preclinical AD as it in healthy controls correlates with aging, and with the neurodegenerative markers CSF-T-tau/P-tau and the amyloid biomarker Aβ42 among controls who are negative for the AD CSF core biomarkers Aβ42, T-tau or P-tau. We are currently exploring sTREM2 in cohorts with other clinical measures and also the basic TREM2-biology in slice models.

Disclosures: K. Henjum: None. **I.S. Almdahl:** None. **V. Årskog:** None. **L. Minthon:** None. **O. Hansson:** None. **T. Fladby:** None. **L.N. Nilsson:** None.

Poster

789. HIV-Related Neuroinflammation and Neurotoxicity

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 789.01/K14

Topic: C.06. Neurotoxicity, Inflammation, and Neuroprotection

Support: NIH Grant AA023165-01A1

Title: Fine motor control impairment in chronic HIV is similar to and less severe to that seen in Parkinson's disease

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Abstract: Objective: People with human immunodeficiency virus (HIV) infection now live longer due to antiretroviral therapy and may show age- or disease-related Parkinsonian motor deficits and neurodegenerative changes in the basal ganglia. We hypothesized that subjects who have aged with HIV infection will exhibit deficits in fine motor control similar to mild/moderate Parkinson's disease (PD). We have shown that the rhythmicity of repetitive alternating finger tapping on a keyboard (Quantitative DigitoGraphy (QDG)) was the most highly correlated with bradykinesia and of total motor disability in PD (Bronte-Stewart 2000, Taylor-Tavares 2005, Trager 2015).
Methods: Twenty-four healthy controls (age 56.6 +/- 8.0), ten HIV subjects (age 58.8 +/- 7.5), and thirteen moderate stage PD subjects (67.3 +/- 9.3) performed rapid alternating finger tapping (RAFT) on an engineered keyboard and the Unified Parkinson's Disease Rating Scale (motor, UPDRS III). HIV and controls were of similar age but the PD group was older than both other groups($P<0.05$). The PD subjects were tested in the off therapy state. Analysis was performed in MATLAB (The MathWorks, Inc.) to determine inter-strike interval (ISI) and amplitude (AMP) of key presses and their variability using the coefficient of variation (CV_{ISI}, CV_{AMP}). A two-way ANOVA was performed for each parameter in SigmaPlot (Systat Software).
Results: HIV subjects were significantly less rhythmic/regular than controls in RAFT in both the frequency and amplitude of tapping (CV_{ISI} : $P=0.006$, CV_{AMP} : $P=0.001$), yet significantly more rhythmic/regular than the PD group ($P=0.001$ for both). HIV subjects did not differ from controls in the overall mean frequency or amplitude of RAFT, however there was a wide variation in performance among HIV subjects. Both HIV subjects and controls tapped with greater mean amplitude than the PD group but only the control group tapped with a greater frequency than the PD group. PD group's off therapy UPDRS III score ± SD was 34.5 ± 9.9. The HIV group's

UPDRS III score ± SD was significantly lower at 3.6 ± 3.8 (P<0.001).
Conclusions: These preliminary results demonstrate impairment in fine motor control in a small cohort of people with chronic treated HIV infection compared to normal controls. Their deficits were similar to those seen in Parkinson's disease but of less severity than a group of PD subjects with moderate stage disease. There was a wide variation among HIV subjects and correlations with age, disease duration, and other HIV markers may be possible as the cohort expands.

Disclosures: T. Martin: None. **M. Trager:** None. **A. Velisar:** None. **M. Miller Koop:** None. **E. Müller-Oehring:** None. **K. Poston:** None. **T. Schulte:** None. **H. Bronte- Stewart:** None.

Poster

789. HIV-Related Neuroinflammation and Neurotoxicity

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 789.02/K15

Topic: C.06. Neurotoxicity, Inflammation, and Neuroprotection

Support: CNPq (National Council for Scientific and Technological Development)

FAPERJ (Research Support Foundation of the Rio de Janeiro State)

Brazilian Ministry of Health

Title: Subversion of Schwann cell glucose metabolism by Mycobacterium leprae

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Abstract: Leprosy is a chronic infectious disorder of the peripheral nerves and skin macrophages caused by the intracellular pathogen *Mycobacyerium leprae* (*M. leprae*). There are growing evidences suggesting that leprosy neuropathy is due to Schwann cell dedifferentiation. Of importance, our group demonstrated that *M. leprae* is also able to modulate Schwann cells energy metabolism for its own benefit. Our results clearly show that infected Schwann cells increase glucose uptake with a concomitant upregulation in glucose-6-phosphate dehydrogenase

(G6PDH) activity, the key enzyme of the oxidative pentose pathway. We also found a two-fold reduction in lactate release from infected cells when compared to control ones. In addition, we observed mitochondria shutdown in infected cells *in vitro* and mitochondrial swelling in histological analysis of nerve biopsies from patients diagnosed with pure neural leprosy. When we blocked the key enzyme of the oxidative phase of pentose phosphate pathway, the G6PD, we successfully recover the production of lactate by infected Schwann cells along with a drop in *M. leprae* viability. The pentose cycle is an important pathway that generates NADPH for reductive biosynthesis and glutathione regeneration. We observed that infected Schwann cells have increased G6PD activity and expression, being more resistant to oxidative stress than control non-infected cells. This oxidative stress protection was avoided when we applied 6-ANAM (a specific pentose cycle inhibitor) or by the glutathione synthesis inhibitor BSO, an inhibitor of gamma-glutamylcysteine synthetase. In short, our current data points to the notion that low levels of lactate produced by infected wrapping Schwann cells might induce energy deprivation to their counterparts axonal units, which are highly dependent of this fuel source. As conclusion, we identified the enzyme G6PD, as a new host-target to be explored in leprosy neuropathology treatment, since its inhibition restored lactate levels in infected Schwann cells and, more important, was able to kill the intracellular pathogen.

Disclosures: **B.S. Mietto:** None. **R.C.A. Medeiros:** None. **K.G.C. Vasconcellos:** None. **F.K.L. Cardoso:** None. **T.G.T. Pinto:** None. **L.S. Rodrigues:** None. **M. Gandini:** None. **J.J. Amaral:** None. **S.L.G. Antunes:** None. **S. Corte-Real:** None. **P.S. Rosa:** None. **M.C.V. Pessolani:** None. **J.A.C. Nere:** None. **E.N. Sarno:** None. **L.R.B. Silva:** None. **M. Sola-Penna:** None. **M.F. Oliveira:** None. **M.O. Moraes:** None. **F.A. Lara:** None.

Poster

789. HIV-Related Neuroinflammation and Neurotoxicity

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 789.03/K16

Topic: C.06. Neurotoxicity, Inflammation, and Neuroprotection

Title: Magnetoencephalography as a biomarker of HIV central nervous system impact among young adults with HIV: Preliminary findings

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Abstract: Although central nervous system (CNS) effects of HIV infection have become more subtle in the era of antiretroviral treatment (ART), sensitive biomarkers are critical for monitoring continued impacts of chronic inflammation, ART, and immune activation. Magnetoencephalography (MEG) measures brain functional activation across frequency bands with fine-grained spatial and temporal resolution. This preliminary study compared brain activity of youth with HIV (YWH) and uninfected controls using MEG.
Methods: Twelve male youth age 18-24 with behaviorally acquired HIV (YWH) on ART and 13 age- and education-matched uninfected male controls completed tests of verbal learning and memory, processing speed, verbal fluency, and inhibition; a MEG working memory (N-back with 0, 1- and 2-back) task; and structural MRI. MEG data were processed using Fast-VESTAL source imaging program. Activation for control subjects was subtracted from that of YWH across frequency bands and cortical areas. Task performance and activation differences were compared using t-tests with $p < 0.01$ and an additional cluster analysis with size > 500 voxels. Nadir and current CD4 t-cell count and viral load were abstracted from clinical records for YWH.
Results: Mean current CD4 count for YWH was 494; 10 had undetectable current plasma viral load. HIV+ had significantly lower verbal learning and memory and marginally lower 0-back d' scores. Analysis of MEG during the N-back task showed numerous significant areas of hyper- and hypoactivation in YWH compared to controls. Bilateral hyperactivation across frequency bands and conditions included dlPFC, anterior cingulate/paracingulate gyrus, superior parietal lobe, fusiform and insular cortex; and supplementary motor area in beta and gamma frequencies. Areas of significant hypoactivation included bilateral frontal pole across frequency bands and conditions, and widespread superficial cortical gray areas in beta and gamma frequencies.
Conclusion: YWH show a distinct pattern of both hyper- and hypoactivation on MEG during performance of a working memory task relative to controls. In general, areas of hypoactivation were in more superficial areas in higher frequency bands, possibly reflecting decreased activity in inhibitory GABAergic interneurons. Hyperactivation, seen in deeper areas, may reflect increased excitatory response. The findings support further study of MEG as a sensitive marker of early CNS impact in relatively healthy individuals with HIV. Future research will explore the direct attribution of effects to HIV controlling for comorbid factors, along with correlations with task performance and impact of disease severity.

Disclosures: S.L. Nichols: None. **A. Robb Swan:** None. **A. Angeles:** None. **C. Fennema-Notestine:** None. **R.R. Lee:** None. **M. Huang:** None.

Poster

789. HIV-Related Neuroinflammation and Neurotoxicity

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 789.04/K17

Topic: C.06. Neurotoxicity, Inflammation, and Neuroprotection

Support: NIH Grant R01 NS083164

NIH Grant F31 MH101019

NIH R01 MH085606

Title: MMP-9 facilitation of HIV neuropathogenesis

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Abstract: Activation of macrophages and microglia in the central nervous system (CNS) by HIV plays a pivotal role in the progressive development of neural damage and cognitive deficits. No current treatments are available that effectively reduce the inflammatory response and neural damage. Although it is widely acknowledged that substances secreted from macrophages and microglia induce neuronal damage, the precise mechanisms of pathogenesis are not well understood. To identify potential neurotoxic factors secreted by macrophages we cultured human monocyte-derived macrophages, challenged them with inactive HIV virions, verified neurotoxic activity on primary neurons and then assessed the medium content on an antibody based array to screen for the presence of 507 proteins. The results revealed robust expression of matrix metalloprotease-9 (MMP-9) as well as a variety of other proteins involved in chemotaxis, angiogenesis and growth and differentiation. MMP-9 release was verified by zymography which revealed predominantly proMMP-9. Small amounts of MMP-3, which cleaves proMMP-9 to generate active MMP-9, were also present and correlated with the toxic activity of the medium. Activation by HIV was also associated with a shift in macrophage morphology toward expression of podosomes, adhesive structures associated with the release of MMPs. Based on these observations we evaluated the potential contribution of MMP-9 to neurotoxicity by adding 1-5 ng/ml activated MMP-9 to primary cultures of cortical/hippocampal neurons and assessing calcium and cytoskeletal dysregulation. A gradual rise in mean intracellular calcium was seen over 66 min in the absence of any acute effects of the MMP-9. Individual cells showed calcium spikes which increased in frequency with time and were prevented by co-incubation with the NMDA receptor antagonist AP5. Addition of MMP-9 inhibitors to conditioned medium from HIV treated macrophages strongly suppressed the ability to evoke calcium dysregulation and addition of a neutralizing antibody to tissue inhibitor of metalloprotease-1 (TIMP-1) increased

the toxic activity of the medium. Since MMP-9 is involved in the metabolism of neurotrophins we evaluated NGF content in culture mouse microglia activated with HIV virions. Endogenous NGF was significantly reduced by HIV. These results indicate the MMP-9 may cause neural dysfunction in response to inflammation by enhancing NMDA receptor activity while at the same time reducing neurotrophin support. Compounds that suppress the actions of MMP-9 are protective and have potential application for the prevention of HIV-associated neural damage.

Disclosures: R.B. Meeker: None. **Y. Xie:** None. **K.S. Williams:** None.

Poster

789. HIV-Related Neuroinflammation and Neurotoxicity

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 789.05/L1

Topic: C.06. Neurotoxicity, Inflammation, and Neuroprotection

Support: NIH R01NS083410

NIH T32NS041231

Title: Matrix metalloproteinase-mediated mislocalization of aquaporin-4 and impaired metabolite clearance in HIV

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Abstract: Impaired metabolite waste clearance is implicated in HIV-associated neurocognitive deficits (HAND); however, mechanisms by which this occurs have not yet been explored. Aquaporin-4 (AQP4), the brain's primary water channel, is a major conduit through which waste is cleared from the brain. AQP4 requires polarized localization in perivascular endfeet in order to efficiently clear waste. Total levels of AQP4 are increased in the HIV brain however localization has yet to be examined in this context. AQP4 mislocalization occurs in normal aging and we hypothesize that HIV accelerates this process. Using a mouse model of HIV, this study is evaluating AQP4 localization as well as impaired waste clearance by using *in vivo* magnetic resonance spectroscopy (MRS). Furthermore, we hypothesize that the matrix metalloproteinase (MMP) class of enzymes, which are upregulated in HIV, promote mislocalization through proteolytic cleavage of AQP4-anchoring proteins. Preliminary data suggest that MMP-1 in particular promotes increased GFAP immunofluorescence while concomitantly reducing that of the AQP4-anchoring protein beta-dystroglycan. Additionally, *in vivo* MRS reveals that the hMMP-1 Tg mouse brain has significantly higher levels of the glial metabolite myo-inositol.

This increase in myo-inositol metabolite levels is consistent with enhanced glial production and/or impaired waste clearance. Thus, this study is examining the role of MMP-1 in disrupting AQP4 localization through the use of an *in vitro* model of the blood-brain barrier, whereby cultured astrocyte endfeet exhibiting polarized expression of AQP4 are treated with recombinant MMP-1 or vehicle control. Given these preliminary data it is possible that MMP inhibition could provide a new therapeutic target in treating impaired waste clearance in HAND.

Disclosures: P. Bozzelli: None. **M. Allen:** None. **K. Conant:** None.

Poster

789. HIV-Related Neuroinflammation and Neurotoxicity

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 789.06/L2

Topic: C.06. Neurotoxicity, Inflammation, and Neuroprotection

Support: MH087332

MH104131

MH105330

Title: IFNβ protects neurons in a CCL4-dependent fashion against HIV-1 GP-120 induced injury

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Abstract: Human immunodeficiency virus-1 (HIV-1) invades the central nervous system (CNS) soon after peripheral infection and often causes HIV-associated neurocognitive disorders (HAND). Type I interferons are critical mediators of the anti-viral immune response and interferon-β (IFNβ) has been implicated in the control of HIV and SIV infection in the brain. Key neuropathological features of AIDS patients include the loss of neuronal dendrites and presynaptic terminals, and activation of glial cells, and these hallmarks are recapitulated in transgenic (tg) mice expressing HIV gp120 in the brain (HIVgp120tg). Moreover, we recently identified in a genome-wide, central nervous system (CNS) gene expression analysis of HIVgp120tg mice genes that factors of the innate immune response are differentially expressed in association with the neuropathological phenotype. In the present study we employed quantitative reverse transcription polymerase chain reaction (qRT-PCR) to investigate an anti-viral immune response mounted by HIV/gp120tg mice, inducing the expression of interferon stimulated genes (ISGs). Quantitative RT-PCR analysis confirmed the transient expression of

IFNβ in 1.5 month-old HIV/gp120tg mouse brains, but not in brains from 3- and 6 month-old animals.. A four-week intranasal IFNβ treatment delivered to mice at 3-4 months of age, which is after endogenous IFNβ levels had become undetectable, triggered IFN-induced gene expression and abrogated neuronal damage in HIV/gp120tg mice without altering astrocytosis. In *vitro* experiments showed that the neuroprotective effect of IFNβ against toxicity of HIV gp120 required the presence of IFNα receptor 1 (IFNAR1) and the induction of CCL4, a known HIV-suppressive factor. Taken together, these results identify IFNβ as a neuroprotective agent that can ameliorate HIV gp120-induced brain injury *in vivo* after intranasal application.

Disclosures: V.E. Thaney: None. **M.M. Hoefer:** None. **R. Maung:** None. **M. Kaul:** None.

Poster

789. HIV-Related Neuroinflammation and Neurotoxicity

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 789.07/L3

Topic: C.06. Neurotoxicity, Inflammation, and Neuroprotection

Support: AA023165

AA017347

AA017168

NS075097

AG047366

Michael J Fox Foundation

Title: Aging with HIV - neurofunctional correlates of cognitive interference and motor demands: A comparison with Parkinson's disease

Authors: *E. M. MULLER-OEHRING[1,3], K. L. POSTON[2], H. M. BRONTE-STEWART[2], C. HARDCASTLE[3], T. MARTIN[2], A. PFEFFERBAUM[3], E. V. SULLIVAN[1], T. SCHULTE[3,4]; [1]Dept. Psychiatry & Beh. Sci., Stanford Univ. Sch. of Med., Palo Alto, CA; [2]Neurol., Stanford Univ. Sch. of Med., Stanford, CA; [3]Neurosci. Program, SRI Intl., Menlo Park, CA; [4]Pacific Grad. Sch. of Clin. Psychology, Palo Alto Univ., Palo Alto, CA

Abstract: With the widespread use of antiretroviral therapy, patients with human immunodeficiency virus (HIV) infection live longer and may show age-related functional decline similar to those of Parkinson's disease (PD), given that both diseases affect subcortico-cortical

pathways subserving cognition and motor function. We used functional MRI to assess brain responses in 15 aging HIV-infected individuals compared with 11 PD patients and 15 controls using a Stroop Match-to-Sample task. The task required matching the color of a cue to the font color of a Stroop word and examined cognitive interference from incongruent (inc) Stroop words (the word RED written in blue font) relative to congruent (con) words (the word RED written in red font). Motor functional demands were manipulated by requiring subjects either to switch response types (RS) or to repeat the same response (RR). All groups showed significant behavioral Stroop effects (inc>con). HIV, but not PD, exhibited more cognitive interference and slower response speed than controls. PD showed enhanced cognitive performance (faster response times (RTs), fewer errors) off- compared to on-dopaminergic medication. fMRI analysis was conducted with SPM8 using a full-factorial ANOVA with group (HIV, PD, CTL) and cognitive (inc, con) and motor demands (RR, RS) as factors (analysis threshold $p<0.05$ corrected for multiple comparisons). Fronto-parietal cortices were activated with cognitive demands (inc>con) and fronto-cerebellar regions with motor demands (RS>RR). HIV and PD off-dopaminergic medication did not differ in cognitive and motor demand activation maps despite enhanced cognitive interference and RT slowing in HIV. However, for high motor response demands (RS>RR), PD on-dopaminergic medication exhibited greater fronto-cerebellar activation than off-medication, and greater activation compared to HIV and controls. In controls, older age was associated with less precentral motor cortical activity (to RS>RR) (Rho=-.66); yet, faster RT to high motor demands (Diff. RTRS-RR) correlated with greater cerebellar activation (Rho=-.63) indicative of compensation through redistribution of resources within the fronto-cerebellar system. HIV subjects in our sample did not elicit activation for neurofunctional adaption to manage deficits or counteract RT slowing potentially rendering them vulnerable to functional decline with aging.

Disclosures: E.M. Muller-Oehring: None. **K.L. Poston:** None. **H.M. Bronte-Stewart:** None. **C. Hardcastle:** None. **T. Martin:** None. **A. Pfefferbaum:** None. **E.V. Sullivan:** None. **T. Schulte:** None.

Poster

789. HIV-Related Neuroinflammation and Neurotoxicity

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 789.08/L4

Topic: C.06. Neurotoxicity, Inflammation, and Neuroprotection

Support: NIH grant NS R01084817

NIH grant DA R01033966

NIH grant NS R01060632

Title: Excitability of mPFC pyramidal neurons is increased in older HIV-1 transgenic rats through alteration in K^+ channel activity

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Abstract: The medial prefrontal cortex (mPFC) plays an important role in regulating cognitive function and is profoundly dysregulated in HIV-infected patients. Despite combined antiretroviral therapy (cART), HIV-induced neurological and psychological deficits occur in >50% of HIV^+ patients and these deficits may worsen as the HIV infected population ages. We evaluated the the impact of HIV and age on mPFC using HIV Tg older (12 months) rats. Our previous studies have demonstrated that acute exposure to a toxic HIV-1 protein, Tat, induces an abnormal increase in the excitability of mPFC pyramidal neurons. Such mPFC neuronal hyperactivity is also found in adolescent (6-7 weeks old) and young adult (5-6 months old) HIV-1 transgenic (Tg) rats (which express 7 of 9 HIV-1 genes), and is due in part to over-activation/expression of the voltage-gated Ca^{2+} channels (VGCCs, specifically the L-type). We show here that the excitability of mPFC pyramidal neurons is increased in older HIV-1 Tg rats. To assess the mechanism driving the hyperactivity of mPFC pyramidal neurons in aged HIV-1 Tg rats, we focused on HIV-mediated changes in K^+ channel activity. Whole-cell patch-clamp recordings were conducted under blockade of Na^+ and Ca^{2+} channels, as well as glutamate and GABA receptors, to isolate K^+ channel activity. We found that the input resistance (R_{in}) was increased (reflecting reduced activity of K_{2P} channels), inward rectification was reduced (suggesting reduced activity of K_{ir} channels), and voltage-gated K^+ efflux was also decreased (indicating reduced activity of K_v channels)(all $p<0.05$) in mPFC pyramidal neurons from older HIV-1 Tg rats as compared to those from age-matched non-Tg rats. The reduced K_{2P} and K_v channel activity is in agreement with the decreased rheobase and increased firing, while the reduced K^+ influx via K_{ir} channels could increase extracellular K^+ levels, which ultimately contributes to neuronal hyperactivity. Intriguingly, in a parallel study presented in the meeting (Khodr et al., 2016), we found that there was no significant difference in Ca^{2+} influx through VGCCs in neurons from HIV-1 Tg rats and age-matched non-Tg rats. Together, these novel findings suggest that the increased mPFC neuronal excitability in older HIV-1 Tg rats is mediated mainly by reduction of K^+ channel activity. Thus, K^+ channels could be a potential target for treating HIV^+ patients with neurological and psychological deficits.

Disclosures: **L. Chen:** None. **C.E. Khodr:** None. **L. Al-Harthi:** None. **X. Hu:** None.

Poster

789. HIV-Related Neuroinflammation and Neurotoxicity

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 789.09/L5

Topic: C.06. Neurotoxicity, Inflammation, and Neuroprotection

Support: NIH Grant NSo77873

Title: Co-morbid Effects of Methamphetamine and HIV-1 Tat inMicroglia Neurotoxic Activity: Role of CX3CR1/CX3L1 Axis

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Abstract: Methamphetamine (Meth) abuse not only increases the risk of HIV-1 infection but potentiates HIV-1 associated neurotoxicity as well. The mechanisms underlying this potentiation are not fully understood. Recently, CX3CL1/CX3CR1 axis has gained attention as promising targets for specific immunomodulation. Increasing evidence indicates that deficient neuron-microglia signaling impairs brain functionality and results in neurodegenerative abnormalities and cognitive deficits. It has also been demonstrated that infected brain cells continuously express and release Tat protein despite control viral replication. We hypothesize that Meth and HIV-1 protein Tat may impair CX3CL1/CX3CR1 function leading to an alteration of microglia neurotoxic activity. To test this hypothesis we studied the co-morbid effects of Meth/Tat on rat microglia neurotoxic activity associated with CX3CL1/CX3CR1. Our data showed that Meth/Tat synergistically inhibited microglia CX3CR1 expression and induced microglia neurotoxic secretion. Neutralizing CX3CR1 by a specific CX3CR1 antibody in microglia significantly enhanced Meth/Tat-induced microglia activation and resulting in neuronal injury. Augment of CX3CR1 signaling by treatment microglia with recombinant CX3CL1 (rCX3CL1) protected against Meth/Tat-induced microglia neurotoxicity. These results suggest that Meth/Tat induce microglia neurotoxicity via regulation of CX3CL1/CX3CR1. We also found that rCX3CL1 increase of microglia expression of Rac1 and MFG-E8 was attenuated by Meth/Tat. The increase of Rac1 expression provoked rearrangement of microglia cytoskeleton and propelled microglia migration towards to apoptotic neurons while the increase of MFG-E8 expression promoted microglia engulfment and clearance of apoptotic neurons. Our data suggest that activation of CX3CL1/CX3CR1 axis may have the potential in suppression of Meth/Tat-associated microglia neurotoxicity. Supported by NIH grant R01NS077873

Disclosures: **J. Liu:** None. **E. Xu:** None. **H. Liu:** None. **H.(. Xiong:** None.

Poster

789. HIV-Related Neuroinflammation and Neurotoxicity

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 789.10/L6

Topic: C.06. Neurotoxicity, Inflammation, and Neuroprotection

Support: NIDA R00 DA033878

T32 DA007244

Title: Neuroprotective effects of fatty acid amide hydrolase inhibition in a HIV-1 tat model of neuoAIDS

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Abstract: The advent of combined antiretroviral therapy (cART) has greatly improved the prognosis of patients infected with human immunodeficiency virus type 1 (HIV-1). However, a significant proportion of this population still exhibits a marked decrease in cognitive abilities known as HIV-1 associated neurocognitive disorder (HAND). HIV-1 does not infect neurons but produces viral toxins, such as transactivator of transcription (Tat) protein, that have been shown to disrupt cellular calcium equilibrium resulting in excitotoxic conditions. Loss of calcium regulation can give rise to synaptodendritic injuries and cell death, the former of these is highly correlated with loss of cognitive function in HIV-1 patients. Cannabinoids are known to show neuroprotective effects in several models of neurodegenerative diseases, however, the role of the endocannabinoid system in neuroAIDS is not well known. Here, we investigated neuroprotective effects of inhibiting fatty acid amide hydrolase (FAAH), a major catabolic enzyme of an endogenous cannabinoid N-arachidonoyl ethanolamine (anandamide/AEA). Specifically, we aimed to test whether a selective and potent FAAH inhibitor, PF3845, produces neuroprotective effects in a Tat-treated, murine primary prefrontal cortex neuron culture. To assess neuronal damage and viability after exposure to Tat, with or without PF3845, we used calcium imaging, structural analysis of dendritic volume and length, and measured neuronal survival over 72 hours. PF3845 significantly reduced excitotoxic levels of intracellular calcium and neuronal death induced by Tat. Neuroprotective effects of PF3845 were fully blocked by CB_1, but not CB_2 receptor antagonism. This indicates that effects observed following PF3845 application are mediated by the CB_1 signaling pathway and are likely the result of increased levels of AEA following FAAH inhibition. Finally we showed that neurons exposed to Tat show reduced

dendritic volume and length changes that are partially blocked by PF3845. In conclusion, our results indicate that selective FAAH inhibition protects against Tat-induced neuronal damage and promotes neuronal survival in cell culture. Further studies are necessary to determine the therapeutic potential of endocannabinoid catabolic enzymes in models of neuroAIDS.

Disclosures: D.J. Hermes: None. **C. Xu:** None. **M.J. Niphakis:** None. **K. Mackie:** None. **B.F. Cravatt:** None. **A. Lichtman:** None. **B. Ignatowska-Jankowska:** None. **S. Fitting:** None.

Poster

789. HIV-Related Neuroinflammation and Neurotoxicity

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 789.11/L7

Topic: C.06. Neurotoxicity, Inflammation, and Neuroprotection

Title: Resveratrol analog timbd modifies hiv-1 gp120 associated inflammation in astrocytes

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Abstract: SNIP Abstract
Resveratrol Analog (TIMBD): Implication in HIV-Gp120 Associated Neuro-inflammation in Astrocytes
Human Immunodeficiency Virus (HIV)-associated neurocognitive disorder (HAND) is one of the undermining disorders that affect majority of HIV infected patients. Patients with HAND suffer from both cognitive and motor dysfunction which is characterized by memory loss and changes in personality. Astrocytes are considered the major reservoirs of the HIV in the brain. Resveratrol (Res) is one of the known phytoestrogens with potential anti-inflammatory activity. However studies suggests resveratrol's poor specificity and bioavailability as a reason for its poor efficacy. To overcome these problems associated with Res, our research group has developed novel Res analog (TIMBD). The inflammatory cytokines and chemokines associated with HIV-gp120 in astrocytes plays a critical role in HAND development in HIV patients. Patients with HIV are reported with high levels of IL6 and IL8 which have been shown to be critical in the damage process. In this study we demonstrated that TIMBD downregulated inflammatory mediators-induced by HIV-gp120 transfection in SVG astrocytic cell lines which suggests that TIMBD has the potential to inhibit HIV-gp120 induced neuro-inflammation. Briefly, SVG astrocytic cell line was cultured in growth media. Cells were transfected with mock/or HIV gp120 plasmid and treated with TIMBD for up to 48 h. RNA was isolated and mRNA levels of IL6 and IL8 were quantified. The expression of HPRT RNA was used for

normalization. Protein levels of transcription factors AP1, pSTAT3 and NFKB were measured using western blotting. We demonstrated increased expression of inflammatory cytokines IL6 and IL-8 with gp120 transfection in SVGA astrocytes cell line. TIMBD but not Res was able to decrease the expression of those pro-inflammatory mediators. We concluded that Res analogs TIMBD is able to modify the inflammatory mediators in HIV-gp120-transfected astrocytes.

Disclosures: F.E. Abdalla: None. **A. Nookala:** None. **A. Kumar:** None. **H. Bhat:** None.

Poster

789. HIV-Related Neuroinflammation and Neurotoxicity

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 789.12/L8

Topic: C.06. Neurotoxicity, Inflammation, and Neuroprotection

Support: R01 MH089722

R01 MH102151

U54 EB020403

Title: longitudinal effects of combinatory antiretroviral therapy on white matter microstructure during childhood brain development

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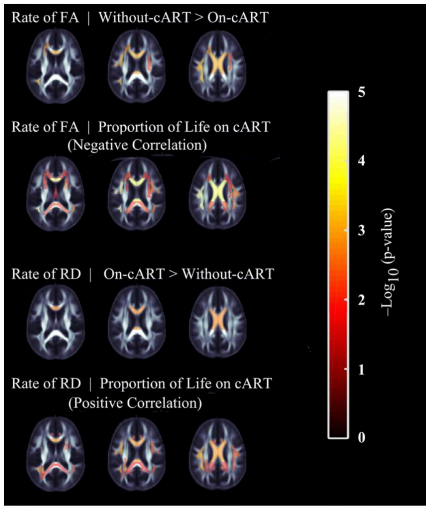
Abstract: *Background*: Combination antiretroviral therapy (cART) has been shown to improve cognitive performance and suppress its decline. However, the effect of cART, and the timing of its initiation in prenatally infected children may have affects on brain development. Here, we set out to compare brain white matter microstructure development in HIV-infected children to that

of uninfected individuals, HIV+ children on cART to those who are not on cART, and look further at differences between those administered cART at the start of the study compared to those who deferred initiation until they met past global criteria based on immunosuppression set by the WHO. *Methods*: T1- and diffusion- weighted images (DWI) were collected one year apart from 92 children (39 HIV+, 30 on cART at the initial scan and 53 HIV-; Figure 1) from the PREDICT study (Figure 1. Right). Fractional anisotropy (FA) and diffusivity averages in regions of interest (ROIs) were extracted from DWIs processed using ENIGMA-DTI protocols and the rate of change in the measures was calculated. The false discovery rate ($q<0.05$) was used to account for multiple tests. *Results*: We found a lower rate of change in FA and higher rate of change in radial diffusivity (RD) in children on cART compared to children without treatment for regions including the corpus callosum (CC). The rate of change in FA and RD was also found to be significantly associated with proportion of life on cART, (time on cART over age) (Figure 2. Left). The annual change in FA of the CC in children not on cART at the time of the first scan was found to be higher than for the HIV- children (P=0.0181, Beta=0.0266); no difference was found between HIV+ children initially on cART and HIV- children. *Conclusion*: Results indicate differences in white matter microstructure between on-cART and without-cART children, which are correlated with proportion of life on treatment. On-cART children show similar diffusivity as HIV- group, suggesting neurodevelopment in HIV+ children without-cART is altered. Additional follow up is needed to determine long-term deficits.



	HIV-infected	HIV-uninfected	P-value
Subjects, (N)	39	53	0.09
Age at baseline, Mean (sd), yr	10.81 (2.17)	11.01 (2.80)	0.65
Sex, % Male	%56	%42	0.24
School Attendance, % Attended	%100	%100	1.0
Caretaker income, (N)*			0.07
Less than average	7	16	
Average	22	27	
Greater than average	1	10	
Imaging Site, (N)			0.77
Chiang Mai University Hospital: Chiang Mai	24	31	
Chulalongkorn University Hospital: Bangkok	15	22	
Exposure status, exposed/unexposed	--	25/28	0.40
cART status, on/deferred	30/9	--	<0.001
Age of cART initiation, Mean (sd), yr	7.91 (2.17)	--	--
Time on cART before assessment, Mean (sd), yr	2.81 (0.72)	--	--
Time between assessments, Mean (sd), yr	1.21 (0.36)	0.88 (0.11)	<0.001

Figure 1. Left) Plot displays diffusion tensor rates of regions that were found to be significantly different between the labeled groups, or correlated with proportion of life on cART. Colors indicate "-log" of the p-value of the performed test for that region; a change in color indicates a change in the region's significance by a factor of 10. **Right)** Participant demographics are listed for each group; (*****) denotes missing data (detailed in Methods). Statistical analyses were performed on non-missing data.

Disclosures: A. Saremi: None. **N. Jahanshad:** None. **W. Prasitsuebsai:** None. **T.M. Nir:** None. **L. Aurpibul:** None. **K. Pruksakaew:** None. **S. Lerdlum:** None. **P. Visrutaratna:** None. **S.J. Kerr:** None. **T. Puthanakit:** None. **R. Paul:** None. **V.G. Valcour:** None. **P.M. Thompson:** None. **J. Ananworanich:** None.

Poster

789. HIV-Related Neuroinflammation and Neurotoxicity

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 789.13/L9

Topic: C.06. Neurotoxicity, Inflammation, and Neuroprotection

Support: NIH Grant P30AI087714

NIH Grant R03MH107261

NSF Grant HRD-100286

NIH Grant 1R01DE019064

NIH Grant 1R01DE022285

NIH Grant P51OD011107

Title: Diminished nestin positive neurons in pediatric SIV infection

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Abstract: Pediatric HIV infection remains a global health crisis with an estimated 650 children under the age of 15 years becoming infected with HIV-1 each day. Perinatally HIV-1 infected individuals are disproportionately affected by HIV-1 related neurological impairments. The proposed studies take advantage of ongoing pediatric SIV pathogenesis and vaccine studies to test the hypothesis that pediatric SIV infection diminishes actively proliferating stem cells and neurogenesis in the dentate gyrus. Newborn rhesus macaques (*Macaca mulatta*) received intravenous inoculation of SIVmac251 or vehicle within 72 hours after birth. After a 6-18 week survival time, the animals were sacrificed and the brains prepared for quantitative histopathological analysis. Serial-sections spanning the entire hippocampus were immunostained for GFAP, nestin, or doublecortin (putative markers for astrocytes and immature neurons respectively). We report here a significant reduction in nestin and doublcortin immunoreactive cells in the dentate gyrus of SIV-infected compared to age-matched control subjects. We also found an elevation in GFAP positive cells, possibly a consequence of inflammation. Matched sections were double labeled for GFAP/nestin or nestin/doublecortin for confocal analysis revealing few/none double-labeled cells. The loss of immature neurons may contribute to the rapid and persistent neurocognitive decline associated with pediatric HIV infection. This model

presents a platform in which to test therapeutic interventions aimed at ameliorating the negative consequences of HIV-1 through the neurogenesis pathway.

Disclosures: **L. Rodriguez:** None. **R. Jobarteh:** None. **M. Swang:** None. **A. Charles:** None. **N. Algarzae:** None. **K. Van Rompay:** None. **K. De Paris:** None. **M.W. Burke:** None.

Poster

789. HIV-Related Neuroinflammation and Neurotoxicity

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 789.14/L10

Topic: C.06. Neurotoxicity, Inflammation, and Neuroprotection

Support: NIH NIGMS SC1GM113691

NIH NIMH G12MD007600

R24 OD 018546-01

UPR-RP NEURO-ID Program R25 NS080687-06

Title: Characterizing cathepsin B/serum amyloid p complex-induced neuronal dysfunction in a mouse model of HIV-associated encephalitis

Authors: *A. M. OGANDO VÉLEZ[1], Y. M. CANTRES-ROSARIO[1], M. PLAUD[1], S. GORANTLA[2], L. M. MELÉNDEZ[1];
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Abstract: HIV-infected macrophages infiltrate the blood brain barrier to the brain, where they secrete viral and cellular proteins, triggering neuronal dysfunction and death. Despite the efficacy of antiretroviral therapy, mild forms of HIV-associated neurocognitive disorders (HAND) remain prevalent. Infected macrophages secrete cathepsin B, a lysosomal protease, which interacts with serum amyloid p component (SAPC) at the extracellular level. Cathepsin B and SAPC secreted from HIV-infected macrophages induce apoptosis of primary rat neurons *in vitro*, which can be decreased by the pre-treatment of macrophage-conditioned media (MCM) with anti-cathepsin B and SAPC antibodies. The pre-treatment of HIV-infected MCM with these antibodies also reduces β-amyloid peptides in neurons. In addition, both proteins co-localize with β-amyloid peptides in tissues from HIV-associated dementia (HAD) patients and Alzheimer's disease patients, compared to healthy individuals, suggesting a role of the complex in neurodegeneration. We have demonstrated that recombinant active cathepsin B added in MCM is

internalized by neurons. Moreover, the levels of cathepsin B internalization are proportional to the levels of HIV infection. Therefore, we hypothesize that targeting cathepsin B/SAPC complex in MCM represents a viable approach to elucidate the mechanism of cathepsin B-induced neuronal dysfunction and test its potential as a candidate for drug development against HAND. To test this hypothesis, we exposed SK-N-SH neuroblastoma cells to histidine-tagged cathepsin B in neuronal culture media alone or in presence of anti-cathepsin B antibody, and localized the histidine tag in neurons by intracellular flow cytometry. Histidine-tagged cathepsin B was internalized by neurons (52.0%), a mechanism that was partially reduced by the pre-treatment of the media with anti-cathepsin B antibody (34.9%). The neuroprotective potential of cathepsin B antibody was confirmed by immunofluorescence, demonstrating increased MAP2 staining and recovered morphology. Then, we examined the presence of cathepsin B and SAPC in the brain of a mouse model of HIV-encephalitis (HIVE), generated by intracranial inoculation of control and HIV-infected human MDM. Cathepsin B and SAPC were identified in the striatum of the mice inoculated with HIV-infected MDM by western blot, along with increased expression of cleaved caspase-3, compared to animals inoculated with uninfected MDM. Our results reveal a novel mechanism by which cathepsin B triggers neuronal dysfunction, and validate the use of HIVE mice as an *in vivo* model to test the effectiveness of anti-cathepsin B and SAPC inhibitors against HAND.

Disclosures: A.M. Ogando Vélez: None. **Y.M. Cantres-Rosario:** None. **M. Plaud:** None. **S. Gorantla:** None. **L.M. Meléndez:** None.

Poster

789. HIV-Related Neuroinflammation and Neurotoxicity

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 789.15/L11

Topic: C.06. Neurotoxicity, Inflammation, and Neuroprotection

Support: OHSU Foundation Grant

ARC Foundation Scholarship

Title: Anti-n-methyl-d-aspartate receptor encephalitis: from model to medicine

Authors: *B. JONES, A. GOEHRING, E. GOUAUX, G. L. WESTBROOK;
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Abstract: Anti-N-Methyl-D-Aspartate Receptor (NMDAR) encephalitis is a severe autoimmune disease associated with anti-NMDAR immunoglobulin (Ig) synthesis. First described by Dalmau

and colleagues in 2007 patients with this condition develop a profound neuropsychiatric syndrome consisting of psychosis, seizures, cognitive impairment, and autonomic instability. The progressive nature of the illness is thought to result from CNS penetrance of antibodies directed against the NMDAR GluN1 subunit. These anti- GluN1 IgG's are hypothesized to induce receptor internalization producing global hypofunction in NMDAR mediated (glutamatergic) synaptic transmission. To investigate the immune complement contributing to anti-NMDAR encephalitis and the electrophysiological aberrations generated by anti- NMDAR immunoglobulins we developed a autoimmune mouse model that recapitulates the pathogenesis of the disease. To create our model we inoculated animals (Balbcj and C57Bl6; male/female @ 2m.o.) with fully assembled NMDA receptor holo-protein embedded in a vesicle-like lipid bilayer. This proteoliposome preparation maintains the quaternary structure of the NMDAR promoting the generation of antibodies with conformational specificity. Unlike mice exposed to NMDAR subunit peptide fragments in adjuvant, mice immunized with NMDAR proteoliposome develop symptomology resembling that observed in human patients including seizures, stereotyped dyskinesias, and hyperactivity. Approximately twenty-five percent of treated mice died suddenly within six weeks of NMDAR proteoliposome exposure. Immunoglobulins isolated from the serum of these mice specifically targeted the GluN1 subunit of the NMDA receptor, confirmed by immunofluorescent labeling of NMDAR expressing HEK293 cells, primary neuronal cultures and in mouse brain sections. At six weeks post inoculation neuropathology conducted in our NMDAR encephalitis model showed significant perivascular lymphocyte cuffing and brain parenchyma infiltration of activated macrophages, T, B and plasma cells. We are investigating the electrophysiological properties of primary neuronal cultures acutely and chronically exposed to antibodies derived from our mouse model.

Disclosures: **B. Jones:** None. **A. Goehring:** None. **E. Gouaux:** None. **G.L. Westbrook:** None.

Poster

789. HIV-Related Neuroinflammation and Neurotoxicity

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 789.16/L12

Topic: C.06. Neurotoxicity, Inflammation, and Neuroprotection

Title: Efficacy and mechanism of action of low dose emetine against human cytomegalovirus

Authors: *R. MUKHOPADHYAY;
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Abstract: Human cytomegalovirus (CMV) is a ubiquitous β-herpesvirus whose infection is a major public health concern. CMV causes serious neurodevelopmental sequelae in congenitally-

infected children, including mental retardation, cerebral palsy, and sensorineural hearing loss. HIV-infected children infected with CMV suffer from rapid neurological deterioration. HIV-associated CMV encephalitis is one of several central and peripheral nervous system infections seen in late-stage disease. Despite highly-active antiretroviral therapy CMV infection is associated with retinitis, encephalitis, ventriculitis, myelitis, radiculoganglionitis, and peripheral neuropathies. These infections usually occur in patients with end stage AIDS or those non-compliant with therapy. Although limited drugs are available for HCMV therapy, development of new agents is desired. Through screening of the LOPAC library, we identified emetine as HCMV inhibitor. Additional studies confirmed the anti-HCMV activities of emetine in human foreskin fibroblasts, with EC_{50} - 40±1.72 nM, CC_{50} - 8±0.56 μM, and selectivity index of 200. HCMV inhibition occurred after virus entry, but before DNA replication, and resulted in decreased expression of viral proteins. Since emetine efficacy decreased significantly in low denstiy cells *in vitro*, virus inhibition through cell cycle regulators was suspected. HCMV favors interaction of MDM2, a cell cycle protein with p53, a cellular protein and IE2, a viral protein. HCMV inhibition by emetine depended on disruption of MDM2 from its interacting partners p53 or IE2. This is achieved by nuclear translocation and binding of ribosomal processing S14 (RPS14) to MDM2. However, in low-density infected cells, despite nuclear localization of RPS14, the pre-existing interaction of MDM2-p53 could not be disrupted by RPS14 resulting in virus escape and loss of emetine effect. Knockdown of RPS14 resulted in lack of HCMV inhibition by emetine, confirming its requirement for emetine activities. Summarized, emetine may represent a promising candidate for HCMV therapy through a novel host-dependent mechanism.

Disclosures: R. Mukhopadhyay: None.

Poster

790. Ischemia: Perinatal and Recovery

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 790.01/L13

Topic: C.07. Ischemia

Support: NIH Grant R01HL104173

NIH Grant R01HL128546

IDDRC Grant P30HD40677

Children's Heart Foundation

Foglia-Hills Professorship in Pediatric Cardiac Research

Title: Altered fractional anisotropy in developing white matter after congenital heart surgery in a piglet model

Authors: ***N. ISHIBASHI**[1], A. V. KOROTCOV[2], L. KOROTCOVA[1], S. LIN[2], S. RAMACHANDRA[1], S. KUMAR[3], K. AGEMATSU[1], P. WANG[2], R. A. JONAS[1]; [1]Childrens Natl. Med. Ctr., Washington, DC; [2]Howard Univ., Washington, DC; [3]George Washington Univ., Washington, DC

Abstract: Clinical studies with standard MRI have demonstrated an important incidence of white matter (WM) injury after congenital heart surgery. Diffusion tensor imaging (DTI) allows measurement of macroscopic organization of WM pathology but has rarely been applied after cardiopulmonary bypass (CPB). The piglet is a suitable size for investigation using CPB and the brain displays a highly evolved gyrencephalic WM. The aims of the present study were: 1) to characterize WM development of the gyrencephalic piglet brain; 2) to define changes in DTI after CPB-induced insults; and 3) to define correlation of DTI changes with cellular events. Normal WM development was assessed between 3w and 7w of age. 3w female piglets were also randomly assigned to one of 3 levels of CPB-induced insults: i) no CPB (Control); ii) CPB-induced systemic inflammatory response syndrome (SIRS)(Mild-CPB); and iii) CPB-induced SIRS with ischemia-reperfusion and reoxygenation (Severe-CPB). 40 DTIs were undertaken on pre-CPB and post-CPB day 3 and week 4. 31 WM structures were constructed and further subcategorized based on: i) deep or superficial WM; ii) 3 fiber categories; and iii) 6 subdivisions. Fractional anisotropy (FA) was analyzed in each WM area. Responses of oligodendrocytes, astrocytes, and microglia to CPB were immunohistologically defined. Correlation between FA and cellular changes were analyzed in corresponding WM regions. Under normal physiological conditions, FA values were significantly different among tested WM structures and at ages 3w vs 7w. FA in the deep WM was higher than in superior WM at both ages. Within 3 fiber categories, FA was highest in projection fibers and lowest in association fibers, demonstrating a region-specific maturation pattern similar to human WM. Using regression analysis we found that FA in piglet WM at postnatal 3w and 7w is equivalent to early infancy in human WM. FA on post-CPB week 4 varied among WM structures and among the 3 CPB groups. Our data suggested maturation dependent WM vulnerability to CPB. In addition FA changes after CPB were both region-specific and insult-dependent. When the correlation between FA changes and cellular responses was analyzed, FA in Control and Mild-CPB positively correlated with oligodendrocyte cell numbers but not after Severe-CPB, suggesting that FA can be used as a biomarker for WM maturation only under normal conditions or after a mild pathological insult. Both CPB-induced astrogliosis and microgliosis affected FA changes after cardiac surgery. In summary the piglet brain is a powerful model to study human WM development. Further studies in this model will provide exceptional data needed to interpret human DTI studies.

Disclosures: **N. Ishibashi:** None. **A.V. Korotcov:** None. **L. Korotcova:** None. **S. Lin:** None. **S. Ramachandra:** None. **S. Kumar:** None. **K. Agematsu:** None. **P. Wang:** None. **R.A. Jonas:** None.

Poster

790. Ischemia: Perinatal and Recovery

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 790.02/L14

Topic: C.07. Ischemia

Support: Swiss National Science Foundation P3SMP3 148367

Title: Modification of commensal gut bacteria induces protection from ischemic stroke brain injury

Authors: *C. BENAKIS[1], C. POON[1], G. SITA[1], M. MURPHY[1], D. BREA[1], J. MOORE[1], G. RACCHUMI[1], L. LING[2], E. PAMER[2], I. COSTANTINO[1], J. ANRATHER[1];
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Abstract: Commensal gut bacteria have a profound impact on the host physiology, metabolism and immune function and influence disease processes from the gut to the brain. We and others have recently shown that intestinal microbiota can impact stroke pathophysiology by modulating the immune or the autonomic nervous systems. Here we sought to determine whether antibiotics that target different classes of intestinal bacteria affect the outcome of ischemic brain injury in a mouse model of transient middle cerebral artery occlusion (MCAo).
To deplete gut microbiota across all phyla, C57Bl/6 male mice received a cocktail of antibiotics in the drinking water that targets a broad spectrum of bacteria (ampicillin, A; metronidazole, M; neomycin, N; vancomycin, V; AMNV). Four weeks later, fecal bacterial numbers were quantitated by PCR of the bacterial 16S ribosomal RNA gene. To rule out off target effects of antibiotics, their administration was discontinued three days prior to MCAo. Infarct volume was measured 3 days after ischemia in cresyl violet stained brain sections. AMNV treatment resulted in a marked reduction of fecal bacterial load ($1.5x10^9$ vs $2x10^4$ copies/mg fecal mass; n=5-6; $p<0.01$) and a significant decrease of the infarct volume (34±22 mm^3, n=9, mean±SD) compared to control mice (56±21 mm^3, $p<0.05$, n=10). Recolonization of AMNV-treated mice with wild type flora for two weeks reestablished the number of fecal bacterial copies to control levels ($1x10^9$ copies/mg; n=4) and abolished the observed neuroprotection (72±18 mm^3, $p>0.05$ from controls; n=8). The protective effect was not due to additive effects of different antibiotics, because treatment with V or A alone reduced infarct volume as much as AMNV treatment (controls: 58±24 mm^3, V: 35±19 mm^3, A: 20±6 mm^3; n=10/group), whereas N treated mice where not protected (N: 52±20 mm^3; n=10). Interestingly, bacterial density in single antibiotic treated mice was not as drastically reduced as in AMNV mice (controls: $1.5x10^9$ copies/mg, N: $1x10^9$ copies/mg, V: $5x10^8$ copies/mg, A: $8x10^7$; n=6/group). Sensorimotor deficits were tested 3 d after MCAo by the contact and removal adhesive tape test. Mice treated with either V or A

performed better than controls and N treated mice (Contact time, controls: 82±55 s, N: 110±72 s; V: 46±31 s; A: 75±71 s and remove time, controls: 149±46 s, N: 169±19 s; V: 140±53 s; A: 105±72 s; n=9-12).
Modification of the intestinal microbiota has a substantial impact on stroke outcome. The bacterial composition involved in the protective effect remain to be defined. Efforts to modify the intestinal flora may provide new preventive approaches to reduce ischemic brain injury in high-risk patients.

Disclosures: **C. Benakis:** None. **C. Poon:** None. **G. Sita:** None. **M. Murphy:** None. **D. Brea:** None. **J. Moore:** None. **G. Racchumi:** None. **L. Ling:** None. **E. Pamer:** None. **I. Costantino:** None. **J. Anrather:** None.

Poster

790. Ischemia: Perinatal and Recovery

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 790.03/M1

Topic: C.07. Ischemia

Support: Grants-in-Aid and by special coordination funds from Grants-in-Aid for Scientific Research (C) (25462458) from the Ministry of Education, Culture, Sports, Science and Technology of Japan

Nakatomi fundation

Title: Involvement of HMGB1-RAGE signaling on the regulation of central post-stroke pain

Authors: ***S. TOKUYAMA**[1], W. MATSUURA[1], S. HARADA[1], K. LIU[2], M. NISHIBORI[2]; [1]Kobe Gakuin Univ., Kobe, Japan; [2]Okayama Univ., Okayama, Japan

Abstract: Central post-stroke pain (CPSP) is one of the most under-recognized consequences of cerebral stroke, but the development of an effective treatment strategy is urgent. High-mobility group box 1 (HMGB1) and the receptor for advanced glycation end products (RAGE, one of the receptors of HMGB1) have recently been shown to be critical in the modulation of nociceptive transduction following peripheral neuropathy. The aim of this study was to determine the interactions between CPSP and HMGB1/RAGE signaling.
Male ddY mice were subjected to 30 min of bilateral carotid artery occlusion (BCAO). The development of hind paw mechanical allodynia was measured after BCAO using the von Frey test. Neuronal damage was estimated by histological analysis on day 3 after BCAO. Expression of each protein levels was analyzed by western blot and immunofluorescence staining.

The expression levels of the HMGB1 protein in the spinal cord and the sciatic nerve were significantly increased on day 3 after BCAO, although no effects of BCAO were noted on RAGE protein expression. HMGB1- or F4/80 (macrophage marker)-positive cells were clearly observed in the spinal cord on day 3 after BCAO and were only marginally observed in the sham group. Furthermore, HMGB1-positive cells were partially co-localized with F4/80-positive cells in the spinal cord. BCAO-induced mechanical allodynia was significantly decreased by the intravenous and intrathecal administration of anti-HMGB1 monoclonal antibody. The BCAO-induced increase of phosphorylation of extracellular signal-regulated kinase (ERK) was canceled by the administration of anti-HMGB1 monoclonal antibody. In addition, BCAO-induced mechanical allodynia was significantly decreased by intrathecal administration of U0126, an inhibitor of ERK.
The results in this study suggest that the regulation of BCAO-induced CPSP involves alterations in HMGB1/RAGE signaling. Furthermore, we can speculate that the suppression of HMGB1 is a potential therapeutic target in efforts to control the painful symptoms of CPSP.

Disclosures: S. Tokuyama: None. **W. Matsuura:** None. **S. Harada:** None. **K. Liu:** None. **M. Nishibori:** None.

Poster

790. Ischemia: Perinatal and Recovery

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 790.04/M2

Topic: C.07. Ischemia

Support: NRF-2014R1A2A1A11052042

NRF-2015M3A9B4067068

Title: *In vivo* reprogramming factor expression promotes functional recovery in a mouse model of ischemic brain injury

Authors: *J. SEO[1,3], J. YU[1,3], S. WI[1,3], Y. SHIN[1,3], M. KIM[1,3], H. KIM[2], S.-R. CHO[1,3]; [1]Dept. and Res. Inst. of Rehabil. Med., [2]Dept. of Pharmacol., Yonsei Univ. Col. of Med., Seoul, Korea, Republic of; [3]Brain Korea 21 PLUS Project for Med. Science, Yonsei Univ. Col. of Med., Seoul, Korea, Republic of

Abstract: Introduction: Recovery from ischemic tissue injury can be promoted by cell proliferation and neovascularization. Transient expression of four pluripotency factors (Pou5f1, Sox2, Myc, and Klf4) has been used to convert cell types but never been tested as a means to

promote functional recovery from ischemic injury. Here we aimed to determine whether in vivo reprogramming factor expression can improve neurobehavioral function, which has not previously been achieved.
Methods: Transgenic mice in which the four reprogramming factors, i.e., *Pou5f1*, *Sox2*, *Myc*, and *Klf4*, are expressed in a doxycycline-inducible manner were used. Global cerebral ischemia was induced by transient bilateral common carotid artery occlusion, after which doxycycline, low (12 ng/day) or high (1,200 ng/day) amounts of doxycycline or control buffer (phosphate buffered saline), was administered into the lateral ventricle for 7 days using a micro-osmotic pump. To label newly generated cells, bromodeoxyuridine (BrdU) was given to the mice. Rotarod and ladder walking tests and histological evaluations were conducted.
Results: Rotarod and ladder walking tests showed that this transient reprogramming factor expression dramatically promoted the best functional restoration from the ischemic injury in high amounts of doxycycline group. This functional recovery was associated with the increases both in the numbers of astrocytes and/or neural progenitors in the subventricular zone and the striatum, but not neurons or glial scar. Furthermore, this reprogramming factor expression increased the number of blood vessels. Dysplasia or tumor development was not observed.
Conclusion: *In vivo* transient expression of the reprogramming factors in the brains of mice with cerebral ischemia leads to functional improvement. These results give us insight into the effects of expressing reprogramming factors and the mechanisms of tissue recovery, potentially providing a basis for novel therapeutic modality development for tissue damage such as cerebral ischemia.
Acknowledgements: This study was supported by grants from the National Research Foundation (NRF-2014R1A2A1A11052042, NRF-2015M3A9B4067068), the Ministry of Science and Technology, Republic of Korea.

Disclosures: **J. Seo:** None. **J. Yu:** None. **S. Wi:** None. **Y. Shin:** None. **M. Kim:** None. **H. Kim:** None. **S. Cho:** None.

Poster

790. Ischemia: Perinatal and Recovery

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 790.05/M3

Topic: C.07. Ischemia

Support: NIH Grant R01NS084057

Title: Disruption of brain cholesterol homeostasis following neonatal hypoxia-ischemia

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Abstract: Brain cholesterol is important for myelination, synaptogenesis and neurotransmission in the developing brain. Cholesterol that is required for rapid brain growth in the neonatal period is produced locally from de novo synthesis with acetyl-CoA as raw material and HMG-CoA reductase (HMGCR) as the rate-limiting enzyme. Brain cholesterol is metabolized through hydroxylation by neuron-specific cholesterol 24-hydroxylase (CYP46A1) to form 24S-hydroxycholesterol, which is able to traverse the blood brain barrier and enter the circulation to the liver for excretion. In this study, we investigated cholesterol synthesis and turnover following neonatal brain hypoxia-ischemia (HI). Using the Vannucci model in postnatal day 9 C57Bl6 mice, we found that HMGCR expression decreased over time during the first 24 hours after HI, indicating that HI disturbs brain cholesterol synthesis. The expression of CYP46A1 was up-regulated significantly at 6hr and 24hr post-HI, which corrected with the higher levels of 24S-hydroxycholesterol at the same time points compared to the sham-operated animals in the brain, as well as in the serum. The increase in 24S-hydroxycholesterol in both brain and serum was sustained until 48hrs after HI and returned to normal levels at 72hr. Our work suggests an imbalance of cholesterol synthesis and metabolism early following neonatal HI. Disruption of cholesterol homeostasis may contribute to pathogenesis of neuronal death and white matter injury, and have adverse effects on brain development.

Disclosures: F. Lu: None. **J. Zhu:** None. **F. Chehab:** None. **D.M. Ferriero:** None. **X. Jiang:** None.

Poster

790. Ischemia: Perinatal and Recovery

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 790.06/M4

Topic: C.07. Ischemia

Title: Spinal grafting of allogeneic neural precursors (NPCs) in a rat model of spinal ischemic and traumatic injury: assessment of descending motor tract and primary afferent synapse formation with grafted cells.

Authors: *T. TADOKORO, M. R. NAVARRO, O. KAKINOHANA, S. MARSALA, M. MARSALA;
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Abstract: BACKGROUND: In previous studies we have demonstrated a functional improvement after spinal grafting of human hNT neurons and human and rat fetal NPCs in rat models of spinal ischemic and contusion injury. In our current study using a novel subpial axon-labeling technique and primary afferent labeling, the time course of synapse formation between descending motor tracts and primary afferents with grafted allogeneic NPCs was studied. METHODS: Sprague-Dawley (SD) rats (200-300 g) were exposed to i) spinal ischemia (10 min), or ii) L4-5 spinal compression injury by placing a 30g circular rod on the exposed L4-5 spinal segment for 15 min. Two weeks after injury, animals received cervical subpial injection of AAV9-SYN-RFP to label descending motor axons. At 4 weeks after spinal injury, animals received spinal grafts of allogeneic fetal (E14-16) NPCs isolated from GFP+ rats. After cell grafting, animals were immunosuppressed for 3 weeks with Prograf (3 mg/kg/day) and then survived without immunosuppression for an additional 1-6 months. Three days before sacrifice animals received sciatic nerve injection of cholera toxin B to label primary afferents. At the end of survival, animals were perfusion fixed with 4% paraformaldehyde. Differentiation profile of grafted cells and development of putative synapses with labeled descending motor axons and primary afferents was studied by immunofluorescence. RESULTS: In both models consistent grafted cell survival was seen at intervals up to 6 months after cell grafting. The presence of mature neurons (NeuN, MAP2) and astrocytes (GFAP) in GFP+ cells was seen. RFP+ descending axons were identified within the grafts. The highest degree of axonal ingrowth was seen at 6 months after cell grafting and was more pronounced in animals with previous spinal ischemic injury (if compared to contusion injury). Similarly, the presence of labeled primary afferents was seen within the graft(s) and was more developed in grafted animals previously exposed to spinal ischemic injury. CONCLUSIONS: i) These data demonstrate that descending motor tracts and primary afferents in rats with previous ischemic or traumatic injury retain their capacity to develop new synaptic contacts with grafted neuronal precursors. ii) In addition, these data suggest that long periods after cell grafting are required for higher density synapse formation with grafted terminally-differentiated neurons. iii) Similarly, these data also demonstrate that a long cell-post-transplant survival interval (6-12 months) will need to be studied to assess the full therapeutic potential associated with cell replacement therapies in spinal ischemic or traumatic injury.

Disclosures: T. Tadokoro: None. **M.R. Navarro:** None. **O. Kakinohana:** None. **S. Marsala:** None. **M. Marsala:** None.

Poster

790. Ischemia: Perinatal and Recovery

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 790.07/M5

Topic: C.07. Ischemia

Support: MOHW grant/HI15C2796

NRF grant/2015R1A2A2A01004202

Title: Extension of therapeutic time window of tissue plasminogen activator with sp-8203 combination therapy in rat embolic stroke models

Authors: *W.-K. KIM[1], A. M. A. ANTHONY JALIN[1], H. SONG[1], C. JU[1], K. PAHK[1], H. NOH[1], C. JOUNG[1], G.-S. CHO[2], B.-S. KIM[2], J.-M. RYU[2];
[1]Col. of Med. Korea Univ., Seoul, Korea, Republic of; [2]Central Res. institute, Shin Poong Pharm. Co. Ltd, Ansan, Korea, Republic of

Abstract: Although tPA is the only approved therapy for ischemia, its clinical use is limited by narrow therapeutic time window; e.g., mostly up to ~3 h after the onset of ischemia. Limited use of tPA for post-ischemic treatment is related with hemorrhagic transformation and reperfusion injury by delayed thrombolysis. Since the hemorrhagic transformation and reperfusion injury by delayed thrombolysis involves multiple cytotoxic pathways including excitotoxicity, oxidative stress and inflammatory responses, the combined use with multi-target directed neuroprotectants has an emerging potential to extend the time window of tPA and simultaneously to reduce tPA- and ischemia-induced brain injury. We recently identified a novel multipotentneuroprotectant SP-8203(Shin Poong Pharm. Co. Ltd, South Korea) and confirmed itsfeasible safety in Phase I clinical studies. Inrodent embolic stroke models, while early 3-h reperfusion with tPA effectively restored perfusion and reduced infarction, late 6-h tPAtreatment did not decrease infarction but instead worsened hemorrhagic conversion and mortality. Treatment of SP-8203 (3 mg/kg, i.v. bolus)1.5 h prior totPA infusion reduced the infarct volume, edema and neurobehavioral deficit aggravated by delayed tPA treatment. Moreover, SP-8203 significantly attenuated delayed tPA treatment-worsened cerebral hemorrhage and mortality.Even simultaneous treatment tPA and SP-8203 at 4.5 h ameliorated survival and brain atrophy over 30 days. In situ zymography study revealed that SP-8203 largely decreased the expressions and activities of matrix metalloproteases, which were significantly correlated with increase of hemorrhage and mortality in delayed tPAtreatment. Accordingly, the combination significantly attenuate the infiltration of inflammatory cells, the BBB leakage, and related degradation of tight junction proteins in penumbral regions.Thus, the combined treatment of SP-8203 with tPA would be a therapeutic strategy to overcome the limitation of tPA therapy, reduce ischemic brain tissue damage and maximize clinical outcome. (W-KK and AMAAJ equally contributed)

Disclosures: **W. Kim:** None. **A.M.A. Anthony Jalin:** None. **H. Song:** None. **C. Ju:** None. **K. Pahk:** None. **H. Noh:** None. **C. Joung:** None. **G. Cho:** None. **B. Kim:** None. **J. Ryu:** None.

Poster

790. Ischemia: Perinatal and Recovery

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 790.08/M6

Topic: C.07. Ischemia

Support: Swiss National Science Foundation

advanced ERC grant (Nogorise)

'Eat to lean to move' ETH network

Christopher and Dana Reeve Foundation

Title: Sprouting and "side-switch" of contralateral corticospinal fibers in the spinal cord after large unilateral cortical stroke in adult mice

Authors: *J. KAISER[1], A. RICCIARDI[2], A.-S. WAHL[2], N. HAGENBUCH[4], C. FÖLDY[5], M. E. SCHWAB[3];
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Abstract: Functional recovery of skilled forelimb movements after a large insult to the primary motor and premotor cortex involves activation of the contralateral hemisphere with the contralesional cortex growing new collaterals crossing the midline into the denervated hemi-cord on cervical levels of the spinal cord. The underlying molecular mechanisms of growth induction in these adult, intact, fully wired and functional corticospinal tract fibers, midline crossing and target innervation are yet unclear. Such mechanisms could be of high importance for future therapies. Microglia, which have repeatedly been linked to brain repair after lesion and are known to react quickly to changes in their environment, are a high priority candidate for participation in sprout induction-, shaping of a growth-permissive tissue environment and attraction of fibers to the denervated hemi-cord. To address the involvement of microglial cells in this lesion paradigm, adult mice were subjected to a unilateral photothrombotic stroke of the right primary as well as pre-motor cortex ablating >90% of the descending projections of the corticospinal tract (CST). Microglial activation was analysed morphologically at different time points in the cervical spinal cord. We show a lesion-dependent transient activation of microglia in the grey matter of the denervated hemicord at early time points, i.e. 2-4 days after the stroke. Activation is correlated in space to the density of CST innervation of the corresponding areas. Molecular analysis of these activated cells will give insights into the microglial involvement into the processes of sprouting, synaptogenesis and and circuit plasticity.

Disclosures: **J. Kaiser:** None. **A. Ricciardi:** None. **A. Wahl:** None. **N. Hagenbuch:** None. **C. Földy:** None. **M.E. Schwab:** None.

Poster

790. Ischemia: Perinatal and Recovery

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 790.09/M7

Topic: C.07. Ischemia

Support: NIH Grant NS073779

Title: Inhibition of glucose transporters attenuate recurrent hypoglycemia-induced increase in intra-ischemic acidosis in insulin-treated diabetic rats.

Authors: ***A. K. REHNI**[1], V. SHUKLA[2], K. R. DAVE[2,3];
[2]Neurol., [1]Univ. of Miami Sch. of Med., Miami, FL; [3]Neurosci. Program, University of Miami Miller School of Medicine, FL

Abstract: Stroke is a serious manifestation of diabetes. Glucose lowering therapies available for correcting diabetic hyperglycemia causes recurrent hypoglycemia (RH). In an earlier study we observed that RH exacerbates ischemic brain damage in insulin-treated diabetic (ITD) rats. We have previously observed that ischemia causes enhanced increase in hippocampal lactate levels and a profound drop in pH in ITD + RH rats compared to controls. We tested hypothesis if administration of alkalizing agent (Tris-(hydroxymethyl)-aminomethane: THAM) modulates intra-ischemic acidosis in ITD + RH rats. Also, since RH is shown to increase levels of glucose transporters (GLUTs), we also determined if glucose transporters are responsible for observed drop in intra-ischemic acidosis in ITD + RH rats. Rats were made diabetic by streptozotocin injection and 2-3 weeks later, received insulin pellets for treating diabetes. After 2-3 weeks, moderate hypoglycemia was induced by insulin injection for 3 hours per day for 5 consecutive days. Animals were divided into following groups: (I) THAM treatment: A. ITD + RH (representing treated diabetic population experiencing RH) (n = 7) and, B. ITD + RH + THAM (0.3 M, 3 ml / kg / hr, i.v.) (n = 6); II: 4,6-O-Ethylidene-α-D-glucose (OEDG; GLUT inhibitor) treatment: A. ITD + RH + Vehicle (n = 6), B. ITD + RH + OEDG (2 mmol / kg, i.v. bolus dose followed by 0.2 mmol / kg / min, i.v. maintenance infusion) (n = 6). On the day after last hypoglycemia exposure, global cerebral ischemia was induced by bilateral carotid artery occlusion with hypotension for eight minutes. Rats were treated with THAM or OEDG from 15 minutes prior to ischemia to 80 minutes of reperfusion. CA1 hippocampal pH and lactate (in microdialysate) were measured using microfiber optic pH meter and lactate plus meter, respectively. The pH drop in THAM-treated rats was significantly lower than in the controls

from 4 minutes of ischemia to 4 minutes of reperfusion and from 11 to 18 minutes of reperfusion compared to the control group (change in Δ pH in THAM group *vs* control group was 37 % to 57 %). The fall in pH in OEDG-treated group was significantly lower than in control group from the onset of ischemia to 80 min of reperfusion (change in Δ pH of OEDG group *vs* control group was 17 % to 64 %). Changes in lactate level in OEDG treatment group was significantly lower than the control group, when measured 4 min after ischemia and from 20 to 60 minutes of reperfusion. Our results demonstrates that ischemia causes pronounced acidosis via a GLUTs mediated increase in acidosis in ITD + RH rats. Studying the mechanism of acidosis in RH exposed ITD rats may help lower ischemic brain damage during diabetes.

Disclosures: **A.K. Rehni:** None. **V. Shukla:** None. **K.R. Dave:** None.

Poster

790. Ischemia: Perinatal and Recovery

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 790.10/M8

Topic: C.07. Ischemia

Support: MHW Grant HI15C2796

NRF Grant 2014R1A1A1037088

NRF Grant 2015R1A2A2A01004202

Title: A multi-potent neuroprotectant LMT356 reduces tissue plasminogen activator-evoked adverse effects in rat embolic stroke

Authors: K. PAHK[1], *C. JU[1], A. M. A. ANTHONY JALIN[1], H. SONG[1], H. NOH[1], C. JOUNG[1], G.-S. CHO[2], W.-K. KIM[1];
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Abstract: Acute ischemic stroke causes over 10% of all deaths in western countries as well as in Korea. Despite severity of ischemic stroke, development of neuroprotectants is still in its infancy. Although tissue plasminogen activator (tPA) is currently approved by FDA for treatment of acute ischemic stroke, its clinical use is strictly limited due to adverse effects caused by delayed treatment of tPA (e.g., over 4.5-h after ischemia onset). The narrow therapeutic time window of tPA is related with its time-dependent adverse effects such as excitotoxicity, radical formation, cerebral hemorrhage, and inflammation. Thus, the combined use of a multi-target directed neuroprotective agent with tPA would be a therapeutic strategy to simultaneously reduce

both tPA and ischemia-induced brain tissue damage. In this sense, we recently designed LMT356 as a multi-target directed neuroprotectant with anti-excitotoxic, antioxidant and anti-inflammatory properties. While early 3-h thrombolysis restored perfusion and largely reduced infarction, late 6-h tPA did not decrease infarction and even worsen hemorrhagic conversion and mortality. LMT-356 (50 mg/kg, i.v. bolus) reduced the aggravation of infarction, edema and neurobehavioral deficits caused by delayed tPA-treatment in embolic stroke. Combined treatments of LMT356 with delayed (6-h post-ischemic) treatment of tPA ameliorated mortality and brain atrophy over 30 days in rats subjected to embolic stroke. LMT356 also reduced the expression and activity of matrix metalloproteases that are closely correlated with cerebral hemorrhage and mortality. Thus, the combined use of a multi-target directed neuroprotectant LMT356 could be beneficial to overcome the limitation of tPA therapy in acute cerebral ischemic stroke. (KP and CJ contributed equally)

Disclosures: **K. Pahk:** None. **C. Ju:** C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Receipt of drugs, Shin Poong Pharm. Co. Ltd. **A.M.A. Anthony Jalin:** None. **H. Song:** None. **H. Noh:** None. **C. Joung:** None. **G. Cho:** None. **W. Kim:** None.

Poster

790. Ischemia: Perinatal and Recovery

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 790.11/M9

Topic: C.07. Ischemia

Support: RESSTORE

Finnish Cultural Foundation

ORION Research Foundation

Title: Effect of CD49d-positive allogeneic mesenchymal stromal cells on transmigration across blood-brain barrier after intra-arterial delivery into rats

Authors: *L. CUI, J. JOLKKONEN;
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Abstract: Cell-based therapy is one of the most attractive treatments to enhance post-stroke recovery. Positive effects of systemic mesenchymal stromal cells (MSCs) transplantation have been seen in some animal models, but the functional outcome is still not optimal. One of the limitations for systemic delivery of MSCs could be the inappropriate homing of the cells, and the

mechanism of MSCs across the blood brain barrier (BBB) is still poorly understood. Intra-arterial infusion can increase the cell homing to the ischemic hemisphere by circumventing the pulmonary circulation. Cell surface engineering might also increase homing capacity by promoting adhesion to endothelium. Alpha4 integrin (ITGA-4) is an important surface integrin for endothelial adhesion of inflammatory cells. Its receptor, vascular cell adhesion molecule-1 (VCAM-1) is upregulated early after stroke. In our experiment, rat bone marrow derived MSCs were genetically modified to over-express ITGA-4 and also labeled with tdTomato. Adult male RccHan Wistar rats (200-300g) undergo sham or transient middle cerebral artery occlusion surgery. 24h later they are transplanted with 1×10^6 ITGA-4 positive rat MSCs or control cells via the external carotid stump. Two photon fluorescent microscope is used to observe the in vivo behavior of infused cells in the brain during and up to 24h after delivery. Rats are perfused 24h after cell transplantation and histology will be done to confirm the imaging results. We hypothesize that ITGA4/VCAM-1 plays an important role in the transmigration of allogeneic MSCs across BBB, and over-expression of ITGA-4 on MSCs could increase cell homing into the injured brain, thereby increase the functional outcome.

Disclosures: L. Cui: None. **J. Jolkkonen:** None.

Poster

790. Ischemia: Perinatal and Recovery

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 790.12/M10

Topic: C.07. Ischemia

Support: NRF-2015R1D1A1A01059980

Title: Roles of protein disulfide isomerase-A3 against neuronal damage induced by spinal cord and transient forebrain ischemia

Authors: *D. YOO[1], I. HWANG[1], J. CHOI[2], J.-H. CHO[3], D. KIM[4], Y. YOON[1];
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Abstract: In this study, we investigated to find out neuroprotective effects of protein disulfide isomerase-A3 (PDI-A3) after transient ischemia of the rabbit spinal cord and the gerbil forebrain. Tat-PDI-A3 fusion protein was made and injected intraperitoneally to facilitate the cross into the

blood-brain barrier and delivery to the spinal cord and the hippocampus immediately after ischemia/reperfusion. Administration of PDI-3A significantly improved the Talove's neurological scores after spinal cord ischemia and ameliorated ischemia-induced hyperactivity after transient forebrain ischemia. In addition, the treatment of PDI-3A significantly ameliorated the reduction of NeuN-immunoreactive neurons in the spinal cord 2 days after spinal cord ischemia and in the hippocampal CA1 region 4 days after ischemia. In addition, the administration of PDI-3A significantly reduced the oxidative stress and increased the Cu,Zn-superoxide dismutase levels after transient spinal cord or forebrain ischemia. These results suggested that PDI-A3 has neuroprotective effects against ischemic damage by modulating the oxidative stress and antioxidant in the central nervous system.

Disclosures: **D. Yoo:** A. Employment/Salary (full or part-time): Research Institute for Veterinary Science and BK21PLUS Program for Creative Veterinary Science. **I. Hwang:** None. **J. Choi:** None. **J. Cho:** None. **D. Kim:** None. **Y. Yoon:** None.

Poster

790. Ischemia: Perinatal and Recovery

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 790.13/M11

Topic: C.07. Ischemia

Title: Neonatal hypoxia/Ischemia in rats - Short term hypothermia induced neuroprotection and tissue sparing as evidenced by MRI

Authors: *L. TOLPPANEN[1], K. LEHTIMÄKI[1], G. VILLETTI[2], A. NURMI[1], F. FACCHINETTI[2];
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Abstract: Therapeutic hypothermia has become standard therapy for term neonates with moderate to severe hypoxic-ischemic encephalopathy (HIE). In rodent animal models of neonatal brain hypoxia-ischemia, hypothermia showed different degrees of tissue sparing and reduced brain swelling and in some cases no protective effects, due also to variables in hypotermia protocols. To date, there is no well described published data about the MRI assessment of the brain tissue viability, lesion and oedema following 5 hours of hypothermia in neonatal H/I. To fill this gap, we evaluated acute brain tissue changes in the neonatal rat brain at 48 h after H/I by using MRI techniques. Postnatal day 7 (P7) rat (Wistar) pups (both genders) were subjected to neonatal hypoxia-ischemia model (Rice et al. 1981) for 120 min followed by either normothermic (+37C) or hypothermic (+33C) condition for 5 h. Absolute T2 mapping for tissue viability and volumetric analysis of tissue loss and oedema were evaluated with 7T small animal

MRI system acutely 48h following H/I insult. At the end-point, immediately following MRI assessments pups were euthanized and brains were processed for histology/IHC analysis to be conducted later. On day 2 (P9) following H/I, under above conditions and interventions, MRI revealed unilateral infarcts/lesions in each neonatal pup equaling to ~60-70 % tissue loss of hemispheric volume. Anatomical T2-MRI analysis revealed significant (~20%) reduction in tissue loss in H/I + hypothermic group when compared to H/I + normothermic group. Compromised tissue viability in ipsilateral hemisphere was seen as elevated T2 values (ms) compared to contralateral non-injured hemispheres. But when T2 values in H/I normothermic group were compared against H/I+ hypothermic group, significantly reduced (normalized) T2 values were seen in the brains of H/I + hypothermic group. T2 mapping allowed also more detailed and accurate delineation of the injured tissue for lesion analysis. Furthermore, analysis revealed significant reduction in brain oedema (volumetric) in H/I + hypothermic group when compared to H/I + normothermic group. Taken together, this study confirms that short term hypothermia is effective method to alleviate ischemic brain injury in the neonatal brain. Hypothermia effectively reduced lesion size and oedema and alleviated the tissue viability change. Furthermore, the use of MRI allowed us to define ischemic lesion more accurately and with the potential of performing longitudinal assessment as opposed to conventional histology and other terminal methods.

Disclosures: **L. Tolppanen:** None. **K. Lehtimäki:** None. **G. Villetti:** None. **A. Nurmi:** None. **F. Facchinetti:** None.

Poster

790. Ischemia: Perinatal and Recovery

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 790.14/M12

Topic: C.07. Ischemia

Support: Supported by the National Research Council of Science & Technology (NST) grant by the Korean government (MSIP) (No. G15120 and CRC-15-04-KIST).

Title: Effects of deletion of peroxiredoxins II on bilateral common carotid artery occlusion-induced impairments of hippocampal function

Authors: ***Y.-S. LEE**[1], W. JEON[2], J.-S. HAN[1];
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Abstract: Peroxiredoxins (Prxs) acts as antioxidant enzymes that reduce peroxide levels. More than one isoform of Prx including at least six Prxs(PrxI-PrxVI) have been identified in mammalian cells. Especially, Prx II immunoreactivity is predominantly found in hippocampal neurons, suggesting that Prx II be associated with physiological function in the hippocampus. Previous studies have demonstrated that Prx II against mitochondrial oxidative damage protects physiological events relating to age-associated cognitive decline. The present experiment was conducted to examine whether Prx II has a protective role for neuronal death which is caused by increased intracellular reactive oxygen species (ROS) in hippocampal pyramidal neurons in response to a sudden injury. Prx II−/− mice received transient bilateral common carotid artery occlusion (BCCAo), one of the experimental animal model for ischemic stroke. Mice were divided into 4 groups, Prx II−/− group with sham-operated procedure, Prx II−/− group with BCCAo, Prx II+/+ group with sham-operated procedure, and Prx II+/+ group with BCCAo. Cognitive status of these mice was examined using the hidden platform version of Morris water maze task, object/location novelty recognition test, and contextual fear conditioning. Prx II−/− group with BCCAo showed poor retention of spatial memory and severe cell damage in the CA1 region of hippocampus relative to the other groups. These findings indicate that Prx II plays a role in the pathological process of ischemia. Supported by the National Research Council of Science & Technology (NST) grant by the Korean government (MSIP) (No. G15120 and CRC-15-04-KIST).

Disclosures: **Y. Lee:** None. **W. Jeon:** None. **J. Han:** None.

Poster

790. Ischemia: Perinatal and Recovery

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 790.15/M13

Topic: C.07. Ischemia

Support: NIH AG12101

NIH AG022374

NIH HL111724

NIH HL118624

NINDS U54NS081765

Title: Obesity moderates racial and ethnic differences in white matter hyperintensity volumes between African Americans and European Americans

Authors: *A. SEIXAS[1], G. JEAN-LOUIS[1], V. NEWSOME[1], M. DE LEON[2], R. OSORIO-SUAREZ[2], A. R. RAMOS[3], T. OYEGBILE[4], L. GLODZIK[2];
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Abstract: Background: The high prevalence of ischemic white matter hyperintensity volume (WMHV), a robust subclinical indicator of future stroke, may explain racial/ethnic stroke disparity comparing African Americans (AAs) and European Americans (EAs). However, the mechanism underlying this disparity is not fully understood. We hypothesized that obesity may explain the racial/ethnic difference in WMHV between AAs and EAs.
Method: Data were collected from 298 individuals enrolled across several NIH-funded studies at NYU School of Medicine's Center for Brain Health. Obesity was derived using body mass index (height/weight, kg/m^2); a body mass index greater than or equal to 30 kg/m^2 was used to categorize obese individuals. WMHV load total was defined, based on FLAIR images, as the sum of deep and periventricular volumes and was scored using the Fazekas scale (0-6 scale), where low-moderate WMHV=0-3 and high WMHV $\geq$4.
Results: Of the total sample, 61.4% were female, 91.6% were EA and 8.4% AA, 42.6% were hypertensive, 92.2% had no smoking history, 22.8% were obese, and 83.1% had low-moderate WMHV and 16.9% had high WMHV. The percentage of obese individuals among AA and EA did not differ. Logistic regression analysis indicated that age and the interaction between race and obesity were significant predictors of WMHV, thus indicating that obesity significantly moderated the relationship between race and WMHV. Age increased the odds of WMHV by 15% (OR=1.15, 95% CI= 1.09-1.22, $p<.001$), and obesity among AAs increased the odds of WMHV by 43% (OR=1.43, 95% CI = 1.04-1.98, $p<.05$).
Conclusion: Based on our findings, obesity significantly moderated the relationship between race/ethnicity and WMHV. Therefore, we argue that obesity explains a significant portion of racial/ethnic differences in WMHV between AAs and EAs.

Disclosures: A. Seixas: None. **G. Jean-Louis:** None. **V. Newsome:** None. **M. de Leon:** None. **R. Osorio-Suarez:** None. **A.R. Ramos:** None. **T. Oyegbile:** None. **L. Glodzik:** None.

Poster

790. Ischemia: Perinatal and Recovery

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 790.16/M14

Topic: C.07. Ischemia

Title: Repositioning of vitamin B_2 for treatment of ischemic stroke patients

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Abstract: Introduction: blood glutamate grabbing has becoming in a novel preclinical strategy to reduce the excitotoxic effect of glutamate released in acute phase of stroke, however its clinical demonstration has not been demonstrated so far. Aiming to demonstrate the clinical efficacy of glutamate grabbing, we have performed a screening analysis of repositioning drugs with blood glutamate grabbing activity and then we have tested the selected drugs in *in vivo* ischemic animal models and then in stroke patients. **Methods**: Prestwick Chemical Library composed of 1120 HITS were used to detect drugs with blood glutamate grabbing activity. The drug selected in the *in vitro* test was later probed in ischemic model animals. Infarct volume (determined by means of MRI), blood glutamate levels and functional test were determined during 7 days after ischemic onset. The drugs selected was then tested in a randomized clinical trial (ClinicalTrials.gov Identifier: NCT02446977) with 50 stroke patients. Two treatment arms were compared; one arm with 25 placebo treatment patients and other arm with 25 durg treatment patients. Primary outcome measures: reduction of serum glutamate concentration defined as difference between serum glutamate concentrations from basal (prior to medication infusion) and levels at 3±1 and 6±1 hours, from administration point of the medication. Secondary outcome measures: 1) days of hospitalization, 2) difference in days, between patient arrival and the patient's discharge, 3) percentage of clinical improvement. **Results:** We have discovered the effect of the Riboflavin (Vitamin B_2) as a novel high blood glutamate grabber, characterized through *in vitro* and *in vivo* analysis. Administration of Riboflavin (1 mg/Kg) in ischemic animal induced a significant ($p<0.05$) lowering of blood glutamate levels and a reduction ($p<0.05$) of infarct volume at 7 days after ischemia. Improvement on neurological deficit was also observed in Riboflavin treated animals. Patients treated with Riboflavin 20 mg (Streuli®) showed a significant ($p<0.05$) reduction of blood glutamate levels, 6 hours after treatment administration and a neurological improvement at 3 months. **Conclusions:** In this study we have described the use the Riboflavin as new a potential treatment for ischemic stroke. Due to Riboflavin has been used previously in humans for other pathologies, human toxicity and pharmacokinetic analysis are not needed before to test its effects in stroke patients. Repositioning

drugs represent an interesting alternative to reduce the risk in the study of new drugs in the field of ischemic pathology.

Disclosures: **F.C. Pérez:** None. **A. da Silva-Candal:** None. **M. Rodríguez-Yáñez:** None. **S. Arias-Rivas:** None. **M. Santamaría-Cadavid:** None. **A. Vieites-Prado:** None. **E. Rodríguez-Castro:** None. **T. Sobrino:** None. **M. Loza:** None. **J. Castillo:** None.

Poster

790. Ischemia: Perinatal and Recovery

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 790.17/M15

Topic: C.07. Ischemia

Support: NIH Grant NS053898

NIH Grant NS084396

Title: Astrocytes and new CA1 neurons in rat forebrain ischemia

Authors: ***Y. OUYANG**, L. XU, L. LI, R. G. GIFFARD;
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Abstract: The pyramidal neurons of the hippocampal CA1 region are essential for spatial learning and memory, and are selectively destroyed after transient forebrain cerebral ischemia. The reappearance of hippocampal CA1 neurons after ischemia was associated with recovery of learning and memory. We found that selective dysfunction of hippocampal CA1 astrocytes contributes to delayed neuronal death after transient forebrain ischemia and astrocyte targeted protection reduces neuronal loss.

Here we examined whether glial fibrillary acidic protein (GFAP) positive cells have a relationship with reappearance of CA1 neurons in a model of forebrain ischemia at 8, 14 and 22 days of recovery. Immunofluorescence microscopy was used to detect bromodeoxyuridine (BrdU), a marker for proliferation, doublecortin (DCX), a marker for immature neurons, brain lipid-binding protein (BLBP), a marker for immature neurons, NeuN, a marker for mature neurons and GFAP a marker for astrocytes and radial glia.

Forebrain ischemia for 10 min caused disappearance of NeuN stained neurons in hippocampal CA1 regions at 8 and 14 days after ischemia (DAI) consistent with previous studies. At 22 DAI there was a tendency to an increased number of NeuN positive cells in CA1. There were no change of neuronal numbers in hippocampal dentate gyrus (DG) regions at all time points.

To detect newly divided cells, rats were intraperitoneally injected with 50 mg/kg BrdU every

other day starting from the ischemic day. BrdU positive cells increased at 8 DAI, peaked at 14 DAI and began to decrease at 22 DAI in DG but no change was observed in CA1 region. Both immature neuronal markers (DCX and BLBP) as well as astrocyte marker GFAP, however, began to increase at 8 DAI, peaked at 14 DAI, and tended to decrease at 22 DAI both in DG and CA1 regions of hippocampus. A low percent of BrdU positive cells co-expressed immature neuronal marker DCX in DG, but a high percentage of new neurons (DCX and BLBP positive) colocalized with GFAP. It is concluded that the DCX and BLBP positive neurons in CA1 region of hippocampus are not from proliferation of cells but from quiescent neural progenitors with radial-glia-like properties (GFAP+). To have a substantial impact on recovery, this potential mechanism for self-repair needs to be enhanced.

Disclosures: Y. Ouyang: None. **L. Xu:** None. **L. Li:** None. **R.G. Giffard:** None.

Poster

790. Ischemia: Perinatal and Recovery

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 790.18/M16

Topic: C.07. Ischemia

Title: Automated assessment of forepaw force production in rodents: Application in a rodent model of cortical ischemia

Authors: *H.-J. PARK, J. COOPERRIDER, H. CHAN, C. WATHEN, J. T. GALE, K. B. BAKER, A. G. MACHADO;
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Abstract: The ability to objectively and reliably quantify motor function is essential to characterizing the natural progression of stroke recovery in preclinical models and the efficacy of experimental interventions. In many cases, however, such tasks can be cumbersome and time-consuming to administer and score. In this study, we developed and evaluated a simple and inexpensive robotic assessment device that required the animal to reach through an aperture to grasp and pull a lever with a specified amount of force in order to trigger delivery of a food reward. The position of the lever is controlled by two servo motors. One servo motor is located underneath the vertical slot in front of the cage, and controls the angle of the lever with respect to the slot opening. The other servo motor controls the distance from the slot using a gear rack. The servo motors are controlled by the PWM output channels of an Arduino board, with the lever position command sent from a Raspberry Pi board through a USB connection. The Raspberry Pi generates the sequence of the lever positions for the task, measures the lever pulling force for given positions using serial parallel interface (SPI) with an analog to digital converter

(MCP3008), and controls the pellet dispenser. A pellet is delivered to the rat when the force transducer detects that the pulling force has exceeded a predetermined threshold. A Raspberry Pi can control more than one robot concurrently using multi-threading. The status of the system is monitored with a personal computer using either Ethernet or Wi-Fi connection. We have built other robot configurations including a two link joint planar robot and a parallel robot. However, the limited range of motion, torque and accuracy of the servo motors in addition to the lack of off the shelf mechanical components made the robots less desirable to use in the measurement of the lever pulling force. A primary advantage of the current design is that it can be implemented using inexpensive, off the shelf components, allowing multiple systems to be made in a cost-effective manner for concurrent assessment of motor performance in large experimental colonies.

Disclosures: **H. Park:** None. **J. Cooperrider:** None. **H. Chan:** None. **C. Wathen:** None. **J.T. Gale:** None. **K.B. Baker:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); IntElect Medical, ATI, Cardionomics. **A.G. Machado:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); IntElect Medical, ATI, Cardionomics.

Poster

790. Ischemia: Perinatal and Recovery

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 790.19/M17

Topic: C.07. Ischemia

Support: 9R01NS090904

RO1HL052246

HL031950

R01NS75345

National Natural Science Foundation of China grant 31371116

Adelson Medical Research Foundation

New York State Stem Cell Research Board (NYSTEM)

Title: 3K3A-APC and human neural progenitor cells for stroke repair in mice

Authors: *Z. ZHAO[1], Y. WANG[2], S. REGE[2], M. WANG[2], G. SI[2], J. GRIFFIN[3], S. GOLDMAN[4], B. ZLOKOVIC[2];
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Abstract: Activated protein C (APC) is a blood protease with anticoagulant activity and cell-signaling anti-apoptotic and anti-inflammatory activities. 3K3A-APC (Lys191-193Ala), a recombinant analog of APC with reduced (90%) anticoagulant activity but normal cell signaling activity, has been shown to provide benefit in preclinical models of neurologic disorders including ischemic stroke, brain trauma, multiple sclerosis and amyotrophic lateral sclerosis, and has advanced as a neuroprotectant to Phase 2 clinical trial in ischemic stroke. Previously, we reported that 3K3A-APC stimulates neuronal production by human fetal neural stem cells (NSCs) *in vitro* via a PAR1-PAR3-sphingosine-1-phosphate receptor 1-Akt pathway. Here, we studied the effects of 3K3A-APC and NSCs combination therapy in a mouse model of stroke. We found that late post-ischemic treatment of mice with 3K3A-APC 7 days after stroke stimulates *in vivo* neuronal production by transplanted human NSCs, promotes restoration of disrupted neural circuitry and improves long-term functional recovery. In the present study, human NSCs were transplanted into ischemic cortex 7 days after distal middle cerebral artery occlusion (dMCAo). Mice were treated with human 3K3A-APC (0.2 mg/kg, i.v.) at 7, 9, 11, and 13 days after stroke. 3K3A-APC substantially enhanced proliferation of NSCs and their differentiation into neuronal cells, and promoted functional integration of transplanted NSCs into the host neural circuitry resulting in significant improvement motor deficits as early as 2 weeks after transplantation. These findings suggest that 3K3A-APC-potentiated neuronal recruitment from engrafted NSCs may offer a new approach to the treatment of stroke and related neurologic disorders.

Disclosures: Z. Zhao: None. **Y. Wang:** None. **S. Rege:** None. **M. Wang:** None. **G. Si:** None. **J. Griffin:** Other; Dr. Griffin is a consultant for ZZ Biotech LLC and inventor for some uses of 3K3A-APC.. **S. Goldman:** None. **B. Zlokovic:** Other; Dr. Zlokovic is a founder of ZZ Biotech LLC, a biotechnology company with a mission to develop APC and its functional mutants for the treatment of stroke and other neurological disorders.

Poster

790. Ischemia: Perinatal and Recovery

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 790.20/M18

Topic: C.07. Ischemia

Title: Intranasal erythropoietin administration protects CA1 hippocampal neurons against cerebral ischemia in wistar rat

Authors: *R. MACIAS-VÉLEZ, M. RIVERA CERVANTES;
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Abstract: Erythropoietin (EPO) in interaction with its receptor (EPOR) transduce multiple signals that activate cellular process like growing, differentiation and survival of hematopoietic stem cells. This receptor has been found not only in bone marrow but also in nervous tissue, in some regions like hippocampus, internal capsule, cortex and midbrain; where, it can activate survival signaling cascades. Research on animal models had demonstrated that EPO might be effective against hypoxic, ischemic, and traumatic brain injuries, administrated by peritoneal and intravenous way. But, a new and non-invasive approach to deliver EPO to the brain could be the intranasal pathway. Establishing this pathway as a potential and useful strategy to treat some CNS disorders, including stroke. The aim of this work was to establish an effective dose and time of administration to treat the detrimental effects of ischemia. For that reason, we administrated EPO in three different doses (500, 1000, 2500 UI/kg bw.) within three different times (1, 6, 24 h after blood reperfusion) after 20 minutes of cerebral ischemia carried on male wistar rats (250-300g bw). Cellularity was assessed by Nissl stain using a cresyl violet solution at 0.13% on coronal 10 um brain slices, counting the total number of cells with normal morphology (neurons with a round or oval nucleus, located in the center and surrounded by a pale cytoplasm) in CA1 hippocampal region. The results show that the dose which causes a higher number in normal cells was 1000 UI/kg and it could be used within the first 24 h after cerebral ischemia. Regarding to 500 UI/kg dose it remains efective just for the first two times (1 and 6 h), after that it seems to lose efficiency. And there was not any important change in number of normal cells by 2500 UI/kg dose administration within the three times used, compared to the ischemic group.

Disclosures: R. Macias-Vélez: None. **M. Rivera Cervantes:** None.

Poster

790. Ischemia: Perinatal and Recovery

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 790.21/N1

Topic: C.07. Ischemia

Support: JSPS KAKENHI 26870408

Title: Intraoperative monitoring of cerebral blood flow during brain tumor and cerebrovascular surgery by laser speckle flow imaging: Reliability and Practicality of measuring regional cerebral perfusion

Authors: *T. INOUE[1], M. IDEGUCHI[1], S. NOMURA[1], H. KOIZUMI[1], H. GOTO[1], Y. HIRAYAMA[1], E. SUEHIRO[1], F. OKA[1], K. SUGIMOTO[1], K. KAJIWARA[2], K. YOSHIKAWA[1], H. ISHIHARA[1], M. SUZUKI[1];
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Abstract: Objective: To determine clinical utility of laser speckle flow imaging (LSFI), we used LSFI to monitor cerebral blood flow (CBF) as a complementary method for the management of during several kinds of neurosurgery. Methods: Intraoperative intensity of CBF by LSFI and pre- and postoperative CBF by 123I-iodoamphetamine single photon emission computed tomography (IMF-SPECT) were measured for 3 patients with internal carotid artery (ICA) aneurysms who were undergoing ICA-trapping surgery, for 16 patients with major cerebral artery occlusion who were undergoing EC-IC bypass surgery, and for 12 patients with mass lesion-related arteries and brain tumor or arterovenous malformation. LSFI device was centered over the surgical field, and the relative (CBF) before and after the temporary interruption of the arteries was measured through continuous recording. Results: The decrease in CBF (16.9% ± 2.3%) upon ICA interruption was equivalent to the decrease in CBF during the preoperative balloon test occlusion, as measured by IMP-SPECT (12.2% ± 4.4%). Whether preserved CBF in LSFI promised postoperative intact CBF was not determined, as no patient showed ischemic tolerance by ICA occlusion. The increase in CBF resulting from EC-IC bypass correlated moderately with the increase in postoperative CBF as measured by IMP-SPECT. However, the increase in CBF was too small to recognize intraoperatively by visual inspection. Good visualization of CBF in the surgical feld and relative CBF measurements in the regions of interest were achieved in real time with excellent spatiotemporal resolution. In 11 patients (92%) and 20 regions of interest, a decline in CBF was observed after temporary interruption of the feeding artery (n=8), passing artery (N=2), and both (n = 2) types. There was a signifcant average reduction in CBF of 15.3% ± 29.0%. There were no ischemic complications. Conclusion: Although LSFI clearly demonstrated a decrease in CBF, the information is taken only from the surface of the brain. LSFI was not sensitive enough to detect increased CBF by STA-MCA anastomosis, because CBF changes are minimized during anesthesia, probably owing to low metabolic activity. To recognition of mass lesion-related vasculature, however, LSFI can be used to avoid ischemic complications as procedure complementary to neurophysiological monitoring.

Disclosures: **T. Inoue:** None. **M. Ideguchi:** None. **S. Nomura:** None. **H. Koizumi:** None. **H. Goto:** None. **Y. Hirayama:** None. **E. Suehiro:** None. **F. Oka:** None. **K. Sugimoto:** None. **K. Kajiwara:** None. **K. Yoshikawa:** None. **H. Ishihara:** None. **M. Suzuki:** None.

Poster

790. Ischemia: Perinatal and Recovery

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 790.22/N2

Topic: C.07. Ischemia

Support: NIH Grant NS34179

NIH Grant NS081179

Title: Transfer of bacterial lipopolysaccharide-primed murine and human monocytes protects the brain from cerebral ischemic injury

Authors: *L. GARCIA-BONILLA, M. MURPHY, C. BENAKIS, D. BREA, C. IADECOLA, J. ANRATHER;
Feil Family Brain and Mind Res. Inst., Weill Cornell Med. Col., New York, NY

Abstract: Administration of a sub-lethal dose of the endotoxin lipopolysaccharide (LPS) renders the brain tolerant to a subsequent ischemic insult (preconditioning) [Nat Neurosci 14, 1363, 2011]. Given the prominent role of monocytes/macrophages as endotoxin sensors [Trends Immunol 30, 475, 2009], and as major players in regulating post-ischemic inflammation [Biochim Biophys Acta,1862, 329, 2016], we tested whether LPS is capable of inducing a protective phenotype in blood monocytes resulting in a reduction in ischemic injury. To this end, we evaluated if transferring of ex vivo LPS-primed monocytes into male C57Bl/6 mice confers protection after cerebral ischemia. Mouse monocytes were isolated from the bone marrow, 92±2% of which were $CD115^{+}Ly6C^{hi}$, and treated with saline or LPS (100 ng/ml). LPS stimulation of monocytes for 2 hours increased the expression of *Chi3l3* and *Retnla* mRNA, genes associated with an anti-inflammatory phenotype in monocytes/macrophages. Next, LPS-primed monocytes were injected ($5x10^5$ cells, i.v) into mice 7 hours after transient middle cerebral artery occlusion (MCAO; n=8-10 per group) and infarct volumes were assessed 72 hours later in cresyl violet-stained brain sections. Remarkably, mice receiving LPS-treated monocytes had a 56±10% reduction in infarct volume while no protection was observed in mice receiving saline-treated monocytes or if LPS stimulated monocytes were lysed before transfer (saline: 54±12 mm^3; LPS: 24±5 mm^3; $p<0.05$; LPS-lysed monocytes: 57±7 mm^3; mean±SE). To test whether this protective activity could also be elicited by human monocytes, we exposed purified human peripheral blood monocytes (79% $CD14^{+}CD16^{low}$) to saline or LPS and transferred them into mice that underwent MCAO as described above. Transfer of human monocytes that were exposed to LPS, but not saline, significantly reduced infarct volumes after MCA occlusion (24±5 vs. 45±8 mm^3; $p<0.05$). Immunohistochemical studies of adoptively transferred monocytes showed that both saline and LPS-primed monocytes were observed in the meninges but not in the brain parenchyma after stroke. Given that adoptively transferred

monocytes are localized to the meninges, a recently recognized gateway for immune cell infiltration into the ischemic brain, LPS primed monocytes might regulate leukocyte trafficking after stroke. In conclusion, our findings provide the rationale for new cell therapies based on the delivery of autologous or allogeneic protective monocytes into patients with ischemic stroke.

Disclosures: L. Garcia-Bonilla: None. **M. Murphy:** None. **C. Benakis:** None. **D. Brea:** None. **C. Iadecola:** None. **J. Anrather:** None.

Poster

790. Ischemia: Perinatal and Recovery

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 790.23/N3

Topic: C.07. Ischemia

Support: NIH Grant NS043277

NIH Grant T32 NS07433

NIH Grant DC007905

Title: A peptide disrupting kv2.1/syntaxin interaction is neuroprotective in cerebral ischemia

Authors: *C.-Y. YEH[1], A. M. BULAS[2], K. A. HARTNETT[2], C. T. ANDERSON[3], R. DI MAIO[4], T. TZOUNOPOULOS[3], D. SUN[4], R. KHANNA[5], E. AIZENMAN[2];
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Abstract: Neurodegeneration in the ischemic stroke penumbra involves caspase activation and represents an important target for therapeutic interventions. The voltage-gated potassium channel Kv2.1 has been shown to play an important role in programmed neuronal apoptosis. Previously, we have identified that Kv2.1 promotes caspase activation by generating a pronounced K^+ efflux through *de novo* channel insertion. This process is modulated by Zn^{2+}-dependent pathways leading to the phosphorylation of Kv2.1 at residues Y124 and S800, allowing interactions between the proximal Kv2.1 C-terminus (C1a) and the SNARE protein syntaxin 1A. Overexpression of the C1a decreases pseudo-apoptotic Kv2.1-S800E currents in CHO cells and improves neuronal survival after oxidative stress. Thus, suppressing apoptosis-permitting Kv2.1 currents through the competitive binding of syntaxin 1A represents a promising neuroprotective approach and is explored here through the evaluation of a peptide aptamer. Far-Western blot analysis of overlapping 15 a.a. segments of the C1a region found a 9 a.a. sequence with high binding affinity to syntaxin 1A. Conjugating the cell-permeable HIV trans-activator of

transcription domain (TAT) to the N-terminus of this sequence resulted in an administrable peptide construct (TAT-C1aB). *In vivo* two-photon imaging with FitC-tagged TAT-C1aB confirmed that i.p. administration of the peptide reaches brain vessels within minutes. Whole-cell patch clamp recordings demonstrated that incubation with 10 μM TAT-C1aB significantly reduces pseudo-apoptotic Kv2.1-S800E current density (vehicle vs TAT-C1aB: 267.2±22.03 vs 189.5±19.64, Mean±SEM pA/pF, n=11; p=0.0159) in CHO cells. Further, 1 μM TAT-C1aB treatment significantly decreased lactate dehydrogenase release in rat cortical neuron cultures after excitotoxic insult (2.45±0.24 vs 1.31±0.077, Mean±SEM normalized LDH readout, n=4 each group, p=0.0038). Proximity ligation assay revealed that post-injury TAT-C1aB incubation prevents the dramatic increase in Kv2.1/syntaxin interactions 3 hr after treatment with an apoptogen. Notably, in a mouse model of transient middle cerebral artery occlusion, injections of TAT-C1aB (i.p., 6nmol/g, at 1+6h reperfusion) significantly reduced infarct size (0.20±0.019 vs 0.12±0.016, Mean±SEM infarct ratio, n=10 and n=7 respectively, p=0.0053). In all above experiments, TAT-conjugated scramble control had no detectable effects. Together, these findings characterized a promising neuroprotectant prototype and established the Kv2.1/syntaxin interaction as a novel molecular target in ischemic stroke as well as other neurodegenerative diseases.

Disclosures: C. Yeh: None. **A.M. Bulas:** None. **K.A. Hartnett:** None. **C.T. Anderson:** None. **R. Di Maio:** None. **T. Tzounopoulos:** None. **D. Sun:** None. **R. Khanna:** None. **E. Aizenman:** None.

Poster

790. Ischemia: Perinatal and Recovery

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 790.24/N4

Topic: C.07. Ischemia

Support: Canadian Partnership for Stroke Recovery

Title: Proportional stroke recovery in the rat: Evidence for a cross-species biological recovery process that incorporates initial impairment, infarct volume and rehabilitation intensity.

Authors: *M. S. JEFFERS, S. KARTHIKEYAN, D. CORBETT;
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Abstract: Objective: Initial post-stroke impairment level and corticospinal tract lesion load have been identified as the most important predictors of functional recovery across time for human stroke. The present study sought to identify if similar biomarkers predict recovery of

post-stroke function in rats, indicating that an endogenous biological recovery process might be preserved across mammalian species. We then further investigated the roles of initial impairment, infarct volume and rehabilitation on this process. **Methods:** In a retrospective analysis of 593 male Sprague-Dawley rats we predicted post-stroke change in pellet retrieval (PR) in the Montoya staircase task based on the proportional recovery rule: $\Delta PR_{Predicted} = 0.7(PR_{Pre\text{-}stroke} - PR_{Initial})$. Stratification of the sample into "fitters" and "non-fitters" of this rule allowed identification of distinguishing characteristics using linear regression. **Results:** Approximately 30% of subjects were identified as "fitters" of the rule. Less severe infarct volumes and initial post-stroke impairments with a higher intensity of rehabilitation distinguished this group from "non-fitters". Interestingly, by using these characteristics to model recovery across the total sample we demonstrated that recovery could only be reliably predicted when rehabilitation is present. **Interpretation:** These findings suggest that proportional recovery is a cross-species phenomenon that can be modeled in Sprague-Dawley rats. Additionally, as infarct volume and initial impairment grow more severe, more intense rehabilitation is required in order to engage biological recovery processes.

Disclosures: **M.S. Jeffers:** None. **S. Karthikeyan:** None. **D. Corbett:** None.

Poster

790. Ischemia: Perinatal and Recovery

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 790.25/N5

Topic: C.07. Ischemia

Support: Ontario Brain Institute (OBI)

NeuroDevNet (NDN)

Title: Effects of constraint-induced movement therapy (CIMT) and neural precursor cell (NPC) transplantation in the corpus callosum of the hypoxic-ischemic hemiplegic mouse model

Authors: ***P. RUMAJOGEE**[1], S. ALTAMENTOVA[1], J. LI[1], D. VAN DER KOOY[2], M. G. FEHLINGS[1];
[1]Genet. and Develop., Univ. Hlth. Network, Toronto, ON, Canada; [2]Mol. Genet., Inst. of Med. Sci., Toronto, ON, Canada

Abstract: BACKGROUND:
Cerebral palsy (CP) is the most common pediatric neurodevelopmental physical disability, with a prevalence of 2.3/1000 births, causing severe motor and developmental disturbances. Clinical

application of the Constraint-Induced Movement Therapy (CIMT) protocol shows functional benefits in hemiplegic CP. The usage of the child's "less-affected" arm is reduced in order to promote the overuse of the other, affected arm. CIMT has been suggested to trigger neural cell generation from endogenous neural precursor cell (NPC). However, the underlying mechanisms and optimal timing/mode of application remain poorly understood.
METHODS:
To investigate the hemiplegic CP, we use a Hypoxic-Ischemic model (HI) model. The right common carotid artery of post-natal day (PND) 7 C57Bl/6 mice is permanently occluded and, after 2 hours of recovery with the dam, the pups are exposed to hypoxic air (8% oxygen for 45 minutes).
The project has 3 major aspects: 1) Regeneration, which will focus on the effects of NPC transplantation in the corpus callosum (CC), known to be impacted early in the course of demyelinating conditions; 2) Rehabilitation, which will focus on the effects of CIMT; and 3) A third aspect is a combinatorial approach using NPCs and CIMT. NPCs are transplanted in the CC at PND21, while Botulinum toxin (Botox) is injected in 3 muscles of the right (unaffected) forelimb to mimic the CIMT protocol.
RESULTS:
Our results support the use NPCs and CIMT on the HI model. We have shown: A) Differences between HI and Control animals, as well as within HI groups (variability of injury): the CC morphology is affected; the HI mice use the unaffected forelimb with a clear preference (85% of the time); B) A good development and integration of NPCs in the CC, and co-localizations with neuronal, astrocytic as well as oligodendrocyte markers; C) A role of NPCs in functional recovery: after 1 month, some mice recover completely (50% use of the unaffected forelimb), while others recover only partially (78%); D) A recruitment of endogenous oligodendrocytes in the CC, most probably partially mediated by the transplanted NPCs; E) A potential synergistic effect between NPCs and CIMT.
CONCLUSION:
The variability of injury observed can recapitulate various aspects of clinical CP. This might be useful when developing translational treatment strategies. This work supports the use of NPC for CP treatment. However, while in our model direct re-myelination processes still remain to be demonstrated, significant recovery is observed after NPC and Botox treatments. Further investigation is needed in order to decipher the mechanisms of CIMT and a potential synergistic effect with NPCs.

Disclosures: P. Rumajogee: None. **S. Altamentova:** None. **J. Li:** None. **D. Van der kooy:** None. **M.G. Fehlings:** None.

Poster

791. In Vivo Studies of Ischemia and Neuroprotection

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 791.01/N6

Topic: C.07. Ischemia

Support: NIH Grant R01 NS046741

Title: Docosahexaenoic acid provides neuroprotection by upregulating Iduna expression in the ischemic penumbra

Authors: N. G. BAZAN[1], P. K. MUKHERJEE[1], V. BALASZCZUK[1], A. OBENAUS[2], *L. KHOUTOROVA[1], S.-H. HONG[3], L. BELAYEV[1];
[1]LSU, New Orleans, LA; [2]Loma Linda Univ., Loma Linda, CA; [3]Baylor Col. of Medicine,, Houston, TX

Abstract: Ring finger protein 146, also called Iduna, has been identified as a neuroprotective protein. Iduna facilitates DNA repair and protects against cell death induced by NMDA receptor-mediated glutamate excitotoxicity or cerebral ischemia. Recently, we have shown that docosahexaenoic acid (DHA; 22:6n-3) therapy improves functional and histological outcomes following experimental stroke. This study evaluated the time course expression of Iduna in the ischemic penumbra and the role of DHA in cerebral ischemia and its potential mechanism. Thirty-six male SD rats were anesthetized with isoflurane and subjected to 2 h of middle cerebral artery occlusion (MCAo) by poly-L-lysine-coated intraluminal suture. DHA (5 mg/kg) or vehicle (saline) was administered IV at 3 h after the onset of MCAo, and animals were sacrificed on days 1, 3 and 7 (n=6 rats per group). Neurological function was evaluated during occlusion (60 min) and on days 1, 3 and 7 after MCAo; a grading scale of 0-12 was employed (0=normal and 12=maximal deficit). *Ex vivo* MRI, Western blot and immunohistochemistry (Iduna/NeuN and Iduna/GFAP) were conducted on days 1, 3 and 7. All animals showed similar values for rectal and cranial temperatures, arterial blood gases, and plasma glucose during and after MCAo. Behavioral deficit was significantly improved by treatment with DHA compared to vehicle on days 1 (by 30%), 3 (by 31%) and 7 (by 32%). DHA treatment rescued the ischemic core and penumbra, reduced T2 values (decreased edema) and cortical, subcortical, total lesion volumes (by 63-87%) on days 3 and 7. Western-blot analysis showed that DHA treatment increased Iduna expression in the ischemic penumbra compared to vehicle on days 1 (2.2±0.3 vs. 0.6±0.1) and 3 (0.44±0.05 vs. 0.3±0.01, respectively). There were no differences in Iduna expression on day 7 between DHA and vehicle-treated groups. Immunostaining revealed that Iduna expression was increased in the penumbra of DHA-treated rats. DHA protected the brain from severe damage caused by MCAo. This effect may be through upregulation of Iduna expression in the ischemic

penumbra. Thus, it is reasonable to hypothesize that DHA has potential for the effective treatment of ischemic stroke in patients.

Disclosures: **N.G. Bazan:** None. **P.K. Mukherjee:** None. **V. Balaszczuk:** None. **A. Obenaus:** None. **L. Khoutorova:** None. **S. Hong:** None. **L. Belayev:** None.

Poster

791. In Vivo Studies of Ischemia and Neuroprotection

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 791.02/N7

Topic: C.07. Ischemia

Support: HU 011D04105001

Title: Differential analysis of oxygen radical formation in vasculature and parenchyma and its suppression by a nitrone (PBN) in an experimental model of ischemia/reperfusion by intravital fluorescence microscopy

Authors: *A. TASKIRAN SAG[1], M. YEMISCI[1], Y. GURSOY-OZDEMIR[1], E. S. ERDENER[1], D. YUCE[2], T. DALKARA[1];
[1]Hacettepe Univ. Inst. of Neurolog. Sci., Ankara, Turkey; [2]Hacettepe Univ. Cancer Inst., Ankara, Turkey

Abstract: Objective: Oxygen/nitrogen radicals are intensely produced on restoration of oxygen supply to the ischemic tissue and contribute to reperfusion injury and radicals reach to highest concentration on the microcirculation. N-tert-butyl-alpha-phenyl-nitrone (PBN), a superoxide scavenger, significantly decreases infarct volume when administered at the time of recanalization. Interestingly, its sulfo-derivative, S-PBN, which is blood-brain barrier impermeable, is equally protective to PBN, raising the possibility that the main site of action of PBN could be vasculature rather than the parenchyma. We investigated the cellular sources of oxidative stress during reperfusion and its suppression by PBN with intravital fluorescence microscopy.**Methods:** In mice under anesthesia, the distal middle cerebral artery was occluded by compression for 1 hour and then recanalized. For the following 1 hour, superoxide formation was monitored in the vasculature and parenchyma with topically applied dihydroethidium (DHE). Vessels with a diameter ranging from 20 to 60 μm were analyzed. PBN (100 mg/kg) was applied intraperitoneally 15 minutes before reperfusion and suppression of the arterial, venous, parenchymal DHE fluorescence was examined. Repeated measures designs in linear models were used for statistical evaluations.**Results:** We observed an intense increase in DHE fluorescence in vasculature as well as parenchyma during reperfusion. PBN significantly and

similarly suppressed DHE fluorescence in all compartments ($p<0.001$ for arterial and venous wall; $p=0.003$ for parenchyma).**Conclusions:** These data suggest that PBN's neuroprotective action is produced by suppression of radical toxicity in vascular as well as parenchymal compartments. However, the possibility that the vascular protection could secondarily reduce parenchymal radical stress should also be considered.

Disclosures: **A. Taskiran Sag:** None. **M. Yemisci:** None. **Y. Gursoy-Ozdemir:** None. **E.S. Erdener:** None. **D. Yuce:** None. **T. Dalkara:** None.

Poster

791. In Vivo Studies of Ischemia and Neuroprotection

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 791.03/N8

Topic: C.07. Ischemia

Support: NIH Grant EY10343

Title: Mechanisms of ischemic post-conditioning in the retina

Authors: ***S. KEIL**[1], B. MATHEW[2], L. TORRES[2], S. ROTH[3];
[1]Univ. of Illinois Chicago, Chicago, IL; [2]Anesthesiol., [3]Anesthesiol. and Ophthalmology, Univ. of Illinois, Chicago, IL

Abstract: We previously described the phenomenon of ischemic post conditioning in the in vivo retina. A brief period of ischemia following a prolonged damaging ischemia was capable of decreasing injury in the rat retina in vivo. We showed "delayed" post-conditioning, in which application of a brief ischemic stimulus as late as 24 h after damaging ischemia significantly improved functional recovery, and preserved structure. In the present study we examined the signaling mechanisms in delayed post conditioning (post-C). Rats were subjected to retinal ischemia by elevation of intraocular pressure. 24 h later, 8 min ischemia was applied, and retinae were harvested from the animals 24 h later. The retinal homogenates were applied to Kinexus antibody microarrays (over 800 proteins). The arrays were analyzed using a microarray analyzer. We compared results in ischemia + post-C to ischemia + sham post-C. Z scores were used to evaluate thresholds for significant increases or decreases in the phosphoproteins. Real time PCR was used to confirm results. We found significant increases in a group of proteins in the ischemia + post-C, which were decreased in ischemia + sham post-C. The proteins were: B23, 4EBP1, COX2, CDK7, LIMK1, Tau, Bcl, MST3, and VHR. These results indicate candidate proteins that may be involved in neuroprotection.

Disclosures: **S. Keil:** None. **B. Mathew:** None. **L. Torres:** None. **S. Roth:** None.

Poster

791. In Vivo Studies of Ischemia and Neuroprotection

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 791.04/N9

Topic: C.07. Ischemia

Support: JSPS KAKENHI Grant-in-Aid for Young Scientists (B) 23700941

JSPS KAKENHI Grant-in-Aid for Scientific Research (C) 16K00932

Title: Auraptene acts as an anti-inflammatory and neuroprotective agent in the mouse brain

Authors: ***S. OKUYAMA**, M. MORITA, M. KAJI, K. SHIMAMOTO, Y. OOKIDO, Y. AMAKURA, M. YOSHIMURA, M. NAKAJIMA, Y. FURUKAWA;
Col. of Pharmaceut. Sciences, Matsuyama Univ., Matsuyama, Ehime, Japan

Abstract: The anti-inflammatory activity of auraptene (AUR), a citrus coumarin, in peripheral tissues is well-studied. Our recent studies indicate the possibility that AUR exerts anti-inflammatory effects not only in peripheral tissues but also in the brain. In the present study, we investigated whether AUR directly exerts anti-inflammatory effects in the brain, and obtained the following results. (1) When a transient global cerebral ischemic mouse model was treated with AUR (25 mg/kg/day) for five days before and another three days after ischemic surgery, AUR suppressed neuronal cell death in the hippocampal CA1 region, microglia and astrocyte activation, and COX-2 mRNA expression in the hippocampus. (2) When cultured astrocytes were pretreated with AUR (25 μM) for 30 min before lipopolysaccharide (LPS)-treatment, AUR suppressed the LPS-induced expression of COX-2 mRNA and the mRNAs of pro-inflammatory cytokines. (3) When mouse was intraperitoneally administered with AUR (50 mg/kg), AUR was still detectable in the brain 60 min. These results suggested that AUR pass through the blood-brain-barrier and directly exerts anti-inflammatory effects on the brain, and that these effects were at least partly mediated by the suppression of inflammatory mediators derived from astrocytes.

Disclosures: **S. Okuyama:** None. **M. Morita:** None. **M. Kaji:** None. **K. Shimamoto:** None. **Y. Ookido:** None. **Y. Amakura:** None. **M. Yoshimura:** None. **M. Nakajima:** None. **Y. Furukawa:** None.

Poster

791. In Vivo Studies of Ischemia and Neuroprotection

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 791.05/N10

Topic: C.07. Ischemia

Support: CONACyT Grant 241655

Title: Establishment of the therapeutic window of the S-allylcysteine in an animal model to 1 hour of ischemia and 14 days of reperfution.

Authors: *C. A. ORTIZ, P. D. MALDONADO;
Patología Vascular Cerebral, Inst. Nacional De Neurología Y Neurocirugía, México, Mexico

Abstract: Background: It has been reported that the SAC is one of the biologically active compounds of aged garlic extract as it has shown to be a potent antioxidant in different models where oxidative stress plays a very important role. Specifically, in the model of cerebral ischemia, it is known that the SAC prevents edema formation because it inhibits lipid peroxidation and free radical production. Also recently in the laboratory was found that administration of SAC 1 h after the beginning of reperfusion decrease cerebral damage at 14 days of reperfusion. **Methods:** Wistar male rats were used with an initial weight between 280-320 g, randomly divided into five groups: the control group (CT); cerebral ischemia (1 h)/reperfusion (14 days) (IR) group; IR+SAC0 group; IR+SAC2 group; and IR+SAC4 group. Animals were anesthetized and underwent surgery to induce ischemic brain damage, temporarily occluding the middle cerebral artery (for 1 h) and allowing reperfusion of animals for 14 days. The SAC was administered orally at a dose of 100mg/kg at the following times: the beginning of reperfusion (time 0 h), 2 and 4 h after the beginning of reperfusion. The neurological deficit was evaluated in rats damaged by ischemia through 5 tests: spontaneous mobility, contralateral turns to injury, try hanging by the tail, ability to hold on to a cable and ability to attach to a cable. Quantification of the damage was made by a person blind to the treatment of samples. The mortality rate in this process is high **Results:** It was observed that the neurological deficits of animals after 14 days of reperfusion improvement SAC administration 2 h after reperfusion compared SAC administered at time 0 and at 4 h. Also a change was observed in the weight of the animals during the 14 days of reperfusion, in which it is noted that in the administration of the SAC at 2 h and 4 h after reperfusion produces greater protection since animals lose less weight and have a recovery after 7 days compared wiyh IR group. **Conclusions:** SAC treatment (100mg/kg) 2 h after onset reperfusion induces a neuroprotection in animals.

Disclosures: C.A. Ortiz: None. **P.D. Maldonado:** None.

Poster

791. In Vivo Studies of Ischemia and Neuroprotection

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 791.06/N11

Topic: C.07. Ischemia

Support: Swiss National Science Foundation Grants 31003A_121963 and 31003A_138382 (to D. B.)

Title: Restoring cell surface expression of GABA (B) receptors: a potential strategy to limit neuronal death in cerebral ischemia

Authors: *K. BALAKRISHNAN[1,2], D. BENKE[1,2];
[2]Inst. of Pharmacol. and Toxicology, [1]Univ. of Zurich, Zurich, Switzerland

Abstract: Cerebral ischemia is a leading cause for long-term disability and mortality in adults due to prolonged massive neuronal death. One major mechanism behind ischemia-induced neuronal death is the excessive release of glutamate upon oxygen and glucose deprivation (OGD) occurring during ischemic stroke. Ischemic overexcitation of neurons downregulates GABA(B) receptors, which normally control excessive excitatory neurotransmission by mediating slow and prolonged neuronal inhibition. Sustained activation of glutamate receptors increases the intracellular Ca^{2+} concentration enhancing the activity of CaMKII, which leads to the phosphorylation of $GABA_B$ receptors at S867 in the C-terminal domain of the $GABA_{B1}$ subunit. This sorts the constitutively endocytosed $GABA_B$ receptors to lysosomal degradation instead of recycling them back to the cell surface. In this study we tested the hypothesis that restoring cell surface expression of $GABA_B$ receptors may prevent neuronal death under ischemic conditions. We identified a short synthetic peptide that prevents the interaction of CaMKII with $GABA_{B1}$ and consequently prevented the phosphorylation of $GABA_{B1}$ (S867). This short-interfering peptide prevented glutamate-induced downregulation of GABA(B) receptors in cultured cortical neurons and limited glutamate and OGD-induced neuronal death. Therefore, we expect that the preserved cell surface $GABA_B$ receptors levels under ischemic conditions counteract the excessive neuronal excitation and thus limit neuronal death in-vivo.

Disclosures: K. Balakrishnan: None. **D. Benke:** None.

Poster

791. In Vivo Studies of Ischemia and Neuroprotection

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 791.07/N12

Topic: C.07. Ischemia

Support: VA Merit I01BX000917

NIH R01NS082308

Title: CD38 knockout mice show significant protection against ischemic brain damage despite high level poly-ADp-ribosylation

Authors: A. LONG[1], J. H. PARK[1], N. KLIMOVA[2], D. J. LOANE[2], *T. KRISTIAN[2,1]; [1]Veterans Affairs Maryland Hlth. Ctr. Syst., Baltimore, MD; [2]Dept Anesthesiol, Univ. of Maryland Sch. of Med., Baltimore, MD

Abstract: Several enzymes in cellular bioenergetics metabolism require NAD^+ as an essential cofactor for their activity. NAD^+ depletion following ischemic insult can result in cell death and has been associated with over-activation of poly-ADP-ribose polymerase PARP1 as well as an increase in NAD^+ consuming enzyme CD38. CD38 is an NAD^+ glycohydrolase that uses NAD^+ to generate second messengers cyclic ADP-ribose and ADP-ribose, playing an important role in inflammatory responses.

To determine the contribution of CD38 activity to the mechanisms of post-ischemic brain damage we subjected CD38 knockout (CD38KO) mice and wild-type (WT) mice to transient forebrain ischemia. The CD38KO mice showed a significant amelioration in both histological and neurologic outcome following ischemic insult. These mice exhibited only a 26% decrease in CA1 surviving neurons as compared to 50% in the WT. In general control CD38KO mice had significantly higher number of CA1 neurons when compared to control WT mice. Decrease of hippocampal NAD^+ levels detected during reperfusion in WT mice was only transient in CD38KO animals, suggesting that CD38 contributes to post-ischemic NAD^+ catabolism. Surprisingly, pre-ischemic poly-ADP-ribose (PAR) levels were 140% higher in CD38KO animals compared to WT animals and exhibited reduction post-ischemia in contrast to the increased levels in WT animals. The high PAR levels in CD38 mice were due to the reduced expression levels of poly-ADP-ribose glycohydrolase (PARG) in these animals. PARG catabolizes PAR and converts it to ADP-ribose. Thus, the absence of CD38 activity can not only directly affect inflammatory response, but also result in unpredicted alterations in the expression levels of enzymes participating in NAD^+ metabolism. Although the CD38KO mice showed significant protection against ischemic brain injury, the changes in enzyme activity related to NAD^+ metabolism makes the determination of the role of CD38 in mechanisms of ischemia-induced brain damage ambiguous.

Disclosures: **A. Long:** None. **J.H. Park:** None. **N. Klimova:** None. **D.J. Loane:** None. **T. Kristian:** None.

Poster

791. In Vivo Studies of Ischemia and Neuroprotection

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 791.08/N13

Topic: C.07. Ischemia

Title: Ischaemia-induced erased perineuronal nets and damaged, but persisting GABAergic neurons in the nucleus reticularis thalami of wildtype and 3xTg mice

Authors: *W. HARTIG[1], S. APPEL[1], A. SUTTKUS[1], J. GROSCHE[2], D. MICHALSKI[3]; [1]Univ. Leipzig, PFI, Leipzig, Germany; [2]Effigos GmbH, Leipzig, Germany; [3]Univ. Leipzig, Dept of Neurol., Leipzig, Germany

Abstract: Treatment of ischaemic stroke is limited to intravenous thrombolysis and mechanical thrombectomy as recanalizing approaches. The urgently requested translation of further treatment options requires clinically relevant stroke models and should consider co-morbidities, age-dependency of neuropathological alterations and the complexity of the neurovascular unit (NVU). The NVU comprises not only neurons but also affected vessels, glial cells and the extracellular matrix (ECM) with perineuronal nets (PNs). These highly anionic, chondroitin sulphate proteoglycan-rich surroundings of certain neurons were comprehensively characterized in the naive brain. However, the role of PNs during ischaemia and as potential target for treatments is poorly understood. Therefore, this study is focused on stroke-induced alterations of PNs and GABAergic neurons with emphasis on the nucleus reticularis thalami (NRT). Mice underwent focal cerebral ischaemia by an occlusion of the middle cerebral artery, resulting in clinically relevant, predominantly striatal lesions. Experiments were performed with 3- and 12-month-old wild-type mice and co-morbid triple-transgenic (3xTg) mice displaying age-dependent Alzheimer-like alterations. One day after ischaemia onset, forebrain sections comprising the NRT were applied to double fluorescence labelling of biotinylated *Wisteria floribunda* agglutinin (WFA) as established marker for PNs and parvalbumin in fast-firing GABAergic neurons. Semiquantitative analyses revealed staining intensities, staining areas and cell counts for WFA and parvalbumin. The ischaemia-affected NRT displayed a drastic decline of WFA-staining compared with the contralateral, non-affected side. In parallel, parvalbumin-immunoreactivity was affected by ischaemia to a much lesser degree. Additional immunostaining detected the ischaemia-induced loss of aggrecan and neurocan in PNs and allocated neuropil. Further multiple immunofluorescence labelling demonstrated clearly

damaged GABAergic neurons in the ischaemic NRT, persistingly expressing the calcium-binding proteins parvalbumin and calbindin, the potassium channel subunit Kv3.1b and the glutamate decarboxylase isoforms GAD65 and GAD67 as their marker enzymes. In conclusion, our data show PNs as highly vulnerable constituents of the ECM under ischaemic conditions. Therefore, components of the extracellular matrix appear as promising targets of future neuroprotective strategies in acute ischaemic stroke which might also include ECM-degrading enzymes such as metalloproteinases, chondroitinases and aggrecanases.

Disclosures: W. Hartig: None. **S. Appel:** None. **A. Suttkus:** None. **J. Grosche:** None. **D. Michalski:** None.

Poster

791. In Vivo Studies of Ischemia and Neuroprotection

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 791.09/N14

Topic: C.07. Ischemia

Support: MINECO-FEDER BIO2013-49006-C2-2-R

MINECO-FEDER RTC-2015-4094-1

JCyL grant EDU/346/2013

Title: Neuroprotection by BDNF following OGD is higher in hippocampus than in cerebral cortex in an "*Ex vivo*" model of rat brain slices.

Authors: *P. GONZALEZ-RODRIGUEZ[1], E. FONT[1], B. ANUNCIBAY-SOTO[1], D. PÉREZ-RODRÍGUEZ[1], C. PÉREZ-GARCÍA[2], A. FERNÁNDEZ-LÓPEZ[1];
[1]Univ. de Leon, Inst. de Biomedicina, Leon, Spain; [2]Univ. de Leon. Area de Medicina, Cirugia y Anatomia Veterinaria, Inst. de Biomedicina, Leon, Spain

Abstract: Brain derived neurotrophic factor (BDNF) is a neurotrophin reported to present a neuroprotective effect on stroke. In this study, we analyze the effect of the presence of BDNF on slices of cerebral cortex (Cx) and hippocampus (Hp) in an "ex vivo" model, correlating the cell mortality and viability as well as the expression of some prosurvival genes. The study was carried out on 350 μm thick brain slices under oxygen and glucose deprivation (OGD) for 30 minutes followed by 60 and 180 minutes in normoxic solution (reperfusion-like condition). Hp and the Cx above it were analyzed independently. Mortality and viability were measured in BDNF dose-response curves by testing LDH and MTT respectively. Protein and mRNA levels of different AKT pathway markers were measured by Western blot and qPCR respectively. The

neuroprotective role reported for BDNF was consistent with the decreased mortality and increased survival observed in our "ex vivo" assays. In spite of its higher vulnerability, Hp presented a higher BDNF-response than Cx which could be related to the higher amount of the BDNF receptor, tropomyosin receptor kinase B (TrkB), in Hp. Furthermore BDNF significantly increased the expression of some genes in the AKT pathway, such as Nrf-2 induced genes, bcl-2 and c-fos in Hp but not in Cx. We conclude that the neuroprotective effect of BDNF can be already detected in the first hour of reperfusion. Furthermore this effect is stronger in Hp than in Cx.

This work was supported by the Spanish Ministerio de Economia y Competitividad cofinanced with FEDER funds "una manera de hacer Europa" (References BIO2013-49006-C2-2-R and RTC-2015-4094-1), which also supports B. Anuncibay Soto. P. Gonzalez-Rodriguez and E. Font are supported by University of Leon grants and D. Perez-Rodriguez by Junta de Castilla y León (EDU/346/2013).

Disclosures: **P. Gonzalez-Rodriguez:** None. **E. Font:** None. **B. Anuncibay-Soto:** None. **D. Pérez-Rodríguez:** None. **C. Pérez-García:** None. **A. Fernández-López:** None.

Poster

791. In Vivo Studies of Ischemia and Neuroprotection

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 791.10/N15

Topic: C.07. Ischemia

Support: NIH Grant P30 EY13079

NIH Grant R01NS077897

Title: The impact of BDNF-Val66Met polymorphism upon GABAergic innervation of cortical pyramidal neurons and spiny striatal neurons in an animal model of ischemic stroke

Authors: H. ACTOR-ENGEL[1], B. S. RANA[1], Y.-W. CHEN[1], S. CHO[2], *C. J. AOKI[1]; [1]Ctr. Neural Sci., New York Univ., New York, NY; [2]Brain and Mind Res. Inst., Burke Med. Res. Inst., Weill Cornell Med. Coll, White Plains, NY

Abstract: Stroke induces structural plasticity and behavioral adaptation. Previously, it was shown that mice expressing the genetic variant of BDNF (Val66Met) exhibit greater acute motor deficits but unexpected enhancement of motor/gait function during the recovery phase, due to contribution by the intact hemisphere, when challenged by unilateral ischemic stroke (Qin et al., J Neurosci 34: 2493, 2014). We hypothesized that these bi-directional effects of BDNF-

Val66Met upon motor function recovery may be due to the multifaceted functions of BDNF: while BDNF is important for GABAergic synaptogenesis, it also reduces GABA release from mature synapses and supports LTP of excitatory synapses. Its bi-directional effect may additionally be due to the altered intracellular distribution pattern of BDNF within neurons: Val66Met SNP causes reduction in the intracellular trafficking of BDNF-mRNA and proteins, thereby reducing BDNF secretion from distal neurites but accumulating it within neuronal cell bodies. To test this hypothesis, we sought to determine whether ischemic stroke induced by 30 min occlusion of the middle cerebral artery (MCAO) leads to alterations in GABAergic synaptic inputs upon spiny neurons of cortex and striatum of the intact hemisphere, contralateral to ischemia, and whether this response differs across two genotypes of mice: $BDNF^{+/+}$ versus $BDNF^{Met/Met}$ (homozygous for the SNP). Mice of each genotype underwent MCAO at 3 months of age or were sham-operated. These and naïve animals were euthanized at 9 to 10 mo of age. Histology confirmed that MCAO caused drastic degeneration of the ipsilateral cerebral cortex and striatum, while sparing the contralateral hemisphere, thereby serving as a good animal model for studying the contribution made by the non-lesioned hemisphere in recovery from ischemic stroke. GABAergic innervation of neurons within these brains have begun to be assessed by quantifying the number and lengths of GABAergic synapses forming upon cell bodies and distal dendrites of neurons by EM-ICC, using anti-glutamic acid decarboxylase (GAD), the rate-limiting synthetic enzyme of GABA, to immunolabel GABAergic neurons. Details of the procedure are as described in a previous publication (Yi-Wen Chen et al., Cerebral Cortex, 2015). Based on data obtained from naive $BDNF^{Met/Met}$ brains analyzed at 2 months of age, we expect to observe decreased innervation of distal dendrites in both regions, which would be the cellular substrate for hyper-excitability within the striatum and of the cortico-striatal and striatal-nigral pathways.

Disclosures: **H. Actor-Engel:** None. **B.S. Rana:** None. **Y. Chen:** None. **S. Cho:** None. **C.J. Aoki:** None.

Poster

791. In Vivo Studies of Ischemia and Neuroprotection

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 791.11/N16

Topic: C.07. Ischemia

Support: National Natural Science Foundation of China 81471173

National Natural Science Foundation of China 81271295

National Natural Science Foundation of China 81571109

Title: The glucagon like peptide 1 receptor agonist exendin4 ameliorates warfarin associated hemorrhagic transformation after cerebral ischemia

Authors: *M. CUI, F. Z. CHEN, W. F. WANG, H. Y. DING, Q. YANG, Q. DONG;
Fudan Univ. Huashan Hosp., Shanghai, China

Abstract: Background: As the number of patients with cardioembolic ischemic stroke is predicted to be double by 2030, increased burden of warfarin-associated hemorrhagic transformation (HT) after cerebral ischemia is an expected consequence. However, thus far, no effective treatment strategy is available for HT prevention in routine clinical practice. While the glucagon-like peptide-1 receptor (GLP-1R) agonist exendin-4 (Ex-4) is known to protect against oxidative stress and neuronal cell death caused by ischemic brain damage, its effect in preventing warfarin-associated HT after cerebral ischemia is yet unknown. Therefore, we hypothesized that Ex-4 would stabilize the blood-brain barrier (BBB) and suppress neuroinflammation through PI3K-Akt–induced inhibition of GSK-3β after warfarin-associated HT post-cerebral ischemia.
Methods: We used male C57BL/6 mice for all experiments. A 5-mg warfarin sodium tablet was dissolved in the animals' drinking water (effective warfarin uptake: 0.04 mg [2 mg/kg] per mouse). The mice were fed for 0, 6, 12, or 24 h with ad libitum access to the treated water. To study the effects of Ex-4, temporary middle cerebral artery occlusion (MCAO) was performed. Then, either Ex-4 (10 mg/kg) or saline was injected through the tail vein, and in the Ex-4 + wortmannin group, PI3K inhibitor wortmannin was intravenously injected, after reperfusion. The infarct volume, neurological deficits, and integrity of the BBB were assessed 72 h post MCAO. One- or two-way ANOVA was used to test the difference between means followed by Newman–Keuls post-hoc testing for pair-wise comparison.
Results: We observed that Ex-4 ameliorated warfarin-associated HT and preserved the integrity of the BBB after cerebral ischemia through the PI3K/Akt/GSK-3β pathway. Furthermore, Ex-4 suppressed oxidative DNA damage and lipid peroxidation, attenuated pro-inflammatory cytokine expression levels, and suppressed microglial activation and neutrophil infiltration in warfarin-associated HT post-cerebral ischemia. However, these effects were totally abolished in the mice treated with Ex-4 + the PI3K
inhibitor—wortmannin. The PI3K/Akt-GSK-3β signaling pathway appeared to contribute to the protection afforded by Ex-4 in the warfarin-associated HT model.
Conclusions: GLP-1 administration could reduce warfarin-associated HT in mice. This beneficial effect of GLP-1 is associated with attenuating neuroinflammation and BBB disruption by inactivating GSK-3β through the PI3K/Akt pathway.

Disclosures: M. Cui: None. **F.Z. Chen:** None. **W.F. Wang:** None. **H.Y. Ding:** None. **Q. Yang:** None. **Q. Dong:** None.

Poster

791. In Vivo Studies of Ischemia and Neuroprotection

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 791.12/N17

Topic: C.07. Ischemia

Support: NS090904

Title: L Nio induced focal subcortical white matter stroke in mice

Authors: *Y. WANG, Z. ZHAO, A. MONTAGNE, B. ZLOKOVIC;
Zilkha Neurogenetic Inst., Keck Sch. of Medicine, USC, Los Angeles, CA

Abstract: Up to 30% of strokes in humans occur initially as silent infarcts in the white matter (WM), which increases risk for vascular cognitive impairment and dementia (VCID). Subcortical WM stroke model has been induced by vasoconstrictor N5-(1-iminoethyl)-L-ornithine, dihydrochloride (L-Nio). In this study, L-Nio (Calbiochem) was injected into subcortical WM of the anterior cingulum (AC) of the corticolimbic circuit using the Neurostar motorized ultra-precise small animal stereotaxic instrument (Model 963SD). The ischemic injury was verified by cresyl violet staining and MRI 24 h after L-Nio injection. Remote memory test and foot-fault test were performed two weeks after L-Nio injection in AC. The results showed that L-Nio can produce dose-dependent brain infarcts and focal mini-stroke confined to AC. The mice with L-Nio injection in AC developed impaired remote memory retrieval, a deficit of the corticolimbic circuit, but did not have deficits in motor function. These results demonstrated that L-Nio provided a reliable and reproducible model of focal stroke in WM.

Disclosures: **Y. Wang:** None. **Z. Zhao:** None. **A. Montagne:** None. **B. Zlokovic:** None.

Poster

791. In Vivo Studies of Ischemia and Neuroprotection

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 791.13/N18

Topic: C.07. Ischemia

Support: AHA Grant 12GRNT12060222

AHA Grant 14POST20130024

AHA Grant 15POST25680013

NIH grant NS075338

NIH grant NS085568

VA National Merit Grant

Title: Pharmacologically induced hypothermia extends the therapeutic window for tpa to 6 hr after onset of embolic stroke in mice

Authors: *J. LEE, S. WON, L. WEI, S. YU;
Dept. of Anesthesiol., Emory Univ., Atlanta, GA

Abstract: Preclinical and clinical studies have shown therapeutic potential of mild-to-moderate hypothermia for treating stroke patients. Our recent studies showed that pharmacologically induced hypothermia (PIH) using our neurotensin receptor 1 (NTR1) agonists is effective in inducing therapeutic hypothermia and protecting the brain from ischemic and hemorrhagic stroke in mice and rats. We here tested the hypothermic and neuroprotective effect of HPI-363, a second-generation NTR1 agonist, in combination with delayed thrombolytic therapy in a mice model of embolic stroke. Adult mice subjected to embolic middle cerebral artery (MCA) occlusion were treated with HPI-363 at 0.5 hr after stroke and maintained hypothermia (31-33°C) until delayed treatment of tissue plasminogen activator (tPA) 4.5 or 6 hrs after stroke. In stroke mice the 4.5-6 hr-delayed tPA treatment caused significant increases in infarct volume and hemorrhagic transformation at 24 hr after stroke compared with saline-treated stroke mice. However, the HPI-363-induced hypothermic treatment significantly reduced infarct volume, hemorrhagic transformation, and the embolus volume at the site of the MCA occlusion at 24 hr after stroke compared with stroke plus tPA treatment alone. Furthermore, HPI-363 treatment with tPA reduced the expression and activity of matrix metalloproteinase-9 (MMP-9), improved microvascular density, and protective effects on BBB integrity. In conclusion, a combination of PIH early treatment with delayed tPA administration extended the therapeutic window for stroke to 6 hrs without increasing the incidence of hemorrhagic transformation. This combination approach may benefit clinical treatments of embolic strokes.

Disclosures: **J. Lee:** None. **S. Won:** None. **L. Wei:** None. **S. Yu:** None.

Poster

791. In Vivo Studies of Ischemia and Neuroprotection

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 791.14/DP03 (Dynamic Poster)

Topic: C.07. Ischemia

Support: LASERLAB-EUROPE Grant 284464

NANOMAX

Human Brain Project Grant 604102

Title: Robotic rehabilitation promotes stabilization of peri-infarct cortical circuits and inter-hemispheric connectivity: *In vivo* study of structural and functional plasticity

Authors: *A. ALLEGRA MASCARO[1,2], E. CONTI[1], S. LAI[3], C. SPALLETTI[4], A. P. DI GIOVANNA[1], C. ALIA[4,5], A. PANARESE[3], L. SACCONI[1,2], S. MICERA[3,6], M. CALEO[4,5], F. S. PAVONE[1,2];
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Abstract: Stroke affects 15 million people worldwide every year and is one of the leading causes of long-term disability. Neurorehabilitation protocols based on the use of robotic devices provide a highly repeatable therapy and have recently shown promising clinical results. Little is known about how rehabilitation molds the brain to promote motor recovery of the affected limb. We used a custom-made robotic platform that provides quantitative assessment of forelimb function in a retraction test. Complementary imaging techniques allowed us to access to the multiple facets of robotic rehabilitation-induced cortical plasticity after unilateral photothrombotic stroke in mice Primary Motor Cortex (Caudal Forelimb Area - CFA). First, we analyzed structural features of vasculature and dendritic reshaping in the peri-infarct area with two-photon fluorescence microscopy. Longitudinal analysis of dendritic branches and spines of pyramidal neurons suggests that robotic rehabilitation promotes the stabilization of peri-infarct cortical excitatory circuits, which is not accompanied by consistent vascular reorganization towards pre-stroke conditions. To investigate if this structural stabilization was linked to functional remapping, we performed mesoscale wide-field imaging on GCaMP6 mice while performing the motor task on the robotic platform. We revealed temporal and spatial features of the motor-triggered cortical activation, shining new light on rehabilitation-induced functional remapping of the ipsilesional cortex. Finally, by using an all-optical approach that combines optogenetic activation of the contralesional hemisphere and wide-field functional imaging of

peri-infarct area, we dissected the effect of robotic rehabilitation on inter-hemispheric cortico-cortical connectivity.

Disclosures: **A. Allegra Mascaro:** None. **E. Conti:** None. **S. Lai:** None. **C. Spalletti:** None. **A.P. Di Giovanna:** None. **C. Alia:** None. **A. Panarese:** None. **L. Sacconi:** None. **S. Micera:** None. **M. Caleo:** None. **F.S. Pavone:** None.

Poster

791. In Vivo Studies of Ischemia and Neuroprotection

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 791.15/O1

Topic: C.07. Ischemia

Support: CIC 522386 UMSNH

PRODEP PD 45492

Title: Neuroprotective effects of melatonin under chronic cerebral hypoperfusion, in rats.

Authors: *G. LETECHIPIA-VALLEJO[1], M. CERVANTES[2], M. LÓPEZ-RODRÍGUEZ[3], L. FLORES-DOMÍNGUEZ[2], V. ZAMORA-LANDA[2,4], M. OLVERA-CORTES[4];
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Abstract: Chronic cerebral hypoperfusion, among other pathophysiological processes, is a causal factor accounting for the development of cognitive decline and dementia in the elderly. Consequently, inhibition of several pathophysiological pathways of neuronal damage is an attractive neuroprotective strategy for the clinical management of these disorder. Melatonin, protects the brain against several insults through its antioxidant and anti-inflammatory properties. Sprague- Dawley rats with permanent bilateral common carotid artery occlusion (2VO), a well-established model of chronic cerebral hypoperfusion, were used. Melatonin 5mg/ml was administered to rats (2VO + MEL group) by continuous IV infusion from a subcutaneously implanted osmotic pump ALZET, Model 2ML1 (10µl/hr., 7 days, 2ml), or vehicle ethanol 15% in saline (2VO+VEH group),starting one day, after 2VO. A SHAM group was also included. Fifteen days after melatonin treatment, the neuroprotective effect of melatonin, was evaluated by means of spatial learning /memory tests performance (Morris Water Maze). In addition, the pyramidal neuron population of the CA1 segment of hippocampus was assessed at the end of the behavioral testing period. Impairment of place learning in the 2VO+VEH group, while a similar

performance of the 2VO + MEL group and SHAM group were observed. A significant loss of pyramidal neuron population in the CA1 segment of hippocampus (28.4 % less than in the SHAM group) was observed in the 2VO+VEH group. By contrast, a 95% pyramidal neuron population of the CA1 segment of hippocampus remained in the 2VO + MEL group. Overall these results emphasize the efficacy of melatonin in counteracting the pathophysiological processes induced by chronic cerebral hypoperfusion. Financial support by: CIC UMNSH, PROMEP SEP 150419

Disclosures: G. Letechipia-Vallejo: None. **M. Cervantes:** None. **M. López-Rodríguez:** None. **L. Flores-Domínguez:** None. **V. Zamora-Landa:** None. **M. Olvera-Cortes:** None.

Poster

791. In Vivo Studies of Ischemia and Neuroprotection

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 791.16/O2

Topic: C.07. Ischemia

Support: Capes Foundation

Title: Hyaluronic acid hydrogel combined with cell therapy in experimental stroke

Authors: *L. SIMOES BRAGA BOISSERAND[1,2], J. PAPASSIN[2], N. COLLOMB[1], E. BARBIER[1], C. ROME[1], O. DETANTE[2];
[1]Grenoble Inst. Des Neurosciences, Grenoble, France; [2]Neurol., CHU Grenoble, Grenoble, France

Abstract: Introduction: Stroke is the leading cause of disability in adults, for which no effective treatment exists after the first 6 hours . Most evidences suggest that stem cell (SC) therapies have the potential to reduce post-stroke disability. Despite of beneficial effects, an important loss of grafted SC is reported when cells are administrated into infarct cavity. Development of biomaterials such as hydrogels in combination with stem cells (SC) or trophic factors can enhance brain remodeling after stroke. Hydrogels can be engineered to polymerize *in situ* allowing an *ex vivo* mixing with SC and an administration using a minimal invasiveness intracerebral (IC) injection.
Objective: Mesenchymal stem cells (MSC) were co-administrated with a hyaluronic acid hydrogel (Hystem, Sigma) with the aim to improve graft survival and potentiate their beneficial effects concerning functional outcome and brain remodeling after stroke.
Methods: 36 Sprague Dawley male rats, aged of 8 weeks were submitted to 90 minutes middle cerebral artery occlusion (MCAo) or sham surgery. One week later, rats were divided in 4 groups

1) IC injection of 10^5 human MSC mixed with hydrogel (n = 9); 2) IC MSC in Phosphate-buffered saline (PBS) (n=8); 3) IC PBS alone (n=2); 4) control group (sham for MCAo and treatment; n=6). The rats were followed during 4 weeks and assessed once a week by sensory-motor tests (n=36) (modified neurological severity score (mNSS) and adhesive removal test (ART)) and MRI (n=26 among the 36 rats). MRI scans were performed at D3, 9, 14, 21 and 28 on a 4.7T system (Bruker).
Results and discussion: Two days after MCAo, a mild neurological deficit was observed, without any significant difference among them. Combined MSC-hydrogel transplantation non significantly decreased neurological deficit from 28 days onward (mean +/- SD; mNSS: MSC-Hydrogel group 1.9 ± 1.8 vs. MSC group 2.9 ± 2.3; ART for left impaired forelimb 33.8s ± 35.2 vs. 45.1s ± 47.5 respectively). MRI analysis put in evidence an increase on Apparent Diffusion Coefficient (ADC) at day 29 for the ischemic groups: MSC+gel (1591±657 $\mu m^2/s$), MSC (1690±622 $\mu m^2/s$) in comparison with Sham (860±73 $\mu m^2/s$).
Conclusion: Hyaluronic acid hydrogel added to cell therapy presents no adverse effects after stroke. Longer follow-up will be required to determine if a synergic effect can be observed. Multiparametric MRI analysis is in progress and the number of animals per group will be increased.
References: References: 1. Wang, H. *et al. Sci. Rep.* **5,** (2015); **2.**Liang, Y. *et al.*, *Biomaterials* **34,** 5521-5529 (2013); **3** .Zhong, J. *et al. Neurorehabil. Neural Repair* **24,** 636-644 (2010); **4**.Pakulska, *et al.*M. M., *Mater. Bristol Engl.* **7,** 24101 (2012).

Disclosures: L. Simoes Braga Boisserand: None. **J. Papassin:** None. **N. Collomb:** None. **E. Barbier:** None. **C. Rome:** None. **O. Detante:** None.

Poster

791. In Vivo Studies of Ischemia and Neuroprotection

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 791.17/O3

Topic: C.07. Ischemia

Support: NSERC Grant EG1502

Title: Impact of crhr1 blockade on the expression of bdnf, trkb, and th in the vta following global cerebral ischemia

Authors: *N. F. NARVAEZ LINARES, J. ISAA, P. BARRA DE LA TREMBLAYE, H. PLAMONDON;
Behavioral Neurosci., Univ. of Ottawa, Ottawa, ON, Canada

Abstract: The ventral tegmental area (VTA) in the brain's reward circuitry is composed of a heterogeneous population of dopamine, GABA, and glutamate neurons that play important roles in mediating mood-related functions including depression. These neurons project to different brain regions, including the nucleus accumbens (NAc) and the medial prefrontal cortex (mPFC). Brain-derived neurotrophic factor (BDNF) protein and gene are upregulated in the NAc and VTA in rodents susceptible to depressive behaviors following chronic defeat stress. Corticotropin-releasing factor (CRF) plays a role in BDNF increase observed at the NAc. Moreover, blockade of CRH type 1 receptors (CRHR1) has been associated with anxiolytic and antidepressant effects in rodents. The current study assessed the role of CRHR1 in regulating expression of Tyrosine Hydroxylase (TH) and BDNF and its receptor, TrkB in the VTA after a global ischemia. Wistar male rats (N = 70) received an injection of antalarmin (Ant, 2µg / µl), a specific antagonist CRHR1, or a saline solution (Sal) before global ischemia. Expression of cerebral plasticity factors in the VTA was assessed 30 days following 10 min global ischemia. This study demonstrated that lasting dysregulation of neuroendocrine function following global cerebral ischemia could be blocked by the pre-ischemic administration of a CRHR1 antagonist, Antalarmin. Thereby, this research is one of the first assessing the role of CRHR1 signaling in regulation of BDNF and its receptor TrKB in dopaminergic neurons of the VTA following global cerebral ischemia.

Disclosures: N.F. Narvaez Linares: None. **J. Isaa:** None. **P. Barra de la Tremblaye:** None. **H. Plamondon:** None.

Poster

791. In Vivo Studies of Ischemia and Neuroprotection

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 791.18/O4

Topic: C.07. Ischemia

Support: Robert W. Spayne Research Grant

Title: Nesting environment impacts hypoxic-ischemic injury in rodents

Authors: *B. M. MASON, V. ROMERO, L.-G. ROLLINS, S. LAMOUR, N. WALTON, P. LONDOÑO, S. DONALDSON, S. EID;
Univ. of Massachusetts, Boston, Boston, MA

Abstract: Hypoxic-ischemic encephalopathy (HIE) is a brain injury that follows difficult perinatal birth conditions and can lead to substantial white matter damage, neuron loss in motor and cognitive brain areas, motor impairment and cognitive decline. Adverse environments such

as poverty and stress may worsen these consequences. In rodent models, a strong link has been established between levels of maternal care-taking behavior (mCTB) and neurogenesis in neonatal pups, where high mCTB may decrease stress and promote neuroprotection. Therefore, we hypothesized that cage modification with a closed nestbox (CN) during pre-weaning would promote mCTB and pup weight gain, and in turn, protect again neuronal loss in HI injured postnatal day (PND) 7 Long Evans rats. Utilizing a cohort of both male and female pups (*N = 42 - 51*) under three conditions (control, sham, hypoxic-ischemic/HI injury) reared in CN or standard facility (SF), we recorded offspring weight and development through PND 60, tested anxiety-like behavior (elevated plus maze/EPM), and spatial learning (Morris Water Maze/MWM). Our findings show that CN rearing significantly increased weight gain for males [$F(13, 520)=4.818, p < 0.001$] and shifted the appearance of neurological characteristics (i.e., earlier eye opening, ear unfolding, and day of incisor eruption) for pups reared in CN versus those raised in SF. In addition, CN housing decreased anxiety-like behavior on the EPM by increasing the number of open-arm entries [$F(1,49)=4.191, p < 0.05$] and diminished mean latency to find the invisible platform in MWM trials for females and CN-reared HI pups. Finally, preliminary evidence from morphometry analysis shows that CN rearing altered HI injury infarct size and lead to greater retention of ipsilateral and contralateral hippocampus and cortex for both male and female pups. These results support our hypothesis that the CN environment would facilitate neurological development following HI, and highlight the importance of environment in mediating lifetime outcome following an early-life brain injury.

Disclosures: B.M. Mason: None. **V. Romero:** None. **L. Rollins:** None. **S. Lamour:** None. **N. Walton:** None. **P. Londoño:** None. **S. Donaldson:** None. **S. Eid:** None.

Poster

791. In Vivo Studies of Ischemia and Neuroprotection

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 791.19/O5

Topic: C.07. Ischemia

Support: Daiichi Sankyo Co., Ltd.

Title: DS-1040, a novel selective thrombin-activatable fibrinolysis inhibitor does not increase hemorrhagic risk in a mechanical model of stroke in rats.

Authors: T. ISHRAT[1,2], B. PILLAI[1,2], A. Y. FOUDA[1,2], W. ELDAHSHAN[1,2], H. AHMED[1,2], *K. NOGUCHI[3], S. C. FAGAN[1,2];
[1]Program in Clin. and Exptl. Therapeut. Col. of Pharm., Univ. of Georgia, Augusta, GA; [2]Charlie

Norwood VA Med. Ctr., Augusta, GA; [3]End-Organ Dis. Labs., Daiichi Sankyo Co., Ltd., Tokyo, Japan

Abstract: **Background:** Activated form of thrombin-activatable fibrinolysis inhibitor (TAFIa) attenuates fibrinolysis and inhibition of TAFIa is a promising target for treatment of acute ischemic stroke. The aim of the present study was to elucidate the effect of DS-1040, a novel selective TAFIa inhibitor, on hemorrhagic risk in a mechanical model of stroke in rats.
Methods: Male Sprague-Dawley rats underwent a 3 hour-middle cerebral artery occlusion (MCAO) and were treated at reperfusion with tissue plasminogen activator (tPA, 10 mg/kg, bolus + infusion for 30 min), saline, or DS-1040 (1500 μg/kg injected intravenously, followed by subcutaneous infusion of 567 μg/kg/hour with micropump, SMP-200, for 21 hours). Behavioral outcome measures (Bederson, Beam walk, paw grasp) were obtained prior to sacrifice. The brains were evaluated for infarct size, cerebral hemorrhage (visual score and hemoglobin content) and edema. A separate set of groups of animals was used to determine the plasma concentration of DS-1040 at 24 hours post stroke.
Results: Treatment with tPA significantly ($p<0.05$) increased hemorrhagic risk and worsened functional outcome compared to the saline treated groups. DS-1040 treatment did not augment hemorrhagic risk or worsen outcome compared to saline. Mean plasma concentration of DS-1040 was 713 ng/mL, 10 x above the maximum effective concentration required for TAFI inhibition (ECmax, 64.7 ng/mL in a rat venous thromboembolism model).
Conclusion: These findings suggest that DS-1040, a TAFIa inhibitor, does not augment hemorrhagic risk compared to saline treatment at 24 hours after MCAO, and may be safer than tPA for acute ischemic stroke.

Disclosures: **T. Ishrat:** None. **B. Pillai:** None. **A.Y. Fouda:** None. **W. Eldahshan:** None. **H. Ahmed:** None. **K. Noguchi:** A. Employment/Salary (full or part-time): Daiichi Sankyo Co., Ltd. **S.C. Fagan:** B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution; Daiichi Sankyo Co., Ltd., VA Merit Review, the National Institutes of Health.

Poster

791. In Vivo Studies of Ischemia and Neuroprotection

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 791.20/O6

Topic: C.07. Ischemia

Support: NIH EY10343

Title: Rescuing the ischemic retina

Authors: *B. MATHEW[1], L. TORRES[1], S. KEIL[2], S. ROTH[1];
[1]Anesthesiol., Univ. of Illinois At Chicago, Chicago, IL; [2]Neurosci., Univ. of Illinois, Chicago, IL

Abstract: We have previously shown that treatment 24 h after ischemia with conditioned media from bone marrow stem cells (BMSCs), as well as ischemic post-conditioning (Post-C) using a transient, non-damaging ischemic stimulus, significantly improved retinal function. Based upon these findings, we studied the effect of BMSCs delivered 24h after ischemia. Retinal ischemia was produced in adult Wistar rats by increasing intraocular pressure to 130-135 mm Hg for 55 min. BMSCs (approximately 130,000) were injected into the vitreous 24 h after the end of ischemia. Recovery was assessed 7 d after ischemia using electroretinography (ERG), at which time we euthanized the animals and then prepared cryosections of retina for TUNEL. We did Western blotting to evaluate inflammatory cytokines, autophagic and apoptosis proteins. Blood retinal barrier permeability was assessed with Evans Blue. Stem cells were localized in the retina using real time fundus imaging, retinal immunohistochemistry, and flat mounts. Intravitreal injection BMSCs 24 h after ischemia robustly improved retinal function, attenuated apoptosis, decreased blood retinal barrier leakage, decreased inflammatory cytokine levels, and maintained autophagic function compared to vehicle injected group. The BMSCs were found to penetrate into the retina and proliferate more effectively in ischemic vs normal retinae. These results are of relevance to rescuing retina from ischemia in conditions such as diabetic retinopathy.

Disclosures: **B. Mathew:** None. **L. Torres:** None. **S. Keil:** None. **S. Roth:** None.

Poster

791. In Vivo Studies of Ischemia and Neuroprotection

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 791.21/O7

Topic: C.07. Ischemia

Title: Protein synthesis inhibition in the peri-infarct cortex slows motor recovery in rats

Authors: *M. SCHUBRING-GIESE[1,2], J. HOSP[2], S. LEEMBURG[2], A. LUFT[2];
[1]Univ. of Zurich, Zurich, Switzerland; [2]Dept. of Neurol., Univ. Hosp. of Zurich, Zurich, Switzerland

Abstract: Neuroplasticity and reorganization of brain motor networks are thought to enable recovery of motor function after ischemic stroke. Especially in the cortex surrounding the

ischemic scar (i.e. peri-infarct cortex) evidence for lasting reorganization has been found at the level of neurons and networks. This reorganization depends on expression of specific genes and subsequent protein synthesis. To test the functional relevance of the peri-infarct cortex for recovery we assessed the effect of protein synthesis inhibition within this region after experimental stroke. Long-Evans rats were trained to perform a skilled-reaching task (SRT) until they reached plateau performance. A photothrombotic stroke was induced in the forelimb representation of the primary motor cortex (M1) contralateral to the trained paw. The SRT was re-trained after stroke while the protein synthesis inhibitor anisomycin (ANI) or saline were injected into the peri-infarct cortex through implanted cannulas. ANI injections reduced protein synthesis within the peri-infarct cortex by 69% and significantly impaired recovery of reaching performance through re-training. Improvement of motor performance within a single training session remained intact, while improvement between training sessions was impaired. ANI injections did not affect infarct size. Thus, protein synthesis inhibition within the peri-infarct cortex impairs recovery of motor deficits after ischemic stroke by interfering with consolidation of motor memory between training sessions but not short-term improvements within one session.

Disclosures: **M. Schubring-Giese:** None. **J. Hosp:** None. **S. Leemburg:** None. **A. Luft:** None.

Poster

791. In Vivo Studies of Ischemia and Neuroprotection

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 791.22/O8

Topic: C.07. Ischemia

Support: NIH Grant GM044842

Title: Quantitative measurements of membrane-bound enzyme activity involved in ischemic damage and neuroprotection

Authors: ***Y. OU**, R. WILSON, B. YIN, S. G. WEBER;
Chem., Univ. of Pittsburgh, Pittsburgh, PA

Abstract: Ectopeptidases are membrane-bound enzymes whose catalytic domain faces the extracellular space (ECS). They hydrolyze and regulate the activity of neuropeptides. In recent years, these enzymes have been identified as important targets for drug development to treat neurological diseases, including ischemia[1-3]. We seek to understand whether the activity of these enzymes is involved in the mechanisms of ischemic damage and neuroprotection. Unfortunately, methods to measure their activity in intact tissues are lacking. We developed a method to determine the activity of these ectopeptidases by coupling electroosmotic push-pull perfusion

(EOPPP) with capillary liquid chromatography and mass spectrometry (cLC-MS). Substrate neuropeptides are hydrolyzed as they pass through hippocampal cultures during perfusion by EOPPP. Product concentration measured by cLC-MS yields estimates of enzyme activity. Computational simulations and *in vitro* experiments show that EOPPP causes little to no damage to surrounding tissue[4], has ~100 μm radial spatial resolution, can tune the residence time of substrates in the ECS to Michaelis-Menten kinetics, and can effectively perfuse and sample from severely ischemic regions. EOPPP-cLC revealed that hydrolysis of neuroprotective Leu-enkephalin by a bestatin-sensitive aminopeptidase (likely aminopeptidase N) is six times greater in CA1 than CA3 of the rat hippocampus. This is the first report of spatially resolved measurement of enzyme activity in live tissue. Inhibition of the aminopeptidase (100 μM bestatin) selectively protected the CA1 against ischemic damage from 40-min oxygen-glucose deprivation (OGD) (80 ± 2% cell death to 57 ± 3%, $p < 0.001$). Bestatin did not significantly change the cell death in the CA3 (58 ± 2% to 54 ± 4%), which is known to be more resilient. This neuroprotection occurs as early as 2-hours post-OGD and was selectively reversed by the addition of 10 μM naltrindole, a selective δ-opioid receptor (DOR) antagonist (86 ± 8%, $p < 0.001$). Thus, we conclude that selective neuroprotection in CA1 resulting from aminopeptidase inhibition was due to extended lifetime of Leu-enkephalin in the ECS, which reduced cell death via activation of DORs. References: 1. Bauvois et al. (2006) Medicinal Research Reviews 26 (1): 88-130. 2. Dirnagl et al. (2009) The Lancet Neurology 8(4): 398-412. 3. Bauer et al. (2011) Journal of Alzheimer's Disease 27(3): 511-520. 4. Rupert et al. (2013) ACS Chemical Neuroscience 4(5): 838-848.

Disclosures: **Y. Ou:** None. **R. Wilson:** None. **B. Yin:** None. **S.G. Weber:** None.

Poster

791. In Vivo Studies of Ischemia and Neuroprotection

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 791.23/O9

Topic: C.07. Ischemia

Support: NIH grant R01 HL071568

Title: Effects of intranasal Orexin-A treatment on neuroinflammation in an asphyxial cardiac arrest rodent Model

Authors: ***H. R. MODI**[1], Q. WANG, 21210[2], E. GREENWALD[3], A. SAVONENKO[3], R. GEOCADIN[3], N. THAKOR[3];
[1]Biomed. Engin. Dept., [2]Biomed. engineering, [3]Johns Hopkins Univ., Baltimore, MD

Abstract: Introduction: Resuscitation after cardiac arrest (CA) entails significant risk of coma and disorders of consciousness resulting in poor neurological outcome. The hypothalamic orexinergic pathway is responsible for arousal in general. We hypothesized that targeting the orexinergic pathway via intranasal orexin-A treatment may improve arousal by decreasing neuroinflammation from post-CA coma. **Methods**: We assessed effects of intranasal orexin-A (50μM) on neuroinflammatory markers on post-CA rat brains region (prefrontal cortex, caudal cortex, hippocampus, striatum, hypothalamus, medulla and cerebellum) at 4 hrs in a blinded post CA rodents. Male Wistar rats (300-350 g) were subjected to 7 minutes of asphyxial CA. All animals received either intranasal vehicle or orexin-A treatment at 30 minutes post-resuscitation. **Results**: Inflammatory markers (mRNA levels) showed selective vulnerability in brain region specific manner following CA. Orexin-A (50μM) treatment showed rescue of inflammation and reduce selective vulnerability by reducing inflammatory markers post-CA. Neural Deficit Score (NDS) and Sub-score showed significant improvement with orexin-A treatment group. With orexin-A treatment, mRNA levels of orexin 1 receptor (OX1R) did not change much while OX2R showed change with orexin-A treatment compare to sham group and CA vehicle treated group. Microglial activation marker Cd11b and proinflammatory makers IL1b, iNOS, tumor necrosis factor alpha (TNFα) were found to be increased significantly in most of brain regions as result of CA whereas they were ameliorated with orexin-A treatment. **Conclusion**: Intranasal Orexin-A treatment attenuated neuroinflammatory response and simultaneously improved arousal and neurological outcomes of CA. This research is supported by NIH grant R01 HL071568.

Disclosures: H.R. Modi: None. **Q. Wang:** None. **E. Greenwald:** None. **A. Savonenko:** None. **R. Geocadin:** None. **N. Thakor:** None.

Poster

791. In Vivo Studies of Ischemia and Neuroprotection

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 791.24/O10

Topic: C.07. Ischemia

Support: Fapesp 2014/15018-5

Fapesp 2014/16117-6

Title: Role of intracellular calcium receptor inositol 1,4,5-triphosphate type 1 (IP3R1) in rat hippocampus after neonatal anoxia

Authors: *J. M. IKEBARA[1], D. S. CARDOSO[1], B. C. V. DE CAMPOS[1], T. A. S. BRETHERICK[1], N. M. M. DIAS[1], G. S. V. HIGA[2], S. H. TAKADA[1], A. H. KIHARA[1]; [1]Univ. Federal Do ABC, São Bernardo do Campo, Brazil; [2]Univ. de Sâo Paulo, São Paulo, Brazil

Abstract: Anoxia is one of the most prevalent causes of neonatal morbidity and mortality, especially in preterm neonates, constituting an important public health problem due to permanent sequelae observed in patients. Oxygen deprivation triggers a series of simultaneous cascades, culminating in cell death, mainly in more vulnerable metabolic brain regions, such as the hippocampus. In the process of cell death by oxygen deprivation, calcium plays a crucial role, since its massive entry into the cell due to activation of glutamatergic receptors results in cell death by excitotoxicity. Considering that calcium participates in various cellular processes, this study focused on intracellular calcium receptor inositol 1,4,5-trisphosphate type 1 (IP3R1) role in cell death after oxygen deprivation. Real-time PCR gene expression analysis revealed a decrease of IP3R1 gene expression 24 hours after neonatal anoxia. A semi quantitative analysis of IP3R-positive cells was performed and we were not able to observe alterations between control and anoxia animals. However, we observed that anoxia animals present a higher colocalization of IP3R1 and nucleus marker (DAPI). This result suggests that neonatal anoxia may cause IP3R1 translocation to the nucleus in hippocampal cells. Futhermore, to analyze the functional role of IP3R1, a blocker of the receptor, 2-aminoethoxydiphenyl borate (2-APB), was injected in hippocampus and staining neurodegeneration tecniques were performed. In this way, this study may contribute to new perspectives in the investigation of neurodenegeration mechanisms triggered by oxygen deprivation.

Disclosures: J.M. Ikebara: None. **D.S. Cardoso:** None. **B.C.V. de Campos:** None. **T.A.S. Bretherick:** None. **N.M.M. Dias:** None. **G.S.V. Higa:** None. **S.H. Takada:** None. **A.H. Kihara:** None.

Poster

791. In Vivo Studies of Ischemia and Neuroprotection

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 791.25/O11

Topic: C.07. Ischemia

Support: Universidad Anahuac. Fondo de Investigación

Title: Polyunsaturated fatty acids potentiates the neuroprotective effect of Cop-1 in a cerebral ischemia/reperfusion model.

Authors: *E. E. GARCIA-VENCES, K. CANTÚ SALDAÑA, Y. CRUZ MARTINEZ, V. GALVEZ SUSANO, R. DE JESUS BENAVIDES, D. LOERA, C. MORENO, A. IBARRA; Univ. Anahuac Mexico Norte, Mexico city, Mexico

Abstract: An ischemic stroke occurs as a result of a disturbance or interruption of cerebral blood flow that significantly reduces the supply of oxygen and glucose to the neural tissue. Consequently, several cell death mechanisms such as necrosis, excitotoxicity, free radical production and inflammation are triggered. Protective autoimmunity (PA) a physiological phenomenon that develops after central nervous system (CNS) damage- might have beneficial effects over the secondary mechanisms of stroke and cerebrovascular diseases. Nevertheless, in order to exert these effects, it must be modulated with neural derived peptides. Copolymer-1 (Cop-1) is a synthetic polypeptide that increases Th2 cytokine secretion patterns and inhibits the production of inflammatory cytokines after cerebral ischemia. On the other hand, the supplementation with polyunsaturated fatty acids (PUFA) have beneficial effects on neuronal function, as well as anti-inflammatory and antioxidant activities. Furthermore, PUFAs improve membrane fluidity, enhance neurotrophic support and their mediators are responsible for certain processes within the CNS: modulation of neuroinflammatory mechanisms, cell survival, structure and function of neurons, glial and endothelial cells. Therefore PUFAs may be novel targets of interest for therapy of several neurodegenerative process like ischemic stroke. The addition of PUFAs to the therapy with Cop-1 could potentiate the neuroprotective effects. Therefore, our group decided to investigate the effect of these combination therapy in a focal cerebral ischemia/reperfusion model. In order to evaluate this approach, 24 rats were randomly allocated into 4 groups (6 rats per group): Group 1, Cop-1 + Complete Freund's Adjuvant (CFA) + PUFAs; Group 2, Cop-1+ CFA; Group 3, PUFAs and Group 4, non-treated animals. All groups were subjected to cerebral ischemia. PUFAs (Omegas 3, 6 and 9) were administered through an orogastric cannula (40/mg/kg/d/) 4 weeks before the ischemic event (groups 1 and 3). Cop-1 was subcutaneously administered (200 μg) at the interescapular space immediately after reperfusion. Neurological deficit was evaluated at 24 hours and 7 days after ischemia using the Zea Longa scale. Infarcted area was revealed by the triphenyl tetrazolium chloride and quantified using an image analysis software (Image J), 7 days after ischemia. Results showed a significant reduction of neurological deficit in rats treated with Cop-1+ CFA+ PUFAs as compared with Cop-1 + CFA. In the same way, the addition of PUFAs reduced the infarct size. This work demonstrated that the use of PUFAs as supplementation potentiates the neuroprotective effect of Cop-1+ CFA.

Disclosures: E.E. Garcia-Vences: None. **K. Cantú Saldaña:** None. **Y. Cruz Martinez:** None. **V. Galvez Susano:** None. **R. De Jesus Benavides:** None. **D. Loera:** None. **C. Moreno:** None. **A. Ibarra:** None.

Poster

791. In Vivo Studies of Ischemia and Neuroprotection

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 791.26/O12

Topic: C.07. Ischemia

Support: MINECO-FEDER RTC-2015-4094-1

MINECO-FEDER BIO2013-49006-C2-2-R

Title: Differences in the unfolded protein response (UPR) between astroglia and microglia following cerebral global ischemia

Authors: *E. FONT BELMONTE, B. ANUNCIBAY-SOTO, M. SANTOS-GALDIANO, P. GONZALEZ-RODRIGUEZ, M. REGUEIRO-PURRIÑOS, A. FERNANDEZ-LOPEZ;
Univ. de Leon, Inst. de Biomedicina, Leon, Spain

Abstract: We have recently demonstrated that the post-ischemic treatment with salubrinal presents a neuroprotective effect decreasing the neuronal demise and modifying differentially the ER stress in different cell types in the neurovascular unit. Salubrinal inhibits the GADD134, a phosphatase of the eIF2α thus enhancing one of the unfolded protein response (UPR) pathways (PERK-ATF4 pathway). In this study we analyzed the effects of the ischemic injury and the post-ischemic treatment with salubrinal in microglia and astroglia (including the eIF2α phosphorylation as a marker of PERK-ATF4 pathway activation) in a rat global cerebral ischemia model (2 vessel-occlusion) following 48 h of reperfusion. Ischemia-induced astrogliosis is reverted by salubrinal but eiF2α phosphorylation in this cell type is very scarce at this reperfusion time. Microglia is also modified by ischemia and the treatment with salubrinal but, in contrast with astroglia, presents a robust eIF2α phosphorylation. We conclude that neuroprotective effect of salubrinal involves a decrease in the reactive gliosis, and hypothesize differences in UPR between microglia and astroglia following global ischemia. This work was supported by the Spanish Ministerio de Economia y Competitividad cofinanced with FEDER funds, references RTC-2015-4094-1, and BIO2013-49006-C2-2-R which also supports B. Anuncibay Soto and M. Santos-Galdiano. E. Font and P. Gonzalez-Rodriguez are supported by grants of the University of León.

Disclosures: **E. Font Belmonte:** None. **B. Anuncibay-Soto:** None. **M. Santos-Galdiano:** None. **P. Gonzalez-Rodriguez:** None. **M. Regueiro-Purriños:** None. **A. Fernandez-Lopez:** None.

Poster

791. In Vivo Studies of Ischemia and Neuroprotection

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 791.27/O13

Topic: C.07. Ischemia

Support: MINECO-FEDER BIO2013-49006-C2-2-R

MINECO-FEDER BIO2013-49006-C2-1-R

MINECO-FEDER RTC-2015-4094-1

JCyL Grant EDU/346/2013

JCyL Grant EDU/310/2015

Title: Unfolded protein response (UPR) and autophagy are involved in the neuroprotection after focal cerebral ischemia mediated by 2-hydroxyarachidonic acid.

Authors: *I. F. UGIDOS[1], P. GONZÁLEZ-RODRÍGUEZ[1], B. ANUNCIBAY-SOTO[1], D. PÉREZ-RODRÍGUEZ[1], M. SANTOS-GALDIANO[1], X. BUSQUETS[2], A. FERNÁNDEZ-LÓPEZ[1];
[1]Univ. de Leon. Inst. de Biomedicina., Leon, Spain; [2]Biología Celular, IUNICS. Univ. des Illes Balears, Palma de Mallorca., Spain

Abstract: Endoplasmic reticulum (ER) stress is a hallmark of many cell homeostasis imbalances, including those derived from cerebral ischemia. In this study, we measured a number of parameters that mirror ER stress levels, mainly the unfolded protein response (UPR) and their link to autophagy. The effect of the neuroprotective agent 2-hydroxyarachidonic acid (2OAA) on these responses was also analyzed. The study was performed in a rat model of transient (1 hour) focal cerebral ischemia by middle cerebral artery occlusion (MCAO) followed by a single oral dose (1 g/kg) of 2OAA, or vehicle, 1 hour after ischemia. Samples from damaged and not damaged hemispheres were collected at 6 h and 24 h after ischemia and protein and mRNA were quantified by Western blot and qPCR respectively. Phosphorylation of eIF2α, as well as GRP78 levels indicates that ischemia induces the increase of ER stress. The treatment with 2OAA increases the phosphorylation of eIF2α, and decreases GRP78 levels indicating that this agent counteracts ER stress. Autophagy markers (Beclin-1, LC3B, p62) were measured indicating that ischemia increases autophagy 24 h after injury, while the treatment with 2OAA modifies the expression of autophagy markers. We conclude that, 24 h after ischemia, the neuroprotective effect of 2OAA involves both the UPR and autophagy homeostatic mechanisms. This work was supported by the Spanish Ministerio de Economia y Competitividad cofinanced with FEDER funds "una manera de hacer Europa", references BIO2013-49006-C2-1-R and

RTC-2015-4094-1, as well as BIO2013-49006-C2-2-R which also supports B. Anuncibay Soto and M. Santos-Galdiano. P. Gonzalez-Rodriguez is supported by a University of León grant and D. Perez-Rodriguez and I. F. Ugidos are granted by Junta de Castilla y León (EDU/346/2013 and EDU/310/2015 respectively).

Disclosures: **I. F. Ugidos:** C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Lipopharma Therapeutics SL. **P. González-Rodríguez:** None. **B. Anuncibay-Soto:** None. **D. Pérez-Rodríguez:** None. **M. Santos-Galdiano:** None. **X. Busquets:** C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Lipopharma Therapeutics SL. **A. Fernández-López:** None.

Poster

791. In Vivo Studies of Ischemia and Neuroprotection

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 791.28/O14

Topic: C.07. Ischemia

Support: MINECO-FEDER BIO2013-49006-C2-2-R

MINECO-FEDER BIO2013-49006-C2-1-R

MINECO-FEDER RTC-2015-4094-1

JCyL grant EDU/310/2015

Title: The treatment with the neuroprotective agent, 2-hydroxyarachidonic acid, after transient focal cerebral ischemia restores the ischemia-induced increases in free fatty acid levels.

Authors: ***A. FERNANDEZ-LOPEZ**[1], I. F. UGIDOS[1], M. IBARGUREN[2], D. J. LÓPEZ[2], M. PADILLA-MARCOS[2], C. JAUME-BOUZÁ[2], P. V. ESCRIBÁ[2];
[1]Univ. de Leon, Inst. de Biomedicina, Leon, Spain; [2]Biología Celular, IUNICS. Univ. des Illes Balears, Palma de Mallorca, Spain

Abstract: We have previously reported that 2-hydroxyarachidonic acid (2OAA), an inhibitor of cyclooxygenases COX1 and COX2, exerts neuroprotective effects in a focal cerebral ischemia model of middle cerebral artery occlusion (MCAO). We analyzed here, in the same MCAO model, the lipid modifications that occur 24 h after ischemia as well as the effects of a single oral dose (1 g/kg) of 2OAA administered 1 hour after ischemia. We observed significant increases in both COX2 expression and relative concentration of free fatty acids (nmol lipid/mg protein) comparing the injured hemisphere with the corresponding contralateral hemisphere. The

treatment with 2OAA induced significant decreases in free fatty acid levels in pyriform cortex and striatum. Transcript levels of COX2 in the injured hemisphere were not decreased by the 2OAA post-insult treatment. Since arachidonic acid (AA) is a free fatty acid and substrate of COX2, we hypothesize that ischemia induces an increase of AA, which in turn promotes COX2 activity and the ensuing production of proinflammatory mediators. The similar response in the contralateral hemispheres treated and non treated with 2OAA indicates that COX2 blockade does not involve changes in its expression. On the other hand, the increases in COX2 expression in both treated and non treated damaged hemispheres suggest increased levels of AA in the damaged areas of treated animals. Additional studies on the ratio of AA in the free fatty acids seem necessary to elucidate the relevance of AA in the total amount of free fatty acids following ischemia.
This work was supported by the Spanish Ministerio de Economia y Competitividad cofinanced with FEDER funds "una manera de hacer Europa", references BIO2013-49006-C2-1-R, BIO2013-49006-C2-2-R and RTC-2015-4094-1. I. F. Ugidos is granted by Junta de Castilla y León reference EDU/310/2015.

Disclosures: **A. Fernandez-Lopez:** None. **I.F. Ugidos:** None. **M. Ibarguren:** A. Employment/Salary (full or part-time): Lipopharma Therapeutics SL. **D.J. López:** A. Employment/Salary (full or part-time): Lipopharma Therapeutics SL. **M. Padilla-Marcos:** None. **C. Jaume-Bouzá:** None. **P.V. Escribá:** C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Lipopharma Therapeutics SL.

Poster

792. Ischemia and Hemorrhage: Translational Studies

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 792.01/O15

Topic: C.07. Ischemia

Support: NIH 1U01 HL117718-03

Title: Chronic anemia is associated with significant white matter atrophy.

Authors: S. CHOI[1], J. COLOGNIER[2], A. D. BUSH[3], T. D. COATES[2], *R. I. WOOD[4], J. C. WOOD[2];
[1]Neurosciences Grad. Program, [2]Dept. of Pediatrics, [3]Dept. of Bioengineering, USC, Los Angeles, CA; [4]Keck Sch. Med. USC, Los Angeles, CA

Abstract: Silent strokes and white matter atrophy are common in patients with sickle cell anemia, but the mechanism is unknown. We have previously shown that resting blood flow is

increased in these patients such that oxygen delivery is preserved under unstressed conditions. However, resting hyperemia results in blunted vasodilatory reserve, potentially leaving patients at risk for cerebral ischemia in response to desaturation events, acute anemia, or increased metabolic demands. To remove the confounding influence of sickle hemoglobin, we measured grey and white matter volumes and cerebral blood flow in 14 thalassemia major patients (hemoglobin level 10.3 ± 0.9 g/dl, age 24.2 ± 6.8 yrs, 36% male) and 37 African-American subjects without sickle cell disease (hemoglobin level 13.5 ± 1.3 g/dl, age 27± 10.6 yrs, 26% male). 3D T1-weighted MR images (1 mm^3 isotropic resolution) were processed using BrainSuite (brainsuite.org) in a semi-automated fashion to extract, classify tissue types, and calculate brain volumes, with manual correction as needed. 3D T2-weighted MR images (1.2 mm x 1.2 mm x 1.2 mm) were collected to quantify number and volume of white matter strokes. Total cerebral blood flow was measured using phase contrast imaging of the carotid and vertebral vessels in a single axial slice placed 5 mm above the carotid bifurcation. Total brain blood flow was normalized to brain volume x an assumed density of 1.05 g/cm^3. Cerebral blood flow was reciprocally related to blood oxygen content (1.34 x Hb x Oxygen Saturation + 0.3) with an r^2 of 0.54, $p<0.0001$, such that resting oxygen delivery was normal in all subjects. Age and sex-corrected white matter volume had a reciprocal relationship with baseline cerebral flow ($r^2 = 0.24$, $p=0.0002$) and a linear relationship with hemoglobin ($r^2 = 0.17$, $p = 0.003$). White matter Z-score was – 0.7 ± 0.7 compared with 0.0 ± 1.0 for the control group, $p=0.007$. Rare white matter hyperintensities were seen in both groups with no significant differences. Taken together, these data indicate the white matter volume is decreased in anemic subjects, proportionally to their hemoglobin levels, independent of silent stroke. We postulate that the increased resting hyperemia observed in these patients limits their vasodilatory reserve, leaving them vulnerable to acute interruptions in oxygen delivery or increased brain metabolic needs.

Disclosures: S. Choi: None. **J. Colognier:** None. **A.D. Bush:** None. **T.D. Coates:** None. **R.I. Wood:** None. **J.C. Wood:** C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); JW receives in-kind research support from Philips Medical Group.

Poster

792. Ischemia and Hemorrhage: Translational Studies

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 792.02/O16

Topic: C.07. Ischemia

Support: NIH NS075035, NS079153

AHA

Title: Leukocyte response is regulated by microRNA let7i in patients with acute ischemic stroke

Authors: ***G. JICKLING**, B. P. ANDER, N. SHROFF, B. STAMOVA, C. DYKSTRA-AIELLO, X. SHAN, D. LIU, F. R. SHARP;
Neurol., Univ. of California Davis, Sacramento, CA

Abstract: Objective: The immune system responds rapidly following ischemic brain injury and can contribute to the final extent of brain damage. microRNA are differentially expressed in leukocytes following ischemic stroke and may regulate the immune response to ischemic brain injury. In this study we evaluate microRNA let7i-5p in ischemic stroke and its regulation of leukocytes.
Methods: A total of 212 patients were studied; 106 with acute ischemic stroke and 106 risk factor matched controls. Let7i-5p miRNA expression was assessed by Taqman qRT-PCR. Target gene expression was assessed by whole genome HTA Affymetrix microarray. Let7i-5p post-transcriptional regulation of target genes was evaluated by 3'UTR luciferase assay. Target protein expression was assessed by ELISA.
Results: Let7i-5p was decreased in patients with acute ischemic stroke (fold change -1.4, $p<0.00001$). Let7i-5p inversely correlated with NIH Stroke Scale at admission ($r= -0.32$, $p=0.02$), infarct volume ($r= -0.21$, $p=0.04$) and plasma MMP9 ($r= -0.46$, $p=0.01$). The decrease in let7i-5p was associated with increased expression of several of its messenger RNA targets including CD28/CD86, CXCL8 and HMGB1. *In vitro* studies confirm let7i-5p post-transcriptional regulation of target genes CD86, CXCL8 and HMGB1. Functional analysis predicted let7i-5p regulates pathways involved in leukocyte activation, recruitment, proliferation including canonical pathways CD28 signaling in T helper cells, HMGB1 signaling, and CXCL8 signaling.
Conclusions: Let7i-5p is decreased in circulating leukocytes of patients with acute ischemic stroke. Mechanisms by which let7i-5p regulates inflammatory response post-stroke include targeting CD28 / CD86, CXCL8 and HMGB1.

Disclosures: G. Jickling: None. **B.P. Ander:** None. **N. Shroff:** None. **B. Stamova:** None. **C. Dykstra-Aiello:** None. **X. Shan:** None. **D. Liu:** None. **F.R. Sharp:** None.

Poster

792. Ischemia and Hemorrhage: Translational Studies

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 792.03/O17

Topic: C.07. Ischemia

Support: Canadian Partnership For Stroke Recovery (to MT)

Canadian Institutes of Health Research (Grant# MOP-125878 to MT)

Title: Effect of light-dark cycle on stroke lesion size and motor deficit in a mouse photothrombosis model of stroke

Authors: A. GOWER[1,2], B. LIANG[1,2], D. LAGACE[1], *M. TIBERI[1,2];
[1]Neurosci., Univ. of Ottawa, Ottawa, ON, Canada; [2]Neurosci., Ottawa Hosp. Res. Inst., Ottawa, ON, Canada

Abstract: Mice and rats are nocturnal animals, yet in many preclinical studies on stroke recovery ischemia, behavioural testing and treatment occurs during the animal's inactive period. Rates of ischemic stroke rise in the mornings in humans, corresponding to circadian increases in blood pressure, activity levels and a myriad of other factors. It is unclear whether there is a difference in the qualities or severity of awake or asleep ischemic stroke in humans, although some studies suggest this. Furthermore, the impact of dark-period stroke induction on animal models of stroke has not been fully examined. The objective of this study is to determine if there are any differences in the outcomes of photothrombotic strokes induced during a mouse's active (dark) period or inactive (light) period, with an aim to better model the majority of human ischemic strokes. 32 ten week old, male C57BL6 mice underwent photothrombosis stroke. Prior to photothrombosis, mice acclimated for two weeks in either Light-Dark(LD) 12h:12h or reverse LD 12h:12h housing and underwent training and prestroke measurements on 3 motor-behavioural tasks, the adhesive removal test, the horizontal ladder test and the cylinder test. After stroke, lesions were confirmed with Magnetic Resonance Imaging. Animals underwent testing on the three behavioural tasks at 2-4 days post stroke and 20-22 days post stroke. At study completion brains were collected and infarct size was determined. Results from our 3 behavioural tests suggest that mice who underwent stroke induction and testing during their dark period have greater motor deficits following stroke, when compared to their pre-stroke performance, which tends to be better than mice tested during their light period. Infarct sizes showed a non-significant tendency to be larger in dark-period mice in our first cohort (n=16). Our second cohort (n=15) is in the analysis stages to confirm our findings. Our data points to a potential difference in stroke outcome when stroke is induced during the animal's dark period. This suggests that using reverse light-dark housing conditions can improve our model of human stroke and stroke recovery. These results will inform the methods of our next goal, to investigate the efficacy dopamine receptor (DAR) agonists, delivered with aerobic exercise, on motor recovery from stroke. This work is prompted by previous work suggesting a role for dopamine receptors when in stroke recovery, such as those studies which have found levodopa improves stroke recovery, and by the link between DARs and plasticity as well as DARs and the growth factors, BDNF and GDNF. This study, will similarly employ the photothrombosis model and the same behavioural tests.

Disclosures: **A. Gower:** None. **B. Liang:** None. **D. Lagace:** None. **M. Tiberi:** None.

Poster

792. Ischemia and Hemorrhage: Translational Studies

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 792.04/O18

Topic: C.07. Ischemia

Support: Funded by Conacyt-México: CB-2011-01- 166241

Funded by Conacyt-México: INFR-2012-01-187757

Title: Cellular mechanisms underlying the ischemic damage in area CA3 of the hippocampus

Authors: *C. TECUATL TOLAMA, E. J. GALVAN ESPINOSA;
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Abstract: The cellular mechanisms underlying ischemic damage in area CA3 of the hippocampus are explored in the present study. Extracellular recordings (Population Spikes, PS and Mossy fibers fEPSPs) on acute slices (30-40 days old) were performed, and controlled exposure to Oxygen-glucose deprivation (10 min), followed by 2 h reperfusion of ACSF was used to assess the alterations of evoked responses after an ischemic insult. OGD suppressed both PS and MF fEPSPs without signs of recovery at 2 hr post-OGD exposure; Input-Output curves at 2.5 h post-OGD confirmed the lack of electrophysiological responsiveness. Similar results were found when the glutamatergic transmission was blocked with Kynurenic acid. When slices were preincubated with BAPTA (n=8) or when sodium was replaced with N-methyl-D-Glucamine (n=8), PS and MF fEPSPs exhibited a partial recovery. Then, we investigated the role of Transient Receptor Potential Cation Channels (TRPVs) as a contributor of Na^+ and Ca^{2+} influx mediating CA3 responses. Slices preincubated with capsazepine (n=8) showed a significant recovery of PS and MF fEPSPs during reperfusion post-OGD. To further investigate the individual contribution of different TRPVs during the ischemic insult, slices were preincubated with AMG9810 or HC-067047 (antagonist for TRPV1 and TRPV4, respectively). Slices preincubated with AMG 9810 show a strong recovery (n=8), whereas blockade of TRPV4 with HC-067047 partially reverts the deleterious effect of OGD (n=8). These results indicate that ischemic damage involves strong cationic influx, independent of ionotropic glutamatergic receptors activity. We also show that TRPVs plays a critical role in the ischemic damage, as blockade of these receptors revert the deleterious effects of OGD on area CA3.

Disclosures: C. Tecuatl Tolama: None. **E.J. Galvan Espinosa:** None.

Poster

792. Ischemia and Hemorrhage: Translational Studies

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 792.05/P1

Topic: C.07. Ischemia

Support: NRF-2014R1A2A1A11052042

NRF-2015M3A9B4067068

Title: *In situ* expression of pluripotency factors improves functional recovery by hippocampal neurogenesis and synaptic plasticity in hypoxic-ischemic brain injury.

Authors: *S. WI[1,2], J. SEO[1,2], J. YU[1,2], Y. SHIN[1,2], M. KIM[1,2], S.-R. CHO[1,2];
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Abstract: Introduction: The resident stem/progenitor cells can be stimulated in vivo by injuries such as stroke, hypoxic-ischemic(HI) brain injury, and traumatic brain injury. Since stem/progenitor cells present in the adult brain and the production of new neurons occurs at specific sites, there is a possibility for the treatment of incurable neurological diseases. Understanding of the molecular control of endogenous neural stem cell (NSC) activation and progenitor cell mobilization will likely provide many new opportunities as therapeutic strategies. Pluripotency factors such as Klf4, Sox2, Oct4, and c-Myc can be used to convert one cell type to another directly. These factors can stimulate proliferation from NSCs to mature neurons in subgranular zone (SGZ) of the dentate gyrus in the hippocampus. In this study, we focused on *in situ* transient expression of pluripotency factors would facilitate endogenous NSC activation, cell proliferation, a critical and essential process for recovery of injured tissue.
Methods: HI brain injury was induced CD-1® mice at 1 week of age by unilaterally right carotid artery ligation and exposure to hypoxia (8% O_2 for 60 min). At six weeks of age, the mice were randomly injected either GFP as control group or four pluripotency factors with GFP as treated group into the right side of the lateral ventricle. Passive avoidance test(PAT) and openfield test were performed before the treatment and 8 weeks after the treatment to evaluate neurobehavioral function. We confirmed the endogenous cell fate of SGZ of the dentate gyrus in hippocampus using immunohistochemistry. To identify hippocampal synaptic plasticity, we conducted western blot and immunohistochemistry.
Results: The number of $BrdU^+$/βIII-tubulin+ neurons was significantly higher in the treated group compared than the control group. Treated group also increased $BrdU^+$/$nestin^+$ and $BrdU^+$/$NeuN^+$, but not $BrdU^+$/$GFAP^+$ cells in the SGZ. Hippocampal synaptic plasticity also increased, and it was confirmed by a synaptic marker, post-synaptic density 95(PSD-95).

Importantly, neurobehavioral evaluations such as PAT and openfield test showed that the treated group improved long-term memory and decreased anxiety in HI brain injury.
Conclusion: *In situ* transient expression of pluripotency factors improved long-term memory and decreased anxiety. The underlying mechanisms of these repair processes increased endogenous neurogenesis of SGZ and increased hippocampal synaptic plasticity.
Acknowledgements: This study was supported by grants from the National Research Foundation (NRF-2014R1A2A1A11052042 and NRF-2015M3A9B4067068)

Disclosures: **S. Wi:** None. **J. Seo:** None. **J. Yu:** None. **Y. Shin:** None. **M. Kim:** None. **S. Cho:** None.

Poster

792. Ischemia and Hemorrhage: Translational Studies

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 792.06/P2

Topic: C.07. Ischemia

Title: Quality and quantity mononuclear cells rescue peri-infarct lesion during acute stroke phase

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Abstract: *Background:* Recently, many studies with iPS or stem cells have published for ischemic stroke. Some studies tried to engraft iPS or stem cells to the brain directly; however, due to lack of neurovascular unit, those were not perfectly succeeded. Previously we reported higher grade quality EPCs (JAHA, 2014) and we investigate therapeutic window and those effects with using those cells for ischemic stroke model mice. We investigated the vasculogenesis around peri-infarct lesion. *Materials and methods:* We made 69 ischemic stroke model mice (10 weeks male C57BL/6 mice) with permanent middle cerebral artery occlusion (MCAO). We injected PBS, PBMNCs, and QQMNCs into external carotid artery at each 1 day (n=37), 3 days (n=23), and 5 days (n=15) after MCAO. At 3 weeks after MCAO, we took the brains and investigated time-lapse physiological parameters including cerebral blood flow and immunohistochemistry against some anti-vasculogenetic factor antibodies. Also, we injected PBS, PBMNCs, and QQMNCs at 1 day (n=27) and sacrificed at 1 week after MCAO.Western bolting was performed to measure the anti-inflammatory cytokines. We injected ink-urethane into untreated mice (n=5) and QQMNCs-treated mice (n=5), due to evaluate vasculogenesis. *Results:* In the stroke model mice at 1 day and 3 days MNCs injections after MCAO, the stroke volume was decreased; however, the positive cells were increased with immunochemistry of IL10 at 1 week after MCAO and VEGF at 1 and 3 weeks after MCAO. The vascular numbers

increased at peri-infarct lesion with treated mice. *Conclusions:* Those results indicate that QQMNCs could repair and regenerate neurovascular units after ischemic stroke, and the better MNCs injection timings might be 1 day and 3 days after MCAO. Vasculogenesis may occur at 1 week after MCAO with QQMNCs-treated mice.

Disclosures: T. Nakayama: None.

Poster

792. Ischemia and Hemorrhage: Translational Studies

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 792.07/P3

Topic: C.07. Ischemia

Support: Academy of Finland

Sigrid Juselius Foundation

Title: Post-stroke intranasal (+)-naloxone reduces microglial activation and improves behavioral recovery in rat model of stroke

Authors: *J. E. ANTTILA[1], K. ALBERT[1], E. S. WIRES[2], K. MÄTLIK[1], L. LORAM[3], L. WATKINS[3], K. RICE[2], Y. WANG[2], B. K. HARVEY[2], M. AIRAVAARA[1];
[1]Inst. of Biotechnology, Univ. of Helsinki, Helsinki, Finland; [2]Intramural Res. Program, Natl. Inst. on Drug Abuse, NIH, Baltimore, MD; [3]Univ. of Colorado, Boulder, CO

Abstract: Inflammation has a major role in the pathophysiology of ischemic stroke. Microglia are the brain resident immune cells that are activated after ischemia but it is still unclear whether microglial activation is harmful or beneficial to the recovery. Both stereoisomers of naloxone, the (+) and (-) enantiomer, have been shown to decrease microglial activation. (-)-naloxone is an opioid receptor antagonist while (+)-naloxone has only very low affinity for opioid receptors. Here we tested post-stroke delivery of (+)-naloxone for the ability to promote functional recovery after cortical stroke in rats. By using (+) enantiomer the possible side effects caused by opioid receptor antagonism can be avoided.
A unilateral cortical infarction was induced in adult male Sprague Dawley rats by transiently ligating the distal branch of the right middle cerebral artery with 10-0 suture and occluding both common carotid arteries for 60 minutes. At post-stroke day 1, the rats were balanced into groups based on neurological deficits and either (+)-naloxone, vehicle or no treatment was given intranasally to the rats twice daily for the next 7 days. The behavioral recovery of the rats was followed for 2 weeks by biased swing activity, Bederson's score as well as horizontal and

vertical activity. Immunohistochemical staining for microglia was carried out with Iba1 and CD11b antibodies from coronal brain sections.
(+)-naloxone decreased biased swing activity and Bederson's score in dose-dependent manner starting from post-stroke day 10. In addition, (+)-naloxone increased horizontal activity on day 14 post-stroke. As measured with unbiased stereology, (+)-naloxone decreased the number of Iba1+ cells by 50% in the striatum compared to the vehicle treatment. The data suggests that post-stroke intranasal (+)-naloxone decreases microglial activation and simultaneously promotes recovery from ischemic brain injury.

Disclosures: J.E. Anttila: None. **K. Albert:** None. **E.S. Wires:** None. **K. Mätlik:** None. **L. Loram:** None. **L. Watkins:** None. **K. Rice:** None. **Y. Wang:** None. **B.K. Harvey:** None. **M. Airavaara:** None.

Poster

792. Ischemia and Hemorrhage: Translational Studies

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 792.08/P4

Topic: C.07. Ischemia

Title: Chronic cerebral hypoperfusion rodent model by bilateral ICA ligation in different species for hemodynamic assessment of human moyamoya disease

Authors: *K.-E. LEE, Y. KWON, G. PARK, E. CHOI, B. YUN, J. LEE, J. HONG;
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Abstract: ***Background:*** Moyamoya disease is a rare but common in Asian, which manifests a chronic blood flow shrinkage due to a progressive occlusion of the proximal intracranial arteries around the circle of Willis. To evaluate the hemodynamic status of such a clinical entity in experimental situations, we intended to establish an appropriate rat model which represents chronic cerebral hypoperfusion by completely ligating bilateral internal carotid arteries (ICA). We analyzed the changes of sequential flow and respective arterial size around the circle of Willis in different rat species. ***Methods****:* Chronic hypoperfusion models were made by bilateral ICAs' ligations (BICAL) in the Wistar and Sprague-Dawley (SD) rats. *Step 1:* Changes of cerebral blood flow (CBF) after bilateral ICA ligations were sequentially observed at different times (D0, 1, 3, 7, 14 and 21) for 3 weeks by the laser Doppler flow measuring device (PIM3). *Step 2:* Arterial changes around the Willisian circle were compared in bilateral ICA ligation and sham operation (without ICA ligation) models after the fixation with blue latex infusion after BICAL operation 21 days in the same species. *Step 3:* To make a mimicking condition for clinical moyamoya patients, sudden cerebral infarction using a permanent middle cerebral artery

(MCA) thread occlusion was induced in an aforementioned set-up model representing ischemic preconditioned properties with different periods (7, 14, and 21 days) of the BICAL, and the infarctions were observed on triphenyl tetrazolium chloride (TTC) stains in different rat species and time-points. ***Results****:* Wistar rat [vs. baseline CBF values (D0)] did not reach the baseline CBF during whole study period, but SD rat did not reflect the chronic hypoperfusion status since 7 days because it exceeded the baseline CBF after 7 days since BICAL. Wistar rat (vs. SD rat) after BICAL is significantly thinner in arterial diameters (internal carotid artery, posterior communicating artery, posterior cerebral artery, and basilar artery, $p < 0.05$ respectively) despite no difference of MCA diameters ($p = 0.35$). Permanent MCA occlusion with a thread insertion in Wistar rat reduced infarction size and mortality according to an increase of BICAL duration. ***Conclusion****:* Our data suggest that Wistar rat using permanent MCA occlusion model after BICAL might be appropriate for a hemodynamic evaluation of moyamoya disease with our observations of less infarct volume and mortality compared with SD rat. This phenomenon can be explained by a cerebral ischemic precondition due to less compensation by thinning Willisian collaterals especially in the Wistar.

Disclosures: K. Lee: None. **Y. Kwon:** None. **G. Park:** None. **E. Choi:** None. **B. Yun:** None. **J. Lee:** None. **J. Hong:** None.

Poster

792. Ischemia and Hemorrhage: Translational Studies

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 792.09/P5

Topic: C.07. Ischemia

Title: Acute but not delayed caffeine administration offers neuroprotection in a mouse model of neonatal hypoxic ischemic brain injury.

Authors: *E. DI MARTINO[1], M. WINERDAL[1], M. E. WINERDAL[2], B. B. FREDHOLM[3], O. WINQVIST[2], U. ÅDÉN[1];
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Abstract: Hypoxic ischemic (HI) brain injury remains an important cause of brain damage in the neonate with potentially life long consequences. It is now acknowledged that perinatal HI triggers a broad inflammatory reaction in the brain. Caffeine, which is a competitive inhibitor of adenosine receptors, is commonly used as treatment for apnea in prematurity. In addition, caffeine treatment is associated with decreased incidences of cerebral palsy and cognitive delay in children born preterm. In this study we investigated the effects of caffeine in a neonatal HI

murine model. Wild type C57BL/6 mice were subjected to HI by unilateral ligation of the common carotid artery under isoflurane anaesthesia at postnatal day (pnd) 10 and then exposed to 10% oxygen for 60 min. A single dose of 5mg/kg caffeine or phosphate buffered saline (PBS) was administered i.p. directly after HI (0h). Open field and rotarod behavioral tests were performed at pnd 24 and the mice were subsequently sacrificed. Infarction size was calculated by loss of MAP-2 staining while immune response was studied by flow cytometry of brain infiltrating cells at 24h, 72h and two weeks after caffeine administration. In a second set of animals, a single dose of caffeine or PBS was administered at 6, 12 or 24 hours after HI. Behavioral tests were performed and infarction size calculated in accordance to first group of mice. An atrophy reduction of 44% ($p<0.05$) was shown only in the group that received an acute administration of caffeine compared to the PBS one, no protection was shown in later treatments. In the open field test, lower locomotor activity was seen in the 0h caffeine group than the PBS one, indicating enhanced learning. No significant difference was shown in the later treatments. A significant reduction of CD8+/CD69 positive cells was detected in the caffeine treated group at 24h but not at 72h and two weeks after the lesion. Our data indicates that an acute single dose of caffeine is a possible neuroprotective treatment after neonatal HI without serious immunological side effects or discernible immunological long-term consequences if administered soon after HI. Later treatments do not show any beneficial effect in mice.

Disclosures: E. Di Martino: None. **M. Winerdal:** None. **M.E. Winerdal:** None. **B.B. Fredholm:** None. **O. Winqvist:** None. **U. Ådén:** None.

Poster

792. Ischemia and Hemorrhage: Translational Studies

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 792.10/P6

Topic: C.07. Ischemia

Support: Soonchunhyang University Research Fund

Title: Anti-neuroprotective effects on neuronal damage following transient forebrain ischemia by garlic extract treatment

Authors: *S. YI[1], D. YOO[2], I. HWANG[2];
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Abstract: In the present study, we investigated neuroprotective effects of oil-macerated garlic products (Z- or E-ajoene) against neuronal damage after transient forebrain ischemia. Male

Mongolian gerbils were divided into 4 groups: sham-operated, ischemia-operated (vehicle), E-ajoene treated, and Z-ajoene treated groups. E- or Z-ajoene (25 mg/kg) was orally administered 30 min prior to the induction of transient forebrain ischemia. One day after ischemia/reperfusion, locomotor hyperactivity significantly reduced in the E- and Z-ajoene- treated groups, compared to that in the vehicle-treated group. Five days after transient ischemia, the number of cresyl violet-positive neurons in the E- and Z-ajoene-treated groups increased, compared to that in the vehicle-treated group. Reactive gliosis in the CA1 region of E- and Z-ajoene- treated groups reduced, compared to that in the vehicle-treated group. These neuroprotective effects were more prominent in animals treated with Z-ajoene, than in those treated with E-ajoene. In addition, Z-ajoene significantly decreased lipid peroxidation, as indicated by 4-hydroxy- 2-nonenal levels in hippocampal homogenates, compared to that observed in the vehicle-treated group at a range of time points after ischemia. These results suggest that Z-ajoene protects I/R-induced delayed neuronal death and gliosis by reducing lipid peroxidation in the gerbil hippocampal CA1 region.

Disclosures: **S. Yi:** B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution; This work is supported by Soonchunhyang University Research Fund. **D. Yoo:** None. **I. Hwang:** None.

Poster

792. Ischemia and Hemorrhage: Translational Studies

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 792.11/P7

Topic: C.07. Ischemia

Support: HI15C0527

Title: Identification of new chemical drugs to protect ischemic brain injury based on the inhibition of AMP-activated protein kinase

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Abstract: We recently reported that AMP-activated protein kinase (AMPK) contributed to zinc-induced neuronal death through the induction of Bim, pro-apoptotic Bcl-2 homology domain 3 (BH3)-only protein in an LKB1-dependent manner. Since many reports showed that AMPK plays a key role in excitotoxicity and ischemic brain injury, and zinc neurotoxicity is one of underlying neuronal death mechanism after ischemic brain injury, we thought that the inhibition

of AMPK could be a therapeutic target for Stroke diseases. Therefore, we tried to find a new chemical drug to reduce the activity of AMPK, zinc-induced neuronal death in mouse cortical cultures, and brain injury after middle cerebral artery occlusion (MCAO) in the mouse to develop the candidate drugs for Stroke. First, by using structure-based virtual screening, we selected 208 chemicals which could bind to the active site of the alpha subunit of AMPK as the putative inhibitor for AMPK. And then we examined whether these chemicals indeed inhibit AMPK activity using *in vitro* AMPK enzyme activity assay. 40 chemicals showed the stronger inhibition of AMPK activity in comparison with compound C, the well-known AMPK inhibitor. Next, we tested the possibility that these 40 chemicals may attenuate zinc-induced neuronal death in mouse cortical neuronal cultures. As a result, 7 chemicals were selected. Since ischemic brain injury has diverse types of neuronal death including excitotoxicity, apoptosis, and oxidative stress, we next examined whether these selected chemicals may also attenuate other types of neuronal death. Among them, 2 chemicals attenuated NMDA-induced excitotoxicity, iron-mediated oxidative stress, and etoposide-induced apoptosis as well as zinc neurotoxicity in mouse cortical cultures. However, one candidate compound showed toxicity at more than 60 microM in the mouse cortical cultures, so we finally chose only one as a candidate compound for brain ischemia. The selected chemical (2G11) was next tested *in vivo* effect on focal cerebral ischemia through permanent middle cerebral artery occlusion. The critical reduction of infarct volume was observed by 2G11. Thus, we suggested that AMPK could be a therapeutic target for Stroke and a new chemical compound having the inhibitory effect of AMPK as the candidate drug for Stroke.

Disclosures: **J. Eom:** None. **T. Kim:** None. **B. Seo:** None. **J. Koh:** None. **Y. Kim:** None.

Poster

792. Ischemia and Hemorrhage: Translational Studies

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 792.12/P8

Topic: C.07. Ischemia

Support: NIH/NINDS

Title: Therapeutic potential of a STEP-derived peptide in cerebral ischemia

Authors: S. RAJAGOPAL[1], R. PODDAR[1], L. WINTER[1], A. M. ALLAN[2], *S. PAUL[3]; [1]Dept. of Neurol., [2]Dept. of Neurosci., Univ. of New Mexico, Albuquerque, NM; [3]Dept Neurol, Univ. New Mexico, Albuquerque, NM

Abstract: Despite advances in understanding the pathophysiology of acute ischemic stroke, successful treatment remains a major challenge in clinical medicine. Reperfusion with recombinant tissue plasminogen activator remains the only pharmacologic therapy. Rapid reperfusion, although necessary for restoration of brain metabolic activity, is also associated with additional risks. The development of neuroprotection strategies, to protect the brain from both ischemia and reperfusion injury is therefore an important goal. Emerging evidence indicate that the brain-enriched and neuron-specific tyrosine phosphatase (STEP) that is activated following glutamate-mediated NMDA receptor stimulation may play a role in neuroprotection against cerebral ischemia. During a transient ischemic insult (middle cerebral artery occlusion or MCAO for 90 min) in Wistar rats activation of STEP promotes neuronal survival by down regulating several detrimental cascades, while degradation of active STEP over time leads to loss of its neuroprotective effects that allows the progression of ischemic brain damage. Maintaining STEP availability through intravenous administration of a brain permeable and constitutively active STEP-derived peptide significantly reduces ischemic brain damage observed 24 hours after the onset of the insult. Conversely, deletion of STEP gene in mice (STEP knockout mice) exacerbates brain injury following a mild ischemic stroke as observed 24 hours after the onset of the insult. Based on these findings the current study evaluated the temporal profile of pathological changes in the brain, by magnetic resonance imaging, over a period of 30 days in Wistar rats subjected to MCAO and treated with the STEP-derived peptide either at the onset of reperfusion or 6 hour after the onset of the insult. Functional assessment was performed throughout the time course to determine alterations in sensorimotor and cognitive functions. The analysis of the long-term pathological changes and behavioral outcome following restoration of the STEP signaling pathway could establish the potential benefit of this approach for stroke therapy.

Disclosures: S. Rajagopal: None. **R. Poddar:** None. **L. Winter:** None. **A.M. Allan:** None. **S. Paul:** None.

Poster

792. Ischemia and Hemorrhage: Translational Studies

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 792.13/P9

Topic: C.07. Ischemia

Support: UHF

CIHR

Title: Newborn piglet brain slices for studying cellular mechanism in cerebral palsy

Authors: *V. RANCIC[1], A. RUANGKITTISAKUL[1], B. RAWAL[1], J. TURNER[2], P.-Y. CHEUNG[2], K. BALLANYI[1];
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Abstract: Cerebral Palsy (CP) and related encephalopathies develop when the brain suffers from insufficient oxygen and/or blood supply before or during birth. Such hypoxia/ischemia (HI) insults can cause brain damage (HI-BD) leading to CP for which no effective treatment is available. Therefore, animal research is needed with an increasing number of in vivo studies using newborn piglets because their gyrencephalic brain is similar to that of humans including perinatal development. To analyze at the cellular level how HI-BD affects neural networks in a CP-proned brain area, we have developed somatosensory cortex (SSC) brain slices from 0-18 days-old piglets. These slices show spontaneous extracellular electrical early network oscillations (ENOs) that can be monitored simultaneously with membrane potential and cytosolic calcium dynamics in visualized SSC neurons. Using two-photon microscopy, we found that a single sodium action potential already triggers a transient cytosolic calcium rise whereas multiple action potentials cause a major calcium elevation. By incubating slices with fluorescent SR-101, the soma and processes of either SSC neurons (165 μM, 20-23 ^{o}C, 30 min) or SSC astrocytes plus white matter oligodendrocytes (1 μM, 36 ^{o}C, 40 min) were labeled, while only astrocytes were selectively immunostained with S100b, thus enabling quantification of HI-BD. Our preliminary findings indicate that blockade of ENOs with cyanide-induced 'chemical anoxia' is followed by long-lasting seizure-like hyperexcitability during the recovery phase that is depressed by activation of A1-type adenosine receptors. Mechanisms of such in vitro 'reperfusion' hyperexcitability will be compared with those in seizure-like hyperexcitability likely occurring in SSC slices from piglets exposed to HI in vivo. The findings indicate that our novel piglet SSC slices are a potent in vitro model to identify mechanisms in hypoxic/ischemic brain damage leading to CP and related encephalopathies and may thus be instrumental for developing effective treatment.

Disclosures: V. Rancic: None. **A. Ruangkittisakul:** None. **B. Rawal:** None. **J. Turner:** None. **P. Cheung:** None. **K. Ballanyi:** None.

Poster

792. Ischemia and Hemorrhage: Translational Studies

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 792.14/P10

Topic: C.07. Ischemia

Support: AHA Grant 14SDG18410020

NIH/NINDS Grant 5R01NS088555

Beatrice Menne Haggerty Endowment for Stroke Research, UTSW

Title: B cell-neuronal interactions induce neuroprotection in an in-vitro stroke model.

Authors: *V. TORRES, S. B. ORTEGA, X. KONG, A. M. STOWE;
Neurol. and Neurotherapeutics, UT Southwestern, Dallas, TX

Abstract: Background: Regulatory B and T cells are thought to play a protective role in the central nervous system by suppressing the inflammatory response and damage, including after stroke onset. Transferred B cells also inhibit leukocyte migration and preserve blood brain barrier integrity during stroke. The direct neuroprotective effects B cells potentially exert on neurons, however, remain unclear. Therefore, by utilizing an *in-vitro* ischemia model, oxygen glucose deprivation (OGD), **we hypothesize that direct B cell and neuronal interactions promote neuronal protection following ischemia.** Methods: Cortical and hippocampal cells were isolated from postnatal day 0-2 pups and cultured until confluent (minimum 7 days). B cells were isolated via negative selection EasySep magnetic beads from spleens of adult 8-12 week old male C57BL/6 mice. For B cell pre-treatment, B cells were co-cultured for 4 days prior to OGD in 1:1, 1:10, and 1:20 B cell:neuron ratios. In B cell post-treatment, B cells were co-cultured for 4 days immediately after OGD. OGD was induced for 2h by exposure to 0.1% O_2 in a hypoxic chamber with serum/glucose-free HBSS. Following a 3-day post-OGD recovery, neuronal protection was assessed using MAP2+ immunofluorescent staining, and confocal microscopy (10x, 4 images/well). Cells were quantified using the counter tool in Photoshop, normalized to non-B cell control, and analyzed by one-way ANOVA, Bonferroni post-hoc (Graphpad Prism). Significance was $p<0.05$. Results: 4-day pre-treatment with B cells at a 1:1 ratio significantly protected neurons with 128±23% increased survival, and preserved dendritic arborization of 423±372%, over non-B cell control. However, a lower 4-day post stroke B cell treatment at a ratio of 1:10 significantly preserved dendritic arborization at 67±32% over non-B cell control, without altering overall cell number. Conclusions: Our pre-treatment condition suggest that B-cells promote neuroprotection, while our post-treatment condition still need further dissection in order to understand the dynamic interplay between B-cells and neurons. Nonetheless, these results are the first to indicate a direct B cell function in neuronal survival following ischemia. Future experiments will aim to elucidate the mechanism(s) of action through ELISA and downstream signaling assays.

Disclosures: **V. Torres:** None. **S.B. Ortega:** None. **X. Kong:** None. **A.M. Stowe:** None.

Poster

792. Ischemia and Hemorrhage: Translational Studies

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 792.15/P11

Topic: C.07. Ischemia

Title: Activated protein C (APC) in the acute phase suppresses the development of cerebral infarction after focal cerebral ischemia

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Abstract: Despite years of research and efforts to translate stroke research into clinical therapy, ischemic stroke remains a major cause of death, disability, and diminished quality of life. Recombinant tissue-type plasminogen activator (tPA) is the only approved therapy for acute ischemic stroke. Although more aggressive thrombolysis was expected to be more beneficial, higher doses of tPA are associated with an increased risk of hemorrhagic transformation and neurotoxicity. In this study, we used activated protein C (APC), a serine protease found in the human blood with anticoagulant activity. APC has also been reported to possess potent cytoprotective activities. We used our original three-vessel occlusion (3-VO) ischemia mouse model (15-minute focal ischemia limited to the cortex), recently reported. Mice received either APC (2, 4 or 8 mg/kg; supplied by The Chemo-Sero-Therapeutic Research Institute), or human albumin as vehicle control, or saline, intravenously, five minutes after the induction of ischemia (N=7-13). The second injection of the same drug or control was performed three hours later. The regional cerebral blood flow was monitored before (control), during, and after ischemia using laser Doppler flowmetry. We evaluated neurological deficit using our original tail suspension test or bar-balance test, at 24 hours after ischemia. Each brain was cut into 1 mm-thick slices, and the volumes of infarcted lesions and edema were analyzed using 2% TTC. The results showed that, APC (2 mg/kg) significantly suppressed infarcted volumes (adjusted by edema) compared to albumin or saline (APC: 14.3±4.7 mm^3, albumin: 19.6±4.8 mm^3, saline: 21.7±6.6 mm^3; $p<0.05$). In the functional analysis, the neurological deficits were less in APC compared to the saline. In the dose-escalation test on the APC-treatment, infarcted volumes in APC (4 or 8 mg/kg) or saline were relatively or significantly larger compared to APC (2 mg/kg) ($p<0.05$). It had been reported that protein C (PC) levels under normal condition were inversely associated with incidence of ischemic stroke but not coronary heart disease, suggesting that PC or APC may be an endogenous brain-protectant. In the present study, APC, when administered after the

induction of focal ischemia (five minutes in mice is regarded as the equivalent of 40 minutes in humans according to the physiological time scale), damage of the brain was significantly reduced, when the dosage of APC was appropriate, along with a trend towards improved neurological deficit at 24 hours after ischemia. The administration of APC for the treatment of ischemic stroke in the acute phase to protect the brain is a promising candidate for a future clinical trial.

Disclosures: K. Yamato: None. **Y. Nakajo:** None. **H. Yamamoto–Imoto:** None. **K. Kokame:** None. **T. Miyata:** None. **H. Kataoka:** None. **J.C. Takahashi:** None. **H. Yanamoto:** None.

Poster

792. Ischemia and Hemorrhage: Translational Studies

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 792.16/P12

Topic: C.07. Ischemia

Support: NIH Grant NS066001

Leducq Foundation Grant 15CVD02

Title: Spatiotemporal synchrony predicts brain viability in a rodent model of ischemic stroke

Authors: *E. G. WANN, N. S. JACOBS, R. D. FROSTIG;
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Abstract: Stroke is the fifth leading cause of death in the United States, and the majority of these cases are due to Middle Cerebral Artery (MCA) ischemia (Mozaffarian et al., 2016). Improved treatments for MCA ischemia are necessary as current therapeutic strategies are only effective for a subset of stroke patients and only reduce damage or its functional consequences. Previous studies from our laboratory have demonstrated that sensory stimulation delivered within 2 hours (‘early treatment’) after permanent MCA occlusion (pMCAO) completely protects the cortex from impending stroke damage, whereas the same intermittent sensory stimulation results in exacerbated damage if delivered 3 or more hours after ischemic onset (‘late treatment’) (Frostig et al., 2012). The interaction between sensory stimulation treatment and the post-ischemic (0-5 hours) neuronal network state is unknown but may be important for understanding the efficacy of sensory stimulation treatment. Using multisite local field potential (LFP) recordings across horizontal locations of S1 and all cortical depths, this research generates for the first time a continuous spatiotemporal profile of neuronal activity from the MCA territory during the acute post-ischemic period. Spatiotemporal synchrony, a measure of coordinated neuronal activity

across recording locations, is increased primarily in the delta band directly after pMCAO and is persistently high throughout the acute post-pMCAO period in pMCAO alone animals. Our data further indicate that high post-pMCAO spatiotemporal synchrony is reduced and baseline spatiotemporal synchrony is reestablished in early treated but not late treated animals. As synchrony is known to be fundamental for cortical function and relevant to many pathological brain states, enhanced spatiotemporal synchrony may be a signature of cortical network dysfunction after pMCAO and predictive of whether damage is incurred after pMCAO and sensory stimulation treatment.

Disclosures: E.G. Wann: None. **N.S. Jacobs:** None. **R.D. Frostig:** None.

Poster

792. Ischemia and Hemorrhage: Translational Studies

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 792.17/Q1

Topic: C.07. Ischemia

Support: CNPQ

Title: Association between diabetes < chronic cerebral hypoperfusion induces cognitive impairments < enhances microglia expression in the hippocampus of middle aged rats.

Authors: *A. N. HUBNER, E. D. F. FERREIRA, R. M. M. W. OLIVEIRA, H. MILANI; Pharmacol. and Therapeut., State Univ. of Maringa, Maringa, Brazil

Abstract: Introduction: Vascular dementia (VD) is a progressive disease, caused by reduced blood flow to the brain that affects cognitive abilities. Diabetes has been established as a risk factor for VD and reported to almost double the risk of VD. The vascular damages caused by hyperglycemia induces a chronic cerebral hypoperfusion (CCH) state. Experimentally, the permanent four vessel occlusion/internal carotid artery model (4-VO/ICA) in rats reproduces some behavioral and cellular aspects of VD, such as memory impairment and hippocampal neurodegeneration. **Aim:** To investigate the behavioral outcomes of the association between hyperglycemia and 4-VO/ICA in middle-aged rats. The expression of microglia in the hippocampus was also evaluated. **Methods**: The Ethical Committee on Animal Research of State University of Maringá approved all experimental procedures (CEUA 15/2014). Male 12 months old Wistar rats received a single dose of streptozotocin (35 mg/Kg, i.v.) to induce diabetes condition. Animals with glycemia values > 250mg/dl were considered hyperglycemic. The animals were trained in the aversive radial maze (AvRM), during 15 days. After, the animals were submitted to sham or 4-VO/ICA surgeries. Four experimental groups were generated:

sham+hyperglycemia; sham+normoglycemia; 4VO/ICA+normoglycemia and 4VO/ICA+hyperglycemia. The animals were assessed for memory performance in the AvRM at 7, 14, 21 days after the surgeries. The following parameters were registered: (i) latency, (ii) number of reference memory errors and (iii) number of working memory errors. The animals then had their brains removed for immunohistochemical analysis of microglial ionized calcium-binding adaptor molecule-1 (Iba-1) expression. Behavioral data were analyzed by two-way ANOVA followed by the *post hoc* Bonferroni test. Histological data were normalized to the meanvalues of the sham group and analyzed by the Student *t* test. **Results**: Significant differences in the latency ($F_{1.60}$ = 15.44; p= 0.0005), reference errors ($F_{1.60}$= 4.313; p = 0.0465) and working errors ($F_{1.60}$= 10.55; p=0.0029) were detected when comparing 4-VO/ICA+normoglycemia *versus* 4-VO/ICA+hyperglycemia groups. The 4-VO/ICA+hyperglycemia group presented increase in the Iba-1 expression compared with the 4-VO/ICA+normoglycemia (t_{10}=3.00;p=0.013), sham+hyperglycemia (t_{10}=4.49;p=0.012) and sham+normoglycemia (t_9=4.14;p=0.0025). **Conclusion:** Association of hyperglycemia and 4VO/ICA induces cognitive impairments and enhances the microglial expression in the CA1 hippocampal subfield of middle-aged rats.

Disclosures: A.N. Hubner: None. **E.D.F. Ferreira:** None. **R.M.M.W. Oliveira:** None. **H. Milani:** None.

Poster

792. Ischemia and Hemorrhage: Translational Studies

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 792.18/Q2

Topic: C.07. Ischemia

Support: AHA Award 15PRE25250009

Merit Award 1I01RX001141 and 1BX001218

Title: Inhibiting post-stroke neuroinflammation by ischemia-targeted complement modulation limits acute injury and promotes motor and cognitive recovery after murine stroke

Authors: *A. ALAWIEH[1], F. LANGLEY[1], L. KULIK[2], M. HOLERS[2], S. TOMLINSON[1,3]; [1]Microbiology and Immunol., Med. Univ. of South Carolina, Charleston, SC; [2]Med. and Immunol., Univ. of Colorado Sch. of Med., Denver, CO; [3]Ralph H. Johnson VA Med. Ctr., Charleston, SC

Abstract: Ischemia leads to the cellular expression of damage-associated molecular patterns (DAMPS) and their recognition by natural IgM antibodies that subsequently activate complement and propagate inflammation. We previously isolated two natural IgM monoclonal antibodies (mAbs) from un-manipulated mice: B4 that recognizes modified annexin-IV, and C2 that recognizes a subset of phospholipids. Both B4 and C2 mAbs specifically recognized ischemic cells and reconstituted cerebral ischemia reperfusion injury in otherwise protected antibody-deficient Rag1-/- mice. Therefore, we developed a novel strategy of site-targeted complement inhibition by fusing a single chain antibody (scFv) derived from the B4 mAb to the complement inhibitor, Crry. We show that the fusion construct, B4scFv-Crry, inhibits complement activation in-vitro and specifically targets the ischemic brain in-vivo following 60 min transient middle cerebral artery occlusion (MCAO). A single dose of B4scFv-Crry administered 5 hr. after reperfusion inhibited IgM and complement deposition in the ischemic brain, and significantly reduced infarct volume and neurological deficit scores in both young and aged mice as measured 24 hr. after ischemia. B4scFv alone provided similar levels of improvement at 24 hr. after ischemia, but only B4scFv-Crry provided protection into the chronic phase (15 days), yielding significant reduction in cell death and tissue scarring, and significant improvement in gross motor deficits, forelimb asymmetry and cognitive performance. Following MCAO, we observed a sustained neuro-inflammatory response manifesting as continuous IgM and complement deposition and robust M1 (pro-inflammatory)-type activation of microglia lasting beyond 15 days after reperfusion. However, acute administration of B4scFv-Crry after stroke interrupted the inflammatory neurodegenerative cycle by significantly inhibiting complement and IgM deposition, and shifting microglial polarity to resting and M2-polarized phenotypes in the chronic phase. Finally, we demonstrated that both B4scFv and B4scFv-Crry bound specifically within the ischemic core and penumbra of brain samples obtained from patients who died after acute stroke. No binding was observed in sections prepared from normal brain tissue from the same patient, or from age-matched controls. These data indicate a similar DAMP recognition system occurs in the brains of mouse and man, and that B4scFv-targeted complement inhibition has translational potential for inhibiting inflammatory neurodegenerative cascades after stroke in order to improve motor and cognitive outcomes.

Disclosures: **A. Alawieh:** None. **F. Langley:** None. **L. Kulik:** None. **M. Holers:** None. **S. Tomlinson:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); S.T. is a patent holder of CR2-based and B4scFv-based targeted complement inhibitors..

Poster

792. Ischemia and Hemorrhage: Translational Studies

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 792.19/Q3

Topic: C.07. Ischemia

Support: NS056839

R44NS086344-01A1

Title: Modeling upper extremity impairments after subcortical white matter stroke in rats: forelimb strength and skill decrements in an isometric pull task after focal infarcts of the posterior limb of the internal capsule

Authors: *E. NUDI[1], B. R. BARKSDALE[2], S. K. YOUNG[1], T. A. JONES[3];
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Abstract: Stroke affects around 800,000 people in the United States each year and is the fifth leading cause of death. It is common for stroke survivors to experience lasting upper limb motor impairment and many of these have damage only to subcortical white matter. Upper limb impairments after strokes involving the posterior limb of the internal capsule are especially common. However, most animal stroke models do not specifically target the posterior limb of the internal capsule. This study aims to characterize forelimb motor function over time following focal ischemic damage to the posterior limb of the internal capsule, induced via slow microinfusion of the vasoconstricting peptide, endothelin-1. An angled infusion approach was used to minimize direct damage to motor cortex. Male Long-Evans rats were pre-trained on an isometric pull task (Vulintus, Mototrak) until proficiency on the task was reached (~90% success rate). In this task, rats in a chamber reach through a window to grasp and pull a lever. Pulls that are made with sufficient force are rewarded by release of a banana flavored food pellet into the chamber. The success rate and force generation during the pull are measured. After lesion induction, animals were then given a 4-5 day recovery period, followed by periodic retesting on the same task. As measured on the first post-infarct testing day, there was a more than 50% reduction in success rate and pull force, which subsequently partially improved towards baseline. The assessment period is ongoing with behavioral testing being conducted weekly for at least 3 months. These preliminary results support that this model of subcortical white matter stroke results in weakness and impaired motor skill, reproducing important clinical characteristics of upper extremity motor impairment after stroke.

Disclosures: **E. Nudi:** None. **B.R. Barksdale:** None. **S.K. Young:** None. **T.A. Jones:** None.

Poster

792. Ischemia and Hemorrhage: Translational Studies

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 792.20/Q4

Topic: C.07. Ischemia

Support: NIH Grants NS091585, NS062097, NS085568

AHA Grant 12GRNT12060222

VA National Merit Grant RX000666

NSF Grant 1512826

AHA Postdoctoral Fellowship 15POST25710112

National Natural Science Foundation of China 81500989

Title: Optogenetic stimulation improves iPS-NPCs transplantation therapy after ischemic stroke

Authors: D. CHEN[1,2], Z. Z. WEI[1,2], K. BERGLUND[3], X. GU[1,2], M. SONG[1], O. MOHAMAD[1], *S. YU[1,2], L. WEI[1,2,3];
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Abstract: Stroke remains a leading cause of human death and long-term disability with very few effective treatments. Stem cell transplantation therapy provides the possibility to regenerate and repair damaged brain tissues after ischemic stroke. In this study, we tested the hypothesis that a combination strategy of iPS-NPCs transplantation and optogenetic manipulation could enhance regenerative properties of transplanted cells, resulting in better tissue repair and functional recovery after stroke. The blue light sensitive channelrhodopsin 2 (ChR2) channel was expressed in iPS cell-derived neural progenitor cells (iPS-NPCs). These optogenetic-engineered iPS-NPCs could differentiate to functional neurons that fire action potentials evoked by current injection or blue light stimulation. Light stimulation increased mRNA levels of synaptic markers Synapsin-1 and PSD95, and growth factors FGF, BDNF and SDF-1 in differentiated neurons. Light stimulation also increased the axonal outgrowth of iPS-NPCs derived neurons. ChR2-engineered iPS-NPCs were transplanted into the ischemic core and penumbra 7 days after focal ischemic stroke in mice. One day after cell transplantation, blue light stimulation (10 Hz, 15 min) was performed 3 times daily until 14 days after stroke. Immunochemistry staining results showed that light stimulation of grafted iPS-NPCs resulted in higher level of Synapsin-1 in the peri-infarct region compared to animals received iPS-NPC transplantation but without stimulation. The adhesive removal test revealed that iPS-NPC transplantation plus optogenetic stimulation

significantly promoted sensorimotor function and whisker touching behavior 14 days after stroke compared to no stimulation controls. These results suggest that optogenetics can be used to promote the iPS-NPCs transplantation therapy after stroke for tissue repair and functional recovery.

Disclosures: **D. Chen:** None. **Z.Z. Wei:** None. **K. Berglund:** None. **X. Gu:** None. **M. Song:** None. **O. Mohamad:** None. **S. Yu:** None. **L. Wei:** None.

Poster

792. Ischemia and Hemorrhage: Translational Studies

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 792.21/Q5

Topic: C.07. Ischemia

Support: NIH Grant 5RO1NS071072NINDS

Title: Ripk mediates outcome after intracerebral hemorrhage in mice

Authors: ***S. LULE**[1], L. M. MCALLISTER[1], Y. ZHENG[1], L. WU[1], J. BERTIN[2], M. J. WHALEN[1];
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Abstract: Intracerebral hemorrhage (ICH) results in high mortality and severe neurological deficits in survivors. ICH lacks specific therapy in part because mechanisms of cell death after ICH are incompletely understood. Necroptosis is a form of programmed necrosis mediated by receptor interacting protein kinases (RIPK) 1 and 3. Our previous report suggested a role for RIPK3 in plasmalemma damage typical of necrosis in a collagenase ICH model (Zhu et al, 2012). Here, we used RIPK1 kinase dead mutant mice to test the hypothesis that necroptosis is a predominant mechanism of cell death after ICH in mice. We induced ICH in mice using stereotactic injections of 30µl autologous blood into the right striatum (0.1mm anterior, 2.5mm lateral, 3mm ventral to bregma). Propidium iodide (PI) was injected intraperitoneally to label brain cells with plasmalemma damage. Fluoro Jade B was used to label degenerating neurons. Cell counts were performed blindly in 8 core and 8 peripheral regions of the ICH. Grid walk, wire grip, context fear conditioning, and Morris water maze (MWM) were used to assess sensorimotor and cognitive function after ICH. Mice containing loss of function point mutations in the RIPK1 kinase domain (D138N or K45A) were used to assess RIPK1 function in the ICH model. RM ANOVA was used to analyze weight loss, motor and MWM data and cell count data were analyzed by ANOVA/t-test. Plasmalemma damage was an early and persistent feature of

neuronal and non-neuronal cellular injury. PI+ cells were identified at 6 h, peaked at 24-48 h ($p<0.05$ vs. sham ICH 24 h), and few were detected at 7 d. At 24 h, over 90% of FJB+ cells colocalized PI+, with over 75% of FJB+ cells co-localizing PI at 48 and 72 h. In pulse labeling experiments, the majority of PI+ cells disappeared from injured brain between 1 and 6 h of labeling. $Ripk1^{D138N/D138N}$ mutant mice had significantly reduced PI+ cells at 24 h (Core: 19±3, Periphery: 20±4) compared to WT (Core: 120±29, Periphery: 51±10/x200 field, $p<0.01$) and 50% less FJB+ cells in core and periphery regions ($p<0.05$). Both $Ripk1^{D138N/D138N}$ and $RIPK1^{K45A/K45A}$ mutant mice had significantly improved postinjury weight gain ($p<0.05$) and improved postinjury MWM performance ($p<0.01$ RM ANOVA) but no differences in swim speeds, corner turn, foot fault, wire grip, Y-Maze, and contextual fear learning. The data suggest a predominant role for necrosis in autologous blood ICH-induced cell death. RIPK1 appears to play a significant role in neuronal and non-neuronal cell death as well as in recovery of weight gain and cognitive function after ICH. The data suggest that RIPK1 may be a novel therapeutic target to improve outcome after ICH.

Disclosures: S. Lule: None. **L.M. McAllister:** None. **Y. Zheng:** None. **L. Wu:** None. **J. Bertin:** None. **M.J. Whalen:** None.

Poster

792. Ischemia and Hemorrhage: Translational Studies

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 792.22/Q6

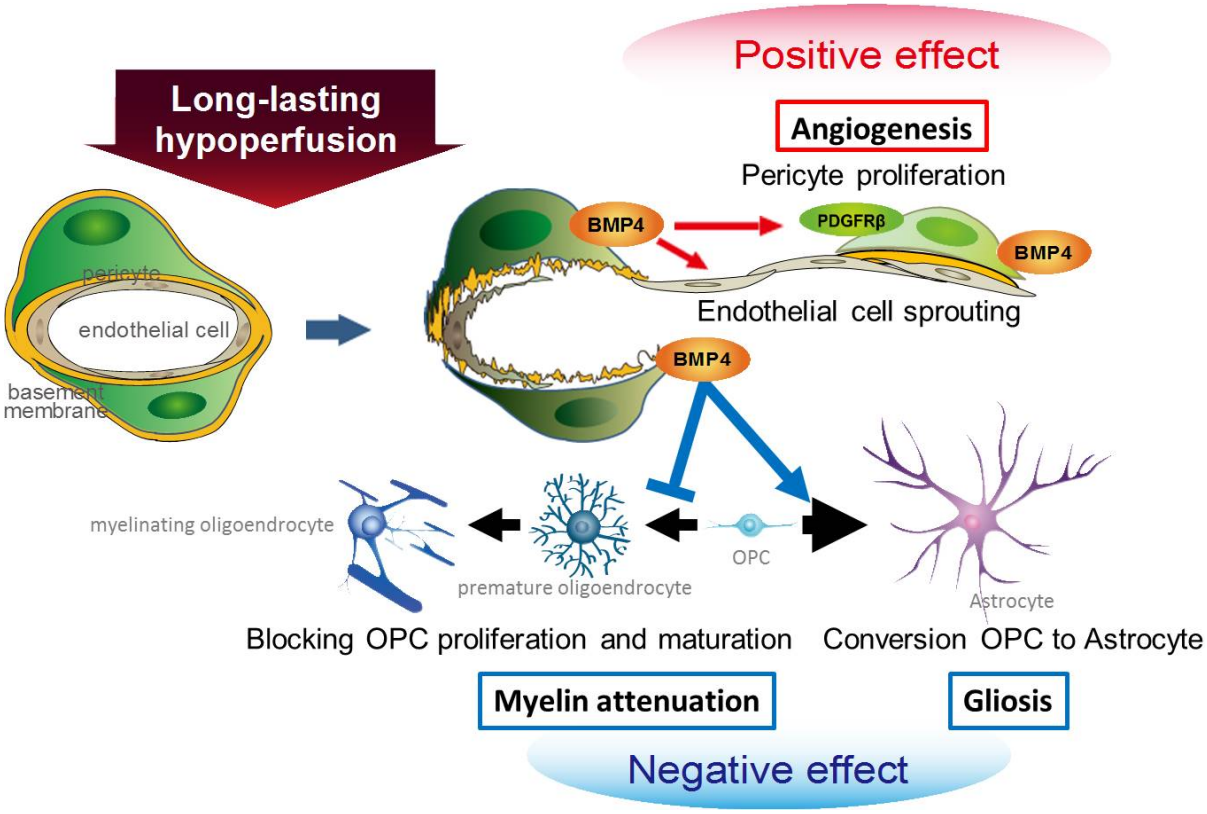
Topic: C.07. Ischemia

Title: BMP-4 expression by pericytes after ischemia aggravates white matter damage.

Authors: *M. UEMURA;
Kyoto Univ., Kyoto, Japan

Abstract: ***Objective*** Dysregulated transforming growth factor beta (TGFβ) signaling is considered to play a detrimental role in pathogenesis of cerebral autosomal recessive arteriopathy with subcortical infarcts and leukoencephalopathy (CARASIL), a hereditary type of vascular cognitive impairment (VCI). However, the largest group of TGFβ superfamily members, bone morphogenetic proteins (BMPs), has not been explored in dementing disorders. The aim of this study was therefore to characterize signaling abnormalities of BMP family in VCI. ***Methods*** To investigate the role of BMPs in VCI, we performed an immunohistochemical study using post-mortem frontal lobe tissues from 6-7 cases of VCI, Alzheimer's disease, and age-matched controls. Brain sections were immunostained with antibodies against TGFβ1 and BMPs (BMP-2/4/6/7/9), as well as two pericyte markers and an oligodendrocyte precursor cell (OPC) marker.

We subsequently tested oxygen-glucose deprivation (OGD) in cultured pericytes to simulate ischemia, and also investigated effects of BMP-4 on cultured vascular cells and myelin related cells. ***Results*** Among the TGFβ superfamily members, BMP-4 was highly expressed in pericytes in the white matter of VCI, and its expression correlated with the degree of myelin loss. The number of OPC was fewer in the subventricular zone with higher BMP-4 expression. In cultured pericytes, continuous OGD induced BMP-4 expression. Recombinant BMP-4 induced tube formation of endothelial cells and proliferation of pericytes. Meanwhile, BMP-4 suppressed maturation of OPCs and strongly induced conversion of OPCs to astrocytes. ***Conclusions*** Our findings suggest that ischemic myelin damage evolves in parallel with BMP-4 upregulation in pericytes. BMP-4 expression promotes angiogenesis but induces astrogenesis at the expense of OPC maturation and proliferation, which may aggravate myelin damage. These results may explain why white matter is particularly vulnerable to chronic hypoperfusion. Regulation of BMP-4 signaling has the potential as treatment strategy for VCI.



Disclosures: M. Uemura: None.

Poster

792. Ischemia and Hemorrhage: Translational Studies

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 792.23/Q7

Topic: C.07. Ischemia

Support: NIH Grant NS45048 (to JC)

NIH Grant NS089534 (to JC)

NIH Grant NS095671 (to JC)

Department of Veterans Affairs Senior Research Career Scientist Award and RR&D Merit Review RX000420 (to JC)

Title: Post stroke dietary supplementation of omega3 polyunsaturated fatty acids combined with docosahexaenoic acid treatment promote neurological recovery in aged mice after cerebral ischemia

Authors: *X. JIANG[1,2], J. SUENAGA[3], H. PU[3], Z. WENG[3,4], Y. SHI[3], X. HU[2,3,4], J. CHEN[2,3,4]; [1]Univ. of Pittsburgh Sch. of Med., Inst. of Brain Disorders & Recovery, Pittsburgh, PA; [2]State Key Lab. of Med. Neurobio. and Inst. of Brain Sciences,Fudan Univ., Shanghai, China; [3]Inst. of Brain Disorders & Recovery, Univ. of Pittsburgh Sch. of Med., Pittsburgh, PA; [4]Geriatric Research, Educational and Clin. Center, Veterans Affairs Pittsburgh Hlth. Care Syst., Pittsburgh, PA

Abstract: Stroke is a leading cause of serious long-term disabilities in adults in the US. Nowadays, treatment to ischemic stroke is largely limited to tPA thrombolytic therapy. Previous studies have demonstrated that prophylactic food supplement of omega-3 polyunsaturated fatty acids (n-3 PUFAs) and docosahexaenoic acid (DHA) could ameliorate brain injury after ischemic stroke. However, the therapeutic effect of post-stroke n-3 PUFA or DHA supplementation in aged mice is not well characterized and is what we aimed to find out in this study. 18 months old C57BL/6J mice induced with distal middle cerebral artery occlusion (dMCAO) were randomly assigned to 4 groups: 1) vehicle, 2) DHA, 3) n-3 PUFAs and 4) DHA+n-3 PUFAs groups. All measurements were made by investigators blinded to experimental groups. DHA (10mg/kg) was given intraperitoneally 24h after dMCAO and then once daily until 10 days after dMCAO. Dietary n-3 PUFA supplementation (50 mg in every gram of regular diet) started from 5 days after dMCAO until sacrificed. Neurological deficits and brain tissue loss, neurogenesis, angiogenesis and oligodendrocyte regeneration were assessed up to 35days after dMCAO. The results show that n-3 PUFA or DHA treatment did not reduce brain tissue loss (n=8-10 per group, $p>0.05$ vs. vehicle by ANOVA). Although the infarct volume was limited to

the cortex and showed no difference among groups, rotarod test and adhesive removal test indicated significant sensorimotor deficits which last up to 35 days after injury. Aged mice which received n-3 PUFA with combined DHA demonstrated significantly attenuated deficits (n=6-8 per group, $p<0.05$ vs. vehicle by ANOVA and *post hoc* turkey test). In the Morris water maze test, DHA alone or combined with n-3 PUFAs promoted the learning and memory ability in aged mice, reflected by decreased latency to find the hidden platform and increased time in the goal quadrant (n=9-11 per group, $p<0.05$ vs. vehicle by unpaired t-test). Further immunostaining show that angiogenesis was enhanced in n-3 PUFAs alone or combined with DHA treatment group as demonstrated by increased number of $BrdU^+CD31^+$ vessels in both cortex and striatum at 35 days post injury (N=8 per group, $p<0.01$ vs. vehicle by ANOVA and *post hoc* turkey test). Interestingly, newly proliferated neurons ($BrdU^+NeuN^+$ cells) and oligodendrocytes ($BrdU^+APC^+$ cells) were seldom found in all the groups. Our results suggest that n-3 PUFAs dietary supplementation combined with DHA treatment showed beneficial effects in the aged mice after dMCAO by attenuating neurological deficits and promoting angiogenesis. Also, it may be a clinically translatable treatment for ischemic stroke in the aged population.

Disclosures: **X. Jiang:** None. **J. Suenaga:** None. **H. Pu:** None. **Z. Weng:** None. **Y. Shi:** None. **X. Hu:** None. **J. Chen:** None.

Poster

792. Ischemia and Hemorrhage: Translational Studies

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 792.24/Q8

Topic: C.07. Ischemia

Support: 5R01NS092875-02

Title: Lacunar stroke in the rat using an optrode and rose bengal causes selective lesion of the forelimb representation of the internal capsule

Authors: *T. WEN[1], A. SINDHURAKAR[1], V. CONTRERAS[1], H. PARK[1], J. B. CARMEL[1,2]; [1]Burke Med. Res. Inst., White Plains, NY; [2]Brain and Mind Res. Inst. and Departments of Neurol. and Pediatrics, Weill Med. Col. of Cornell Univ., New York, NY

Abstract: Subcortical stroke leads to significant neurological impairment and represent an important public health challenge. Available animal models are limited in the variability of the targeting and the size of the stroke. The aim of this study was to use the combination of an optic fiber and an electrode to establish a reproducible lacunar stroke in the rat. We first performed tract labeling and electrophysiological motor mapping of the rat IC to better characterize the IC

somatotopy. For tract labeling, we injected AAV2 viruses expressing green and red fluorescent protein into the forelimb and the hindlimb areas of the cortex, respectively. For mapping, we used a microelectrode to stimulate the IC and characterized the responses as forelimb, hindlimb, or both. From both anatomy and physiology, we found largely separate representations of the forelimb and hindlimb in the IC. We used this map to target the forelimb representation at 7.0-7.5 mm ventral to the dura mater. The electrode was used to locate the hot spot of the forelimb representation, where forelimb movements could be elicited at low stimulus intensity. At this location, the optic fiber was used to activate systemically administered rose bengal using green wavelength light to cause the lesion. The lesion was selectively confirmed in the target posterior limb of the IC by TTC (2,3,5-triphenyltetrazolium chloride) staining and cresyl violet staining 48 hours after lesion. We compared our new method against local injection of the vasoconstrictor endothelin-1. Endothelin injection caused more widespread damage to the cortex and the corpus callosum of the injected hemisphere. In sum, the new method is both highly reproducible and selective for the forelimb representation of the IC. Thus, we can use this model to mimic the human clinical condition and to study which circuits help mediate functional recovery after subcortical stroke.

Disclosures: **T. Wen:** None. **A. Sindhurakar:** None. **V. Contreras:** None. **H. Park:** None. **J.B. Carmel:** None.

Poster

792. Ischemia and Hemorrhage: Translational Studies

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 792.25/Q9

Topic: C.07. Ischemia

Support: NIH Grant NS088986

CSL Behring

Title: Effect of systemic hemopexin therapy after intracerebral hemorrhage

Authors: Y. CAO, Z. YAN, J. CHEN-ROETLING, *R. F. REGAN;
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Abstract: Erythrocyte lysis after intracerebral hemorrhage (ICH) exposes adjacent cells to toxic concentrations of hemoglobin, which rapidly oxidizes to methemoglobin and releases its heme moieties. Experimental evidence suggests that heme and its degradation products initiate oxidative and inflammatory injury cascades that may be amenable to targeted therapies. The

primary defense against heme toxicity is provided by hemopexin, a glycoprotein that binds it with extraordinary affinity and mitigates its pro-oxidant and pro-inflammatory effect. A prior study demonstrated that hemopexin knockout increased striatal injury in both the collagenase and blood injection ICH models. The present study tested the hypothesis that exogenous human hemopexin protected wild-type mice in these models. Pharmacokinetic studies demonstrated that 70 mg/kg hemopexin i.p. daily maintained serum human hemopexin concentrations at 0.9-1.2 mg/ml, a range similar to human physiologic levels, and had no sustained effect on mouse hemopexin levels. Injection of collagenase into the right striatum of Swiss-Webster mice reduced perihematomal cell viability to 50±6% of contralateral, as measured by MTT assay after striatal dissociation. Treatment with 70 mg/kg human hemopexin i.p. daily beginning two hours after collagenase increased striatal cell viability to 85±9% (P= 0.013). Hemopexin at this dose also provided significant blood-brain barrier protection, with leakage of Evans blue decreasing from 71±7 to 40±8 ng/striatum. However, a lower hemopexin dose (35 mg/kg) provided no benefit. A more variable effect was observed using C57BL/6 mice expressing the red fluorescent protein dTomato in neurons, with significant protection observed at 8 days after collagenase injection, but not at 3 days. The blood injection model produced somewhat less injury, reducing striatal cell viability to 67±2% of contralateral at three days in control mice, increasing to 84±4% with 35 mg/kg hemopexin treatment ($P < 0.05$). These results indicate that systemic therapy with human hemopexin may mitigate perihematomal cell loss after experimental ICH, and suggest that further investigation of its therapeutic potential is warranted.

Disclosures: **Y. Cao:** None. **Z. Yan:** None. **J. Chen-Roetling:** None. **R.F. Regan:** B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution; Grant support and study drug provided by CSL Behring.

Poster

792. Ischemia and Hemorrhage: Translational Studies

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 792.26/Q10

Topic: C.07. Ischemia

Support: NS056839

R44NS086344-01A1

Title: Quantifying deficits in forelimb force generation using an automated skilled reaching task after middle cerebral artery occlusion in rats

Authors: *K. S. VALENZUELA, N. MITTAL, T. A. JONES, T. SCHALLERT;
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Abstract: Reaching tasks are commonly used to assess various facets of forelimb function following stroke in rat models. These tasks provide valuable information about skilled forelimb performance and movement quality, although they do not directly quantify the strength of movement. The Isometric Pull Task (MotoTrak, Vulintus), a fairly new behavioral neuroscience task, is a fully automated system that incorporates reach-to-grasp motion and provides quantitative data on forelimb force generation. Furthermore, forelimb force generation in clinically relevant stroke models such as middle cerebral artery occlusion (MCAo) has not been examined. Male Long Evan rats (n=8) were trained with their preferred limb to reach outside a chamber, grasp a handle attached to a stationary force transducer, and pull with a predetermined amount of force to receive a banana flavored food pellet. Transient focal ischemia was induced in the hemisphere contralateral to the preferred limb by an intraluminal middle cerebral artery occlusion suture method. Focal ischemic time was 60 mins and was confirmed via Laser Doppler flow. Animals were then probed for deficits of forelimb strength during 30 min probe sessions with the Isometric Pull Task on days 5, 10, 15, 21, and 28 post-MCAo. An adaptive setting on MotoTrak was used post-MCAo to accommodate for the severity of the impairments. Additionally, an arm barrier was inserted in order to prevent compensation with the unimpaired limb. Average forelimb force dropped from 189 grams at pre-MCAo baseline to 40g on Day 5 post-MCAo. At Day 28 post-MCAo, average forelimb force was only 75g. Additionally, the average number of pull attempts per session was 188 at pre-MCAo baseline and dropped to 5 at Day 5 post-MCAo. The average number of pull attempts at Day 28 was 67. Forelimb weakness is often seen in stroke patients. We demonstrated that the Isometric Pull Task is sensitive to robust deficits in forelimb force generation following MCAo. This task provides an additional measure that can be used to evaluate motor dysfunction that is characteristic of upper extremity impairments in clinical stroke populations.

Disclosures: K.S. Valenzuela: None. **N. Mittal:** None. **T.A. Jones:** None. **T. Schallert:** None.

Poster

792. Ischemia and Hemorrhage: Translational Studies

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 792.27/Q11

Topic: C.07. Ischemia

Support: NINDS RO1 NS056839

Title: Learned-subordinate use of the paretic forelimb after motor cortical infarcts in rats: effects of prior task experience

Authors: *D. MILLER[1,2], K. V. TRUONG[3], E. T. NUDI[4], T. A. JONES[1,4];
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Abstract: The impact of stroke on the performance of unimanual tasks with the paretic side has been extensively studied in animal models and clinical populations. Its impact on bimanual coordination has not received as prominent attention, though both hands are normally used together for most manual tasks. We recently developed a bimanual skill task, the popcorn retrieval task, which rats perform using coordinated asymmetrical reach and grasp movements with both forelimbs (Dutcher et al., 2013). In rats that are skilled in unimanual reaching, *de novo* training on the popcorn retrieval task after unilateral motor cortical infarcts results in a progressive shift from dominant use of the paretic (uni-manually trained pre-infarct) to the nonparetic forelimb over weeks of training. That is, the task revealed practice-dependent learned subordinant-use of the paretic limb. The present study aimed to characterize (1) how intact animals learn the popcorn retrieval task and (2) how, once established, the bimanual reaching skill is affected by unilateral infarcts of the caudal forelimb area (CFA) of motor cortex. After a shaping period, rats were trained for 20 days (1 session/day) on the popcorn retrieval task, followed by ischemic (endothelin-1 induced) CFA lesions contralateral to the dominant-for-task limb and 20 additional days of testing on the same task. Limb dominance was defined by asymmetries in the number of reach attempts and reach initiations made by each limb. Before the lesions, limb asymmetries progressively increased over the first 11 days of training and then plateaued, suggesting the establishment of a stable inter-limb coordination strategy. This was followed by peak performance (12-14 days), as measured by successful retrievals. After the lesions, the proportions of reaching movements made with either limb converged over the first 2 days, with approximately symmetrical proportions thereafter. There were reductions in reach initiations with the paretic (previously dominant limb), but this limb continued to initiate most reaches. These effects contrast with the complete reversal of limb dominance that was observed with *de novo* post-lesion training on the task. Thus, the pattern of change in bimanual coordination strategies after CFA infarcts varies between a newly learned versus well-established skill.

Disclosures: D. Miller: None. **K.V. Truong:** None. **E.T. Nudi:** None. **T.A. Jones:** None.

Poster

793. Ischemia: Human

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 793.01/Q12

Topic: C.09. Brain Injury and Trauma

Title: Cerebral blood flow is impaired in concussed rugby players immediately following injury and affected by previous concussion history

Authors: *J. M. SERRADOR, M. FALVO;
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Abstract: Increasing evidence is suggesting that concussions are a possible significant cause of long term cognitive and health problems among athletes. Despite this increasing evidence, there is a lack of data on the physiological effects of a concussion on cerebral blood flow regulation. The goal of this work was to determine if concussions cause impairment of cerebral blood flow regulation in the first few hours after injury. In addition we were interested if history of previous concussions affected the response.

During a recreational rugby tournament a total of 91 players were recruited. Of these players, 59 were recruited as controls (12 females) and 34 had suffered a concussion (8 females). All testing was performed on the field to assess cerebral blood flow using Doppler, beat-by-beat blood pressure, and end-tidal CO_2. Subjects performed three sit to stand maneuvers. Data was collected 131±23 min following the head trauma.

We had previously found that concussed players demonstrated greater mean arterial pressure than controls and this was associated with significantly lower internal carotid blood flow. Examining history of concussion, we found that concussed rugby players with a history of concussion had significantly higher mean arterial pressures than those without (No H_x: 93.5±11.9 vs H_x: 102.1±14.9 mmHg, P=0.03). In contrast there was no difference in blood pressure in the non-concussed group. Examining internal carotid flow in the non-concussed group there was a tendency for flow to be lower in players with a history of concussions (Controls: No H_x: 515±186 vs H_x: 450±165 mL/min) but not in players who had just suffered a concussion (No H_x: 309±168 vs H_x: 330±101 mL/min). Surprisingly, players with a current concussion but no history had greater drops in blood pressure when standing than those with a history of concussion (No H_x: -23.4±12.1 vs H_x: -17.5±7.6 mmHg, P=0.016). They also demonstrated greater drops in middle cerebral artery flow velocity when standing (No H_x: -19.2±5.6 vs H_x: -15.0±6.7%, P=0.031)

These data suggest that while cerebral blood flow is impaired immediately following concussion, a previous history of concussion may also be associated with lower cerebral blood flow at baseline. Surprisingly previous history of concussion seemed to be protective to maintaining blood pressure and cerebral blood flow when standing, following a concussion. Further work is needed to determine how previous history of concussion may affect both blood pressure and cerebral blood flow regulation. This work was supported by the War Related Illness and Injury Study Center within the Department of Veteran Affairs.

Disclosures: J.M. Serrador: None. **M. Falvo:** None.

Poster

793. Ischemia: Human

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 793.02/Q13

Topic: C.09. Brain Injury and Trauma

Support: Indiana Spinal Cord and Brain Injury Research Fund

NIH Grant 5R21DC013974

Title: The effects of concussion-prone athletics on the brain: A comparison of football, cross-country, and socioeconomically matched non-athletes using diffusion-imaging.

Authors: B. A. CARON[1], D. A. KELLAR[2], F. PESTILLI[2], H. CHENG[2], S. D. NEWMAN[2], *N. L. PORT[3];
[1]Program in Neurosci., [2]Psychological and Brain Sci., [3]Indiana Univ., Bloomington, IN

Abstract: With the upward trend in early deaths and retirements by American football players, the topic of behavioral and structural deficits caused by concussion is an increasingly important one in the related research fields. With an incidence rate of 2.9 competition concussions per 1,000 athlete exposures (NCAA 2013) in collegiate football, the concussion risk to athletes is significant. However, even subconcussive blows, or blows that do not lead to a concussion diagnosis, appear to create health risks for athletes. On average, non-concussed Division 1 football players experience 503 impacts at 54G's or above (McAllister et al., 2014). These subconcussive blows appear to lead to significant neural changes, the severity of which may depend on the number of hits. In a study of non-concussed high school football players, Talavage et al (2014) found that athletes with a higher number of subconcussive blows were significantly different in fMRI and neurocognitive testing paradigms than athletes with a lower number of subconcussive blows. Similarly, McAllister et al (2014) demonstrated that white matter measures both FA (fractional anisotropy) and MD (mean diffusivity) correlated with neurocognitive test scores and head impact exposure. The present study attempted to replicate previous studies measuring changes in white matter measures (FA and MD) of 19 Division I upperclassmen football players, a group that we hypothesized experiences a high number of subconcussive blows, with 16 male cross-country athletes and 12 socioeconomically matched male non-athlete undergraduates using diffusion-weighted MRI and tract-based spatial statistic analyses. The present study went furthered established findings by measuring white matter tissue changes using advanced microstructural metrics, such as neurite-orientation dispersion and density (Zhang et al., 2012). No statistical differences were found between the football players and the other groups in regards to FA, statistical differences were found instead for MD, with football players having lower values than either control group. Importantly, football players showed higher neurite-orientation dispersion and density in the thalamus and extending through the frontal

cortex. No significant differences were found between the cross-country and the non-athlete control groups for any of the measures tested. These results support the hypothesis that multiple subconcussive blows result in microstructural white matter tissue changes. Future research is needed to determine a causal relationship between subconcussive blows and white matter tissue changes, and the mechanism/s by which these changes are produced.

Disclosures: B.A. Caron: None. **D.A. Kellar:** None. **F. Pestilli:** None. **H. Cheng:** None. **S.D. Newman:** None. **N.L. Port:** None.

Poster

793. Ischemia: Human

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 793.03/Q14

Topic: C.09. Brain Injury and Trauma

Support: VA Merit Grant I01-CX000499

VA Merit Grant MHBA-010-14F

VA Merit Grant NURC-022-10F

VA Merit Grant NEUC-044-06S

VA Merit Grant I01-CX000146

Title: Resting-state MEG reveals different patterns of aberrant functional connectivity in combat-related mild traumatic brain injury

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Abstract: Blast mild traumatic brain injury (mTBI) is a leading cause of sustained impairment in military service members and Veterans. However, the mechanism of persistent disability is not fully understood. In the present study, disturbances in brain functioning were investigated in mTBI participants using a source-imaging-based approach to analyze functional connectivity

(FC) from resting-state magnetoencephalography (rs-MEG). Study participants included 26 active-duty service members or Veterans who had blast mTBI with persistent post-concussive symptoms and 22 healthy control active-duty service members or Veterans. The source time-courses from gray-matter regions of interest (ROIs) were then used to compute ROI to whole-brain (ROI-global) FC for two different measures: 1) time-lagged cross-correlation and 2) phase-lock synchrony. FC analyses were conducted for different frequency bands. Compared with the controls, participants with blast mTBI showed increased gray-matter ROI-global FC in beta, gamma, and low-frequency bands, but not in the alpha band. Sources of abnormal increases in FC were from the: 1) prefrontal cortex (right ventro-medial prefrontal cortex, right rostral anterior cingulate cortex), left ventro-lateral and dorsolateral prefrontal cortex; 2) medial temporal lobe (bilateral parahippocampal gyri, hippocampi, and amygdala); and 3) right putamen and cerebellum. In contrast, the blast mTBI group also showed decreased FC of the right frontal pole. Group differences were highly consistent for the two different FC measures. FC of the left ventro-lateral prefrontal cortex correlated with cognitive functioning in mTBI participants. Altogether, our findings of increased and decreased regional-patterns of FC suggest that disturbances in the intrinsic organization of the brain may be due to multiple mechanisms.

Disclosures: **M. Huang:** None. **D.L. Harrington:** None. **A. Robb Swan:** None. **A. Angeles:** None. **S. Nichols:** None. **A. Drake:** None. **T. Song:** None. **M. Diwakar:** None. **C.W. Huang:** None. **V.B. Risbrough:** None. **A. Dale:** None. **H. Bartsch:** None. **R. Lee:** None. **D.G. Baker:** None.

Poster

793. Ischemia: Human

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 793.04/R1

Topic: C.09. Brain Injury and Trauma

Support: NSFC81471269

NSFC81300998

Title: Melatonin attenuates traumatic brain injury induced inflammation

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Abstract: Melatonin functions as a crucial mediator of inflammation; however, the underlying mechanisms of this process remain poorly understood. Dysfunctional mitochondria, a main

source of reactive oxygen species (ROS), are impacted in inflammation activation. Herein, inhibition of mitophagy, the selective degradation of damaged mitochondria by autophagy, enhanced inflammation induced by traumatic brain injury (TBI). Melatonin treatment activated mitophagy via the mTOR pathway, to attenuate TBI-induced inflammation. Furthermore, treatment with melatonin significantly ameliorated neuronal death and behavioral deficits after TBI, while 3-methyladenine reversed this effect by inhibiting mitophagy. Taken together, these results highlight a role for melatonin in protecting against virally TBI-triggered immunopathology, which is accomplished by negatively regulating inflammation activation and IL-1β production via the autophagy of damaged mitochondria.

Disclosures: J. Ji: None.

Poster

793. Ischemia: Human

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 793.05/R2

Topic: C.09. Brain Injury and Trauma

Support: MEXT/JSPS grant (#15H03126)

MEXT/JSPS grant (#16K13113)

MEXT/JSPS grant (#15H05880)

MEXT/JSPS grant (#16H05583)

a MHLW/AMED grant (BMI)

a MEXT/AMED-SRPBS grant (BMI)

Title: Speech comprehension in patients with persistent vegetative state : a neuroimaging approach

Authors: *Y. OKAHARA[1,2], K. UTSUMI[1,3], K. TAKANO[1], K. ODAKA[4], Y. UCHINO[4], K. KANSAKU[1,5];
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Abstract: Patients who represent no evidence of awareness of self and environment, and no evidence of volitional response to passive stimulus like an auditory, visual, and tactile have been diagnosed as persistent vegetative state (PVS), or recently as unresponsive wakefulness syndrome. Previous reports, by using fMRI, suggested that some patients in PVS have preserved cognitive function in imagery tasks (Owen, et al., 2005) and a language task with intelligible speech and unintelligible noise stimuli (Coleman, et al., 2007). In this study, we applied another language task, which employed passive listening to spoken narrative with a global language structure (Kansaku, et al., 2000; Kansaku and Kitazawa, 2001), to access cognitive state in PVS. Three PVS patients participated in this fMRI experiment (one male, mean: 33.6 years old). In the task, each experiment consisted of 8 epochs: 4 narrative epochs alternating with 4 control epochs. Two types of experiments were carried out. In experiment 1, to observe the whole extent of activation elicited by listening to a narrative, the narrative (80 s) was delivered during the four test epochs (epochs 1, 3, 5 and 7) and no sound was delivered during the control epochs. In experiment 2, to exclude activation elicited by processing of auditory voice in general, the narrative was delivered during the test epochs and the preceding test epochs were replayed in reverse during each control epoch. SPM12 (Wellcome Trust Centre for Neuroimaging, London, UK) was used for the analyses.
In experiment 1, significant activation distributed over the primary auditory cortex and the superior temporal gyrus (STG) was found bilaterally in 2 out of 3 subjects. In experiment 2, a patient (female, 20 years old) showed significant activation in the left middle temporal gyrus (MTG) and the temporo-parietal cortex (TPC), which agreed with a language study that investigated the posterior language areas (Kansaku, 2000).
The results suggest that the language task is useful to evaluate the level of speech comprehension; the patient who did not show activation in both experiments may not recognize human voice, the patient who showed activation only in experiment 1 may recognize human voice, and the patient who showed activation in both experiments may comprehend speech.

Disclosures: **Y. Okahara:** None. **K. Utsumi:** None. **K. Takano:** None. **K. Odaka:** None. **Y. Uchino:** None. **K. Kansaku:** None.

Poster

793. Ischemia: Human

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 793.06/R3

Topic: C.09. Brain Injury and Trauma

Support: NINDS-OD09-004

Title: Returning to form: factors affecting sleep disturbance duration and recovery following traumatic brain injury

Authors: *N. R. GRIFFIN[1], E. WICKWIRE[2], G. T. MANLEY[3], P. MUKHERJEE[3], J. YUE[3], M. VASSAR[3], W. A. GORDON[4], D. O. OKONKWO[5], A. B. VALADKA[6], D. M. SCHNYER[1]; [1]The Univ. of Texas At Austin, Austin, TX; [2]Univ. of Maryland, Baltimore, MD; [3]Univ. of California, San Francisco, San Francisco, CA; [4]Icahn Sch. of Med. at Mount Sinai, New York, NY; [5]Univ. of Pittsburgh, Pittsburgh, PA; [6]Virginia Commonwealth Univ., Richmond, VA

Abstract: Traumatic brain injuries are known to cause a range of physiological disturbances, including disturbances in sleep behaviors, which may extend for prolonged periods after injury. The majority of TBI patients suffer from sleep disturbances post-injury in one or more forms including nocturnal insomnia, daytime hypersomnia, frequent awakening from sleep, and delayed sleep onset (Parcell et al., 2006). Although sleep disturbances following TBI are common, the mechanisms underlying the source, duration, and recovery from sleep disturbances is unclear. Potential contributing factors including depression and anxiety, which like sleep disturbances, commonly increase following TBI (Shekleton et al, 2010). Further, while most individuals who experience an increased sleep disturbances, anxiety, and/or depressive symptoms improve during the year following injury, a considerable subset of individuals do not see significant improvement after over a year post-injury (Williams, Lazic, & Ogilvie, 2008). Data collected from the Transforming Research and Clinical Knowledge in Traumatic Brain Injury (TRACK-TBI) pilot study, with follow-up intervals at three months and six months after injury, allows for a more thorough investigation of the pattern of sleep disturbance following TBI and the potential interaction with depressive symptoms more comprehensively than much of the existing research. To examine effects of TBI-related disturbances on sleep, we performed regression analyses on two composite scores of sleep disturbance measures: sleep deficits (trouble falling asleep and sleeping less than usual), and sleep increases (sleeping more than usual and diurnal insomnia). The Brief Symptom Inventory 18 (BSI-18), intake Glasgow Coma Scale, Glasgow Outcome Scale – Extended, age, and sex were used as predictors in our models of sleep disturbance. Consistent with the literature, we found a significant correlation between BSI-18 depression and anxiety scores in our sample ($r = .75$, $p < .001$). Interestingly, both sleep disturbance composites *increased* at the 6-month follow-up relative to the 3-month follow up, and physical outcomes did not significantly improve across follow-ups. Using stepwise regression, we found that anxiety scores and declines in physical outcome best predict both sleep increases and sleep deficits at 6 months. Although depression alone predicts sleep disturbances at 6 months, the model including physical recovery and anxiety provides significantly stronger fit. This suggests that although depression affects sleep abnormalities, lack of physical recovery and increasing anxiety more strongly drive enduring sleep disturbances post-TBI.

Disclosures: **N.R. Griffin:** None. **E. Wickwire:** None. **G.T. Manley:** None. **P. Mukherjee:** None. **J. Yue:** None. **M. Vassar:** None. **W.A. Gordon:** None. **D.O. Okonkwo:** None. **A.B. Valadka:** None. **D.M. Schnyer:** None.

Poster

793. Ischemia: Human

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 793.07/R4

Topic: C.09. Brain Injury and Trauma

Support: NIH F30 grant HD084144

DoD grant W81XWH-11-1-0493

ISMRM Seed Grant

Title: An arterial spin labeling demonstration of decreased functional connectivity following mild traumatic brain injury

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Abstract: Mild traumatic brain injury (mTBI) acutely disturbs both cerebral blood flow (CBF) and functional connectivity in intrinsic brain networks (IBNs). However, the relationship between these, and their relationship to brain recovery, still requires further investigation. While IBNs are usually studied with blood-oxygen-level dependent (BOLD)-based resting state functional magnetic resonance imaging (rsfMRI), recent work has shown that they can be identified with an arterial spin labeling (ASL) method, which is usually performed to obtain information about CBF. Because ASL is more directly related to blood flow than BOLD, it may be better suited for assessing changes in blood flow related to changes in metabolism and therefore more reliably identify IBNs. Additionally, by using one sequence to assess both IBNs and CBF at the same time, we can better identify the relationships between changes in IBN connectivity and CBF. In this study, we performed pulsed ASL (PASL) and rsfMRI in 13 healthy controls and 13 mTBI patients at the acute stage after injury and again one month later. A 20-component independent component analysis (ICA) performed on both the PASL and rsfMRI data revealed 4 IBNs with high similarity between the two methods, including the default mode network (DMN), motor network, subcallosal network, and frontal DMN, as well as similar vascular and cerebrospinal fluid non-network components. The connectivity within the DMN, a network commonly seen to differ in mTBI patients as compared to controls, was compared between patient and control groups and across time points. The only significant between-group results after family-wise error (FWE) correction were found at the second time point, with 108 mm^3 in the right precuneus detected by rsfMRI analysis and 64 mm^3 in the left precuneus and 576 mm^3 in the left angular gyrus detected by PASL as having decreased involvement in the

DMN in patients as compared to controls. Each of these regions was substantially larger before FWE correction, which is known to be very conservative, suggesting that a less conservative method of multiple comparisons correction may better identify the extent of the affected regions. Neither group showed any significant differences between time points after FWE correction. The voxel-wise CBF data was analyzed in the same fashion and revealed no significant differences after FWE-correction. These results suggest that PASL-based functional connectivity analysis can detect similar alterations as rsfMRI-based connectivity analysis and further support the use of ASL for identification of IBNs and associated CBF changes.

Disclosures: N.M. Wiseman: None. **A. Iraji:** None. **E. Haacke:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); MRI patents. **Z. Kou:** None.

Poster

793. Ischemia: Human

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 793.08/R5

Topic: C.09. Brain Injury and Trauma

Support: University of Western Ontario Schulich School of Medicine and Dentistry Dean's Research Initiative Grant

University of Western Ontario Strategic Support Grant

Title: Evidence for neuroreparative mechanisms after a season of concussion-naive play in female varsity rugby players

Authors: *K. Y. MANNING[1], K. BLACKNEY[2], A. BROWN[3], L. FISCHER[6], R. BARTHA[1], T. DOHERTY[4], A. SCHRANZ[1], C. BARREIRA[2], D. FRASER[7], J. HOLMES[5], G. DEKABAN[2], R. MENON[1];
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Abstract: Objective: To determine longitudinal changes in MRI parameters, clinical cognitive measures and blood markers in concussion-naive athletes participating in a contact sport. **Methods:** We followed a female university-level rugby team (n = 54, age 18-23) over a three-year period. Players were evaluated during intense pre-season tryouts and practices and again

after a period of relative rest 2-3 months post-season. Players did not experience a diagnosed concussion during the season or 10-months before the pre-season scan. Diffusion tensor imaging (DTI) was used to quantify white matter structural integrity and resting state fMRI (RS-fMRI) was used to examine functional connectivity between 136 brain regions. Hematology and flow cytometry were used to mechanistically interpret imaging changes, along with Sport Concussion Assessment Tool (SCAT) and Immediate Post-Concussion Assessment and Cognitive Testing (ImPACT) clinical measures. **Results:** After 2-3 months of post-season recovery, there were significant increases in fractional anisotropy and decreases in mean and radial diffusivities along a number of white matter tracts. Decreased RS-fMRI functional connectivity was observed amongst brain regions involving those same tracts. Total leukocyte populations decreased and lymphocytes increased following the 2-3 months of recovery, along with improved verbal, visual, and immediate memory composite scores. Subsequent pre-season data in a subset of returning players did not rebound completely, and exhibited aggregate changes by the next post-season scan. **Conclusions:** The structural and functional MRI changes observed here over single and multiple seasons of contact play suggest transient changes in myelin, a possible neuroreparative mechanism given the recovery of blood inflammatory biomarkers. Future studies are required to investigate the longevity of this structural repair.

Disclosures: K.Y. Manning: None. **K. Blackney:** None. **A. Brown:** None. **L. Fischer:** None. **R. Bartha:** None. **T. Doherty:** None. **A. Schranz:** None. **C. Barreira:** None. **D. Fraser:** None. **J. Holmes:** None. **G. Dekaban:** None. **R. Menon:** None.

Poster

793. Ischemia: Human

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 793.09/R6

Topic: C.09. Brain Injury and Trauma

Support: CERC

Title: Cognitive function in contact sport: effects of cumulative head impact exposure and chronic athletic involvement

Authors: *D. BREWER DELUCE[1,2], T. D. WILSON[2], A. M. OWEN[1];
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Abstract: Repetitive sub-clinical head impacts (SHI) are linked to progressive cognitive decline and post mortem chronic traumatic encephalopathy (CTE) diagnoses in pro contact-sport athletes. Additionally, chronic physical activity seems to provide a neuroprotective benefit

throughout life, and in recovering from concussion. Given this two-pronged interaction we sought to measure the influence of SHI on cognitive function while accounting for long-term athletic participation with non-contact athletic controls.
From 2014-2016 we assessed the cognitive function of 42 male varsity football athletes in the pre- and post-season as well as 13 male varsity rowing athletes on a similar time scale. Cognitive battery scores (www.cambridgebrainsciences.com) were assessed in terms of season-long changes, and in comparison to controls as a representation of career-long SHI and athletic exposure. In the pre-season, there were no significant differences between footballers and rowers, or between rowers and sedentary controls on any metric. In comparison with controls, footballers had impaired scores on 3 tests despite no recent concussion. Importantly, across the season, footballer's demonstrated a decrease in score on a single test of executive function suggesting that a season of SHI exposure may cause measurable cognitive decline.
It is well established that exercise training, while neuroprotective, does not afford robust benefits unless abilities are first compromised by injury or disease. As such, given their chronic SHI exposure, footballers may demonstrate a beneficial effect of exercise allowing them to match the performance of rowers which may be capped by a healthful ceiling effect.
With the addition of post-season rowing scores, we aim to further explore the modulatory effect of exercise on cognition in order to better understand the behavioural representation of cognition in chronic SHI exposure, which is important for developing better assessments of SHI-related cognitive decline and rehabilitative strategies.

Disclosures: D. Brewer Deluce: None. **T.D. Wilson:** None. **A.M. Owen:** None.

Poster

793. Ischemia: Human

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 793.10/R7

Topic: C.09. Brain Injury and Trauma

Support: CDMRP Grant 13129004

Title: Frontal pole cortical deficits in mild, moderate, and severe traumatic brain injuries

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Abstract: Approximately 320,000 service members from Operation Iraqi Freedom/Operation Enduring Freedom have suffered a Traumatic Brain Injury (TBI). Even mild traumatic brain injury (mTBI) may cause chronic disabilities and blast is a common mechanism of TBI. Currently, there are no clear neuroimaging indicators of blast effects.
The following 7 groups (N=620 males) were used in this study: $control_1$ (n=60, age=33.7, SD=8.3), $mTBI_1$ (n=240, age=33.7, SD=8.3), $control_2$ (n=27, age=33.0, SD=8.6), nonblast-mTBI (n=60, age=33.1, SD=7.6), blast-mTBI (n=180, age=33.0, SD=4.9), moderate TBI (N=41, age=33.4, SD=7.8), and severe TBI (n=12, age=32.9, SD=7.1). Patients had chronic TBI symptoms (at least 3 months) before imaging using a 3T Discovery 750 MRI. Individual surface-based cortical thickness maps were generated in FreeSurfer and smoothed using a 10 mm kernel. The first-level analysis calculated a two-sample ($control_1$, $mTBI_1$) cluster based permutation test. It detected a significant cluster (mTBI-mask) in which decreased thickness was seen in mTBI subjects relative to the control group. Regions identified within the mTBI-mask included right-lateralized frontal pole, rostral middle frontal gyrus and sulcus, pars orbitalis, lateral orbitofrontal cortex, superior frontal cortex, and medial orbitofrontal cortex.
Second-level analyses were conducted, comparing cortical thickness values within the mTBI-mask between the remaining groups. Targeted two-sample t-tests resulted in following: $control_2$ > blast-mTBI ($p < 0.004$, d=0.61), $control_2$ > moderate TBI ($p < 0.06$, d=0.41), and $control_2$ > severe TBI ($p < 0.05$, d=0.66). Interestingly, nonblast mTBI > blast-mTBI ($p < 0.03$, d=0.29), which may indicate that the mTBI-mask is sensitive to the blast mechanism as well. P-values are one-sided since the mTBI mask assumes cortical thinning in TBI and blast.
In conclusion, regional decreases in cortical thickness may be used to differentiate between controls and TBI subgroups. Within mTBI, these effects may be further modulated by blast exposure.
Disclaimer: The views expressed in this abstract are those of the author and do not necessarily reflect the official policy or position of the Department of the Navy, Army, or Air Force, the Department of Defense, nor any agency of the U.S. Government.

Disclosures: **C. Eierud:** None. **D.E. Nathan:** None. **T. Teslovich:** None. **G. Riedy:** None. **G. Bonavia:** None. **J. Ollinger:** None.

Poster

793. Ischemia: Human

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 793.11/R8

Topic: C.09. Brain Injury and Trauma

Title: The accuracy of head impact sensors and concussion assessment tools in collegiate football players

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Abstract: Prior research suggests that repetitive head impacts (RHI) in sport correlate with neurological deficits later in life (Bailes et al., 2014; Montenigro et al., 2016). To better establish this relationship, we need sensors that accurately detect head impacts and clinical tools that accurately diagnose concussions. Here, we performed a field study with two objectives: i) to validate a head impact sensor and ii) to explore the diagnostic accuracy of two clinical tools: the Sport Concussion Assessment Tool – 3rd Edition (SCAT3; McCrory et al., 2012) and the King-Devick Test (KDT). Male collegiate football players (n=35) wore the xPatch, a wireless sensor that adheres to the mastoid process and records head impact kinematics, for 1 or 2 football seasons. We collected weekly neurocognitive data and observed 8 concussions (diagnosed by the team physician). Using video, we classified all head impacts detected by the sensor during games as true positives, true negatives, false positives and false negatives and then calculated the sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of the xPatch's impact classification algorithm. We also correlated the cumulative peak head kinematics to the number of impacts detected. Receiver operator characteristic (ROC) curves were generated and the area under the curve (AUC) for each component of the SCAT3 and KDT was calculated using both the absolute score and change from pre-season baseline. The xPatch's algorithm had a sensitivity of 82.2%, specificity of 74.9%, PPV of 80.6%, and NPV of 76.8%. Cumulative head impact kinematics correlated strongly with the number of head impacts (r^2=0.76-0.88) when including all impact events detected by the sensor (true and false positives). These correlations improved (r^2=0.98-0.99) when only true positive and false negative impacts were included. The AUCs for change scores were higher ($p<0.05$) than for absolute scores for the Balance Error Scoring System (BESS; foam trials), Standardized Assessment of Concussion (SAC) and KDT. Using change scores we saw an AUC of 0.91 for the Graded Symptom Checklist (GSC), 0.80 for KDT, 0.65 for BESS and 0.64 for SAC. These findings suggest that a simple measure of RHI (number of impacts) can accurately predict the head's cumulative biomechanics. They also emphasize a need to develop more reliable tests of balance and executive function in concussed patients. Improved impact sensors and concussion assessment tools will allow us to better understand the link between RHI and later-life neurological deficits.

Disclosures: A.D. Rebchuk: None. **H.J. Brown:** None. **G.P. Siegmund:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); MEA Forensic Engineers & Scientists. **J. Blouin:** None.

Poster

793. Ischemia: Human

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 793.12/R9

Topic: C.09. Brain Injury and Trauma

Support: Indiana Spinal Cord and Brain Injury Research Fund

NIH 5R21DC013974

Indiana CTSI

Title: The effects of concussion-prone athletics on brain function: A comparison of football, cross-country, & socioeconomically matched non-athletes using fMRI

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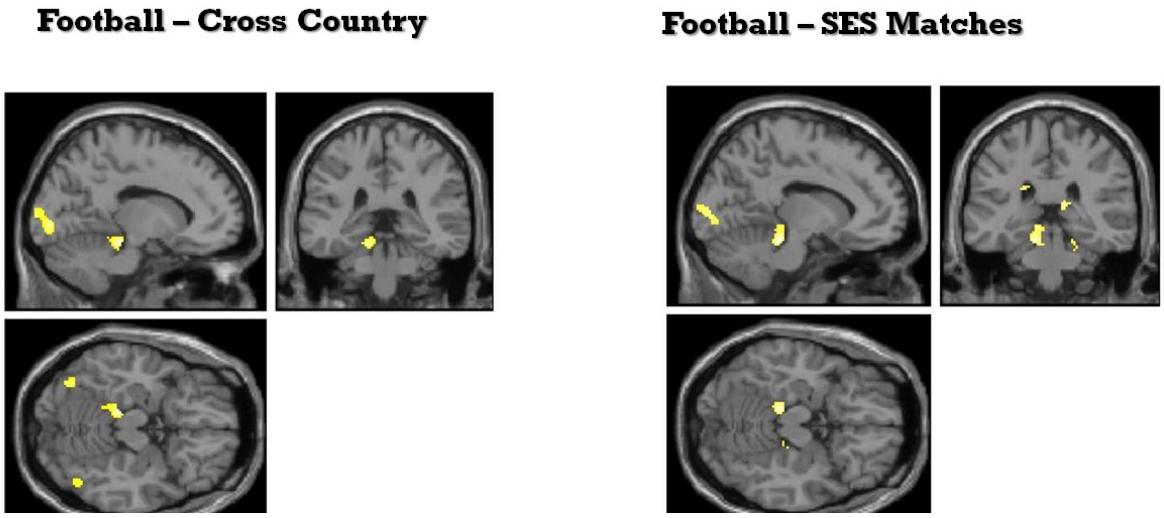
Abstract: Concussion is prevalent in many of the most popular sports. Awareness of the potential negative impact of participation in concussion-prone sports has led to increased research on the topic, including examining the risks of subconcussive impacts. Recent research has shown that sustaining multiple blows to the head, even at subconcussive levels, may affect white matter integrity (McAllister et al., 2014). Whereas concussions are defined by the American Association of Neurological Surgeons as “a clinical syndrome characterized by immediate and transient alteration in brain function” which can be diagnosed with some degree of certainty, multiple high frequency subconcussive blows could result in less overt and immediate behavioral deficits. For example, Talavage et al. (2014) showed fMRI and neurocognitive differences between high-school football athletes that sustained a low number compared to a high number of subconcussive blows throughout a season. To explore the potential long-lasting effects of playing contact sports, the current study recruited 19 college upperclassmen from the Indiana University football team prior to the start of their season and prior to contact practice; therefore none of the athletes reported having a recent concussion. Two control groups were also examined - non-contact sport athletes, cross-country runners, and non-athletes who were socioeconomically matched to the football players. Both groups were recruited from Indiana University. Participants performed an ocular-motor smooth pursuit task during fMRI acquisition. Football players showed significantly increased activation in the occipital cortex and the cerebellum compared to both control groups. Additionally, when comparing the two control groups, they showed no differences in activation. These results suggest that football players require increased effort to perform the ocular-motor task. Further

research is required to determine whether and to what degree subconcussive impacts contribute to such differences, and how long lasting those changes might be.



Disclosures: **D.A. Kellar:** None. **B.A. Caron:** None. **N. Port:** None. **F. Pestilli:** None. **H. Cheng:** None. **S.D. Newman:** None.

Poster

793. Ischemia: Human

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 793.13/R10

Topic: C.07. Ischemia

Support: NIH 1R01 HD049792

Title: Effects of caffeine and hypothermia on neuropathology in P6 rats with experimentally induced hypoxic ischemic brain injury

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Abstract: Neonatal hypoxic ischemic (HI) injury reflects reductions in blood and/or oxygen supply, as often seen preterm/low-birthweight infants. Neural HI injuries in this populations stem from hemorrhagic or ischemic vascular events, and/or or systemic hypoxia, and typically manifest as white matter damage (with more subtle gray matter damage in older preterms). HI injuries are associated with later deficits in cognition and behavior, including motor skills, memory, and language. To improve long-term outcomes, various neuroprotective interventions have been explored. In term infants with HI stemming from birth complications, the primary intervention is hypothermia (aka "cooling"). Mechanistically, hypothermia hinders aspects of apoptosis and thus reduces downstream tissue loss. We recently reported beneficial effects of even brief and subtle intra-insult hypothermia (i.e., during insult) in a postnatal day 7 (P7) HI rat model. More recently, putative benefits of extended hypothermia (3 hours) in a late preterm HI model (P6 HI) were also examined, to assess whether benefits of hypothermia might transfer to a late preterm population. We were surprised to find that hypothermia failed to rescue behavior in P6 HI subjects, and even appeared detrimental to shams (Contreras-Mora et al., 2015). Other therapies under study include caffeine, a non-selective adenosine antagonist used as a respiratory stimulant in ventilated preterm infants. Previous studies in our lab showed a protective behavioral benefit from caffeine when HI injury was induced on postnatal (P) day 7 in rats (Alexander et al., 2013), and more recently, on P6 (Contreras-Mora et al., 2015). Importantly, this protection was optimal when caffeine was administered immediately following the HI insult. The current study sought to investigate the potential combined beneficial effect of caffeine and hypothermia on neuropathology in a P6 HI model. To accomplish this, subjects who had received P6 HI along with either caffeine treatment, extended hypothermia, or no treatement were compared to respective shams. Specifically, we assessed volumes of the cortex, hippocampus, internal capsule, lateral ventricles, and corpus callosum. Measures were quantified *post-mortem* to determine whether caffeine and/or hypothermia was able to ameliorate brain injury. Volumetric measures were also correlated with behavioral measures, to determine whether gross
neuropathology was able to provide an accurate prediction for long-term behavioral outcomes. Results offer important information to aid clinicians in determining the most optimal neuroprotective strategy for at-risk infants with HI.

Disclosures: A.L. Smith: None. **M. Potter:** None. **H.M. Contreras-Mora:** None. **T.S. Rosenkrantz:** None. **R.H. Fitch:** None.

Poster

793. Ischemia: Human

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 793.14/R11

Topic: C.07. Ischemia

Support: Grant-in Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science and Technology of Japan

Title: Metal-metal interactions in zinc-induced neurotoxicity: the possible involvements in the pathogenesis of vascular dementia

Authors: *M. KAWAHARA[1], D. MIZUNO[2], K.-I. TANAKA[1];
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Abstract: Zinc (Zn) is accumulated in the synaptic vesicles and co-released with glutamate during the neuronal excitation. It is widely accepted that excess Zn released into the synaptic clefts under the condition of transient global ischemia plays central roles in the neurodegeneration in vascular dementia. We have investigated the molecular mechanism of Zn-induced neurotoxicity using immortalized hypothalamic neurons (GT1-7 cells). Zn^{2+} caused apoptotic death of GT1-7 cells after 24h. We found that carnosine (beta-alanyl histidine) and anserine (1-methyl carnosine) protected against Zn-induced neurotoxicity. Furthermore, our results demonstrated that carnosine and anserine protected against Zn-induced neurotoxicity not by preventing increases in intracellular Zn^{2+} but by participating in the regulation of the endoplasmic reticulum (ER) stress pathway and the activity-regulated cytoskeletal protein (Arc). We also investigated the role of other metal ions including Cu^{2+}, Mn^{2+}, Fe^{2+}, Fe^{3+}, Ni^{2+}, and Al^{3+} in Zn-induced neurotoxicity. Although the co-existence of Fe^{2+}, Fe^{3+}, or Ni^{2+} did not influence Zn neurotoxicity, Al^{3+} attenuated Zn-induced neurotoxicity in a dose-dependent manner. Meanwhile, Cu^{2+} or Mn^{2+} remarkably enhanced the neurotoxicity of Zn. Carnosine did not attenuate Cu-induced neurotoxicity nor Mn-induced neurotoxicity. Considering that Cu is also accumulated in the synaptic vesicles and released into the synaptic clefts, it is possible that Zn and Cu interact in the synaptic clefts and plays essential roles in the pathogenesis of vascular dementia or other neurodegenerative diseases. Furthermore, given advantageous properties of carnosine and anserine (relatively nontoxic, heat-stable, and water-soluble), dietary supplementation with them may be an effective strategy for the preventionor treatment of neurodegenerative diseases such as ischemia induced neuronal death and VD. Based on this idea, we have developed a convenient system for the quantitative analysis of carnosine and analyzed their amounts in various foods.

Disclosures: **M. Kawahara:** None. **D. Mizuno:** None. **K. Tanaka:** None.

Poster

793. Ischemia: Human

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 793.15/R12

Topic: C.07. Ischemia

Support: Fonds de la Recherche en Santé Québec (FRQS) PhD Training Award

Fonds de la Recherche en Santé Québec (FRQS) Clinical Research Scholar Career Award Junior 1

Canadian Institutes of Health Research (CIHR) Operating Grant

Title: Could sildenafil repair hippocampal brain injuries in term neonatal encephalopathy?

Authors: *A. A. YAZDANI[1], P. BALIAN[1], Z. KHOJA[1], K. CUI[2], G. LUHESHI[2], P. WINTERMARK[1];
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Abstract: INTRODUCTION: Neonatal encephalopathy remains a major cause of mortality and morbidity worldwide. Neonatal encephalopathy often leads to chronic activation of inflammatory cascades that hinders repair of the developing brain. Microgliosis and astrogliosis are activated in the rat model of hypoxia-Ischemia (HI). Hippocampus in particular is a well documented site of neuronal injury in neonatal HI. Sildenafil has been shown to reduce neuroinflammation in rat models of multiple sclerosis and Alzheimer disease, and it is already used safely to treat persistent pulmonary hypertension in human newborns. It may thus also be useful in newborns to modulate neuroinflammation following hypoxia-ischemia.
OBJECTIVE: To determine how hippocampal brain injury develops and neuroinflammation is activated after neonatal hypoxia-ischemia (HI) at term-equivalent age and whether sildenafil may modulate this activation and impact neuronal number and vascular density.
METHODS: Neonatal HI was induced in male Long-Evans rat pups at postnatal day 10 (P10) by left common carotid ligation followed by 2-hour exposure to 8% oxygen. Sham operated rat pups served as control. Both groups were administered 0 (vehicle), 2, 10 or 50 mg/kg of sildenafil twice daily by oral gavage, starting from 12 hours post-HI for 7 consecutive days. At P30, rats were sacrificed and their brains extracted. CA1, CA3 and dentate gyrus (DG) areas of the ipsilateral hippocampus were analyzed for microgliosis (Iba1) and astrogliosis (GFAP), neuronal number (NeuN), and vascular density (collagen IV).
RESULTS: HI caused a significant increase in the number of microglia and astrocytes in CA1, CA3 and DG regions of the hippocampus, compared to sham vehicle rat animals. There were no significant changes in neuronal number or vascular density in the hippocampus of HI vs sham

animals. Higher doses of Sildenafil (10mg/kg and 50mg/kg) significantly reduced the number of activated microglia and reactive astrocytes in CA1 and dentate gyrus of the hippocampus in HI animals. The highest dose of Sildenafil (50mg/kg) significantly increases neuronal number in the dentate gyrus of HI animals compared to sham vehicle animals. There were no changes in vascular density between the treatment groups and the control group.
CONCLUSION: Oral Sildenafil, especially at higher dosage, may reduce neuroinflammation following neonatal hypoxic-ischemia and increases neuronal number in the hippocampus.

Disclosures: A.A. Yazdani: None. **P. Balian:** None. **Z. Khoja:** None. **K. Cui:** None. **G. Luheshi:** None. **P. Wintermark:** None.

Poster

793. Ischemia: Human

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 793.16/R13

Topic: C.07. Ischemia

Support: AHA 14GRNT18190012

NIH R01 NS092645

NIH RO1 NS046072

NIH T32 HD007186

Title: Inhibition of sustained TRPM2 channel activity represents a novel neuro-restorative strategy to improve memory function after global cerebral ischemia

Authors: *R. M. DIETZ[1], J. E. ORFILA[2], G. DENG[2], P. S. HERSON[2];
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Abstract: Introduction: Cardiac arrest (CA) is a major cause of mortality and morbidity and results in global cerebral ischemia and hypoxic-ischemic injury. The consequent neuronal damage results in long-term cognitive impairments, including memory disturbances and more general executive disorders. Memory disorders commonly observed following CA are readily explained by the selective vulnerability and dysfunction of CA1 pyramidal cells of the hippocampus. This study investigated the role of the non-selective cation channel TRPM2 on ischemia-induced synaptic dysfunction.
Methods: Male and female C57Bl/6 mice (20-25g) underwent 8 min CA and cardiopulmonary

resuscitation (CA/CPR). Hippocampal CA1 function and synaptic plasticity were evaluated using acute brain slices 7 days after CA/CPR or sham controls. Synaptic plasticity was measured by long term potentiation (LTP) of synaptic signals following theta-burst stimulation (TBS). Increase in field excitatory post-synaptic potential slope 60 min after TBS was analyzed to measure LTP. Slices or mice were treated with our novel peptide inhibitor of TRPM2, termed tatM2NX, as indicated below.
Results: Recordings obtained in slices from male mice 7 days after CA/CPR exhibited impairment of LTP when cells were exposed to the same TBS stimulation that stimulates robust LTP in sham control mice (161±9%, n=6 in sham compared to 105±9%, n=8 on day 7). Remarkably, bath application of the TRPM2 channel inhibitor tatM2NX (1μM) for 2 hours reversed the CA/CPR-induced loss of LTP, recovering to 149.8±26% (n=3; $P<0.05$ compared to paired 7 day CA/CPR slices recorded from the same animal). In vivo administration of tatM2NX (20 mg/kg administered ip on day 6 after CA/CPR) reversed CA/CPR-induced impairments in LTP, recovering to 171±11% (n=6 recordings from 4 mice treated with peptide; $P<0.05$ compared to 7 day CA/CPR slices). Similar data was observed in female mice (data not shown). Finally, memory function was measured using a well-established hippocampal-specific memory task, contextual fear conditioning. CA/CPR causes a decrease in freezing behavior, indicating lack of memory. This was reversed in CA/CPR mice given tatM2NX (20 mg/kg, single ip injection 24 hr before testing) on day 7 post-CPR compared to vehicle-injected mice
Conclusions: These data indicate that following global cerebral ischemia synaptic TRPM2 channels are chronically activated, contributing to long-lasting impairments of the remaining hippocampal network. Therefore, inhibition of TRPM2 channels at chronic timepoints following ischemia may represent a novel strategy to improve functional recovery after cerebral ischemia.

Disclosures: R.M. Dietz: None. **J.E. Orfila:** None. **G. Deng:** None. **P.S. Herson:** None.

Poster

793. Ischemia: Human

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 793.17/R14

Topic: C.07. Ischemia

Title: Vasodilatory regulation failure in transient postischemic hyperperfusion in rats

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Abstract: [Introduction] Post-ischemic hyperperfusion was observed in transient ischemic tissue 48 hours after middle cerebral artery (MCA) occlusion [1,2]. A possible physiological mechanism would be vasodilatory regulation failure with full relaxation of resistance vessels in ischemic tissue. To confirm the physiological reason, we have performed two photon microscopy observation and experiments for revealing vasodilatory response with carbon dioxide (CO_2) inhalation. [Methods] Six male Sprague-Dawley rats were used. Transient ischemic regions were induced by modified model of MCA occlusion [3]. The model of twisting the monofilament at the left MCA for temporally interruption of blood flow and the right and left common carotid arteries with temporally clipping in thirty minutes. Before the transient ischemic operation, a cranial window (diameter of 2 mm) was prepared for optical access to the cortical vasculature in left hemisphere. We have confirmed the post-ischemic hyperperfusion in continuous arterial spin labeling in 4.7 tesla magnetic resonance image 24 hours after the operation. Then we observed two-photon microscopy with intravenously injected rhodamine-dextran two days after the operation. In the microscopic observation, each animal was mechanically ventilated under paralyzed condition with rocuronium bromide and isoflurane anesthesia. [Results and Discussion] Arterial blood CO_2 tension was increased from 38.0±4.5 to 44.5±3.8 mmHg with 0.4 % CO_2 in anesthetic carrier gas and increased to 52.0±2.8 mmHg with 0.8% CO_2. Vessel image was reconstructed by maximum intensity projection from images acquired from cortical surface to the depth of 0.5 mm. Subtracted image obtained from hypercapnia and normocapnia was evaluated for vasodilatory regulation. Arterial diameter was almost same between CO_2 inhalation and normo-capnia condition. The arterial vasodilated response to hypercapnia in the ischemic tissue was not observed in this study. The post-ischemic hyperperfusion might be related to the vasodilatory regulation failure. [References] [1] Wang et al., JCBFM 22; 253-261(2002), [2] Nakamura et al., Proc IEEE EMBS 30, 839-842 (2008), [3] Chen et al., Stroke 17; 738-743 (1986)

Disclosures: **K. Nakamura:** None. **T. Mutoh:** None. **K. Sasaki:** None. **Y. Taki:** None. **T. Ishikawa:** None. **T. Kinoshita:** None.

Poster

793. Ischemia: Human

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 793.18/R15

Topic: C.07. Ischemia

Support: CoBRE P30GM103400/PI:Liu

Genise Goldenson Foundation Grant

Title: Chronic MRI abnormalities in adult rats following *In utero* insult: modeling the brain injury associated with chorioamnionitis

Authors: *T. R. YELLOWHAIR[1], S. ROBINSON[2], L. L. JANTZIE[1];
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Abstract: Preterm infants are prone to numerous neurological deficits including cerebral palsy, epilepsy, sensory processing impairment and intellectual disability. Improved understanding of chronic microstructural brain abnormalities in preterm infants using complex diffusion imaging will facilitate development of biomarkers and new therapeutic strategies for this vulnerable patient population**.** Here, using our established rat model that combines *in utero* placental perfusion deficits and intra-amniotic inflammation consistent with chorioamnionitis, we hypothesized prenatal injury would induce significant white and gray matter microstructural and diffusion abnormalities on magnetic resonance imaging (MRI). On embryonic day 18 (E18), under anesthesia, laparotomy was performed on pregnant Sprague-Dawley dams with transient (1hr) uterine artery occlusion (TSHI) and intra-amniotic injection of lipopolysaccharide (LPS, 4 μg/sac). Shams had anesthesia with laparotomy for 1hr. Laparotomy was then closed, and rat pups were born at term (E22). *Ex vivo* MRI occurred on postnatal day 35 (P35, n=7-11/group) on a 4.7T scanner. Compared to shams, TSHI+LPS animals have significantly decreased fractional anisotropy (FA) in the corpus callosum (t test, p=0.007), and increased axial diffusivity (AD, p=0.03) and radial diffusivity (RD, p=0.004). Also, TSHI+LPS animals have decreased FA in the external capsule (p=0.0001), striatum (p=0.04), hippocampus (p=0.02) and thalamus (p=0.0004), with concomitant abnormalities in AD and RD. In sum, prenatal hypoxia-ischemia and intra-amniotic LPS yields significant, widespread diffusion abnormalities and impaired microstructural coherence in adult rats. These preclinical data corroborate regional diffusion and microstructural brain abnormalities observed in children with deficits from preterm birth complicated by chorioamnionitis. Sophisticated imaging analyses will define radiological biomarkers of chronic brain injury associated with complications from preterm birth and refine the development and indications for emerging therapeutic interventions.

Disclosures: T.R. Yellowhair: None. **S. Robinson:** None. **L.L. Jantzie:** None.

Poster

793. Ischemia: Human

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 793.19/R16

Topic: C.07. Ischemia

Support: NIH HL118861

AHA WSA winter 2015 Beginning Grant-in-Aid, 15BGIA25750063

Title: Microrna-210/iscu axis mediates neuronal cell death in neonatal hypoxic-ischemic brain injury

Authors: *Q. MA, Y. LI, C. DASGUPTA, L. ZHANG;
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Abstract: Perinatal hypoxia-ischemia (HI) is a leading cause of acute mortality and chronic brain injury in newborns with a high risk of hypoxic-ischemic encephalopathy. MicroRNA-210 (miR-210) is "*the Master Hypoxamirs"* that are regulated by hypoxia. A key target of miR210 is iron-sulfur cluster scaffold protein (ISCU) and the miR-210/ISCU axis has been reported to be involved in pathological processes in response to hypoxia. Our recent study demonstrated that inhibition of miR-210 provided neuroprotection in neonatal HI brain injury; however, the underlying mechanisms remain elusive. Postnatal day 7 (P7) Sprague Dawley rat pups were subject to ligation of right common carotid artery followed by hypoxic (8% O2) treatment. At 4 hours after HI, miR-210 inhibitor, complementary locked nucleic acid oligonucleotides (LNA-miR-210) was administered intracerebroventricularly into ipsilateral hemisphere of rat brains. The results showed that neonatal HI insult significantly reduced ISCU protein levels and respiratory chain complex I activity in isolated brain mitochondria and increased 3-nitrotysine levels in the brain tissue, which were blocked by LNA treatment. In addition in P5 rat pups, miR-210 mimic or ISCU siRNA was injected into right hemisphere of rat brains, 48 hours after injection neonatal HI insult was conducted. The results showed that miR-210 mimic or ISCU siRNA injection resulted in downreguation of ISCU protein levels and increased susceptibility of the neonatal brain to HI brain insult. To investigate the role of miR-210/ISCU axis in intracellular ROS generation and neuronal cell death, primary cortical neurons were isolated and treated with oxygen-glucose deprivation (OGD) at DIV7. Consistent with the *in vivo* findings, OGD induced upregulation of miR-210 in primary cortical neurons, increased caspase 3 and 9 activities and reduced cortical neuron viability by increasing LDH release. In addition, OGD significantly reduced ISCU protein levels and complex I activity and increased intracellular ROS, which were revered by LNA treatment. Thus, the results demonstrate that miR-210/ISCU axis mediates oxidative stress and neuronal cell death in neonatal HI brain injury.

Disclosures: Q. Ma: None. **Y. Li:** None. **C. Dasgupta:** None. **L. Zhang:** None.

Poster

793. Ischemia: Human

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 793.20/R17

Topic: C.07. Ischemia

Support: RGC GRF Award 2010/2011 HKU 773210M

Title: Inflammation and vulnerable blood vessels aggravate ischemic injuries in a mouse model of Type 1 diabetes

Authors: *A. C. LO, A. K. W. LAI;
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Abstract: PURPOSE: Patients with type 1 diabetes are more prone to cerebrovascular mortality after stroke and display a more severe post-ischemic outcome. Their median survival is only half when compared with those in the general population. In the current study, we aim to elucidate the potential mechanisms contributing to the exacerbation.
METHOD: $Ins2^{Akita/+}$ mice, a type 1 diabetic mouse model, and their wildtype ($Ins2^{+/+}$) littermates at 12 weeks of age were challenged with experimental stroke by middle cerebral artery occlusion (MCAO) for 2h followed by 2h of reperfusion. Survival rate and neurological deficits were assessed at the end of reperfusion. Their brain slices were stained with 2, 3, 5-triphenyltetrazolium chloride for estimation of the infarction, hemispheric swelling and hemorrhagic area. Western blot analysis was used to compare levels of ZO-1, VEGF and pErk for assessment of blood vessel integrity and inflammation. ER-stress (ATF6, BiP, CHOP, PERK and IRE-1α) and autophagy (Atg12, Bcn1, LC3-a, LC3-b and p62) response were also assayed using real-time PCR.
RESULTS: Decreased survival rate, increased neurological deficits as well as increased infarct and hemorrhage after MCAO were observed in $Ins2^{Akita/+}$ mice. There were also significant down-regulation of ZO-1 protein and remarkable up-regulation of VEGF and pErk protein. mRNA expression of CHOP was further augmented in $Ins2^{Aktia/+}$ mice.
CONCLUSION: $Ins2^{Akita/+}$ mice displayed high mortality after MCAO, similar to that in type 1 diabetic patients upon stroke. Augmented cerebral hemorrhage and decreased ZO-1 expression indicated a lower blood vessel integrity in $Ins2^{Akita/+}$ mice. Provoked inflammatory response and ER-stress may play important roles in the exacerbation of the ischemic brain, which was evidenced in increased infarction in $Ins2^{Akita/+}$ mice.

Disclosures: **A.C. Lo:** None. **A.K.W. Lai:** None.

Poster

793. Ischemia: Human

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 793.21/S1

Topic: C.07. Ischemia

Support: KAKENHI 25462236

Title: Responses of human mesenchymal stem/stromal cells on brain ischemia.

Authors: *H. OHTAKI[1], S. TANIGUCHI[2], Y. TANAKA[2], J. WATANABE[3,2], K. MIYAMOTO[5], A. YOSHIKAWA[4], K. DOHI[6], K. HONDA[2];
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Abstract: It is increasing evidences that transplantation of human mesenchymal stem/stromal cells (hMSCs) suppressed neuronal cell death after several central nervous system damages such as stroke and trauma. We have reported that transplanted hMSCs modified microglial state to alternative activating phenotype with suppressing inflammatory cytokines after the damages. However, it is still unclear hMSCs' responses in the tissues after the transplantation because the number of hMSCs was obviously smaller than the recipient cells and the responses were masked by the recipient tissues. The purpose of the present study is to understand the reaction of hMSCs in the brain. We exposed condition medium of mouse hippocampal homogenate which obtained from 1day after transient forebrain ischemia (ischemic brain condition medium: ibCM) to mimic hippocampal state after ischemia and surveyed the transcriptome in comparison with non-ischemic hippocampal homogenate (brain condition medium: bCM). Moreover, the hMSCs were exposed by ibCM of different ischemic region to determine the relation of ischemia and the responses. Finally, the hMSCs were exposed ibCM in cytokines knockout (KO) mice. The hMSCs exposed by ibCM increased 98 genes >2-fold more and decreased 78 genes <2-fold more to compare with those by bCM. Up-regulated genes included chemokines and CCL2 was the highest expression. The CCL2 increased in the media after hippocampal ibCM, but not cortical and cerebellar ibCM by ELISA. Moreover, the increase of CCL2 was suppressed by the ibCM in IL-1 and TNF-alpha KO mice. These results suggest that transplanted hMSCs responded to pro-inflammatory cytokines in the ischemic brain and released several chemokines.

Disclosures: **H. Ohtaki:** None. **S. Taniguchi:** None. **Y. Tanaka:** None. **J. Watanabe:** None. **K. Miyamoto:** None. **A. Yoshikawa:** None. **K. Dohi:** None. **K. Honda:** None.

Poster

793. Ischemia: Human

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 793.22/S2

Topic: C.07. Ischemia

Support: UBACYT 20720130100014BA

Title: Synaptic and glial modifications induced by perinatal asphyxia

Authors: *F. CAPANI[1,2], M. HERRERA[2], A. GONZALEZ[3], C. QUARRACINO[1], S. MUCCI[1], R. KOLLIKERS-FRERS[1];
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Abstract: Perinatal asphyxia (PA) induces short and long term synaptic and cytoskeleton alterations that have been associated with neuronal cell death following hypoxia. The aim of this study was to elucidate the mechanisms underlying this dysfunction. We used a well-established murine model of PA, which was modified in our laboratory. After one and 2 months of the PA insult, an increase in the F-actin staining in neostriatum and hippocampus synapses was observed using correlative fluorescent electron microscopy for phalloidin-eosin. Mushroom-shaped spines showed the most consistent staining. Strong alterations in the dendrite and astroglial cytoskeleton organization were found at 4 months of PA. After 6 months of PA, we observed an increase in ubiquitination level and an increment of rat neostriatum post synaptic densities (PSDs) thickness, which was related to the duration and severity of the hypoxic insult. Using 3-d reconstruction and electron tomography we observed clear signs of damage in the asphyctic PSDs. These changes were correlated with intense staining for ubiquitin. Finally, in 18 months old rat we encountered a reduction in the number of synapses in the PA animals related with a decrease in BDNF staining. Overall, these results demonstrate that synaptic dysfunction following PA might be produced by early changes in the actin organization and long-term misfolding and aggregation of proteins in the PSDs.

Disclosures: **F. Capani:** None. **M. Herrera:** None. **A. Gonzalez:** None. **C. Quarracino:** None. **S. Mucci:** None. **R. Kollikers-Frers:** None.

Poster

793. Ischemia: Human

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 793.23/S3

Topic: C.07. Ischemia

Title: Resveratrol sustain neuronal survival through AMPK activation

Authors: *A. P. RAMIREZ, SR[1], I. ALQUISIRAS-BURGOS[2], A. ORTIZ-PLATA[3], J. PEDRAZA-CHAVERRÍ[4], P. AGUILERA[2];
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Abstract: Cerebral Ischemia results from occlusion of a major cerebral artery and involves a sequence of molecular events that induce cell death. Decrease of cerebral blood flow restricts the delivery of substrates predominantly oxygen and glucose with consequent decline in the metabolism of energy. Interestingly, neuronal cell death can be prevented by modulating the energetic state of the cell. Antioxidants such as resveratrol (RSV) exert a neuroprotective effect after ischemia through mechanisms closely associated with activation of ATP generating pathways in which AMP-activated kinase (AMPK) is involved. **Objective**. We investigated the effect of RSV treatment on AMPK activation on ischemia-induced cellular damage. **Methods.** Male Wistar rats (280 to 350 g) were subjected to 2 h of middle cerebral artery occlusion (MCAO) followed by 24 h of reperfusion. RSV was administered (1 mg/kg; i.v; diluted in 50% ethanol) at the onset of reperfusion. Damage to the brain tissue was evaluated by the technique of 2,3,5-Triphenyltetrazolium chloride (TTC) dye. Rat primary neuronal culture (E17) was used at 7 - 8 days in vitro. Cultures were stimulated with glutamate (100 μM) for 10 min and were evaluated after 20 min and 24 h of recovery. Resveratrol (100 μM) was administered at the start of recovery. In cultures, cell viability was assessed by MTT, LDH release and Trypan blue exclusion. Mitochondrial calcium buffer capacity was analyzed with the fluorescent probe Fluo-4 AM. Western blotting was used to evaluated AMPK activation through phosphorylation. **Results.** Administration of RSV to rats subjected to MCAO/reperfusion reduced the infarct area and increased the survival rate. In neuronal cultures, excitotoxicity increased cellular death. This effect was reversed by RSV and restored after AMPK inhibition with compound C. Western Blotting results indicated that excitotoxicity increases AMPK phosphorylation after 20 min of recovery. RSV induced an additional increase on the levels of pAMPK, effect that was diminished with compound C. Excitotoxicity increased the number of cells unable to buffer the cytoplasmic calcium, suggesting that mitochondrial function was altered. RSV partially prevented mitochondrial losing buffer capacity. **Discussion.** We observed that the use of the natural antioxidant RSV at the onset of reperfusion has a beneficial effect against cerebral

ischemia through activation of cell survival pathways dependent on AMPK activation. Our results suggest that the neural activation of AMPK may be an important mediator in the neuroprotective activity of RSV, probably through the restoration of energy metabolism of the cell.

Disclosures: A.P. Ramirez: None. **I. Alquisiras-Burgos:** None. **A. Ortiz-Plata:** None. **J. Pedraza-Chaverrí:** None. **P. Aguilera:** None.

Poster

793. Ischemia: Human

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 793.24/S4

Topic: C.07. Ischemia

Support: NINDS, a division of NIH, RO1075035

AHA Fellow to Faculty Award (GCJ)

Title: Alternative splicing of leukocyte mRNAs differs after intracerebral hemorrhage and ischemic stroke of different etiologies

Authors: *C. J. DYKSTRA-AIELLO, G. C. JICKLING, B. ANDER, X. ZHAN, D. LIU, H. HULL, M. ORANTIA, C. HO, F. R. SHARP, B. S. STAMOVA;
Neurol., Univ. of California, Davis, Sacramento, CA

Abstract: Background: Previous transcriptome research in blood of ischemic stroke (IS) patients has used 3'-biased microarrays, which are unable to capture changes in a majority of alternatively spliced transcripts. Alternative splicing (AS) has been implicated in many diseases, but its role in IS and intracerebral hemorrhage (ICH) is a new domain. Thus, we hypothesized that AS differs among 1) IS, ICH and vascular risk factor controls (VRFC), and 2) three main IS causes (Cardioembolic, Large Vessel and Lacunar), ICH and VRFC.
Methods: We studied differential alternative splicing (DAS) in whole blood of IS, ICH and VRFC males using Affymetrix Human Transcriptome Arrays 2.0 which probe exon junctions (n=36, 12 per group). To study DAS between IS causes, ICH and VRFC, we used RNA-seq (Illumina, 200M 2X100bp reads/sample) on 20 whole blood samples (n=4 males per group). We assessed DAS with ANOVA (FDR $p<0.05$) and calculated differential exon-usage between each group ($p<0.0005$; fold change>|1.2|). We compared the results of RNA-seq-determined differentially expressed exons to a separate set of ICH and VRFC subjects (n=48, 24 per group) using HTA arrays. We evaluated group separation by principal components analysis.

Results: Differential expression of 90 exons separated the IS, ICH and VRFC groups. These included genes such as: HGF (hepatic growth factor), involved in thrombosis and angiogenesis, and NOS1 (nitric oxide synthase 1), implicated in stroke risk. 412 genes displayed DAS and 308 exons with differential expression separated ICH, the three main causes of IS and VRFC. Several genes with DAS belonged to NF-kB and PPAR signaling pathways including: SRA1, steroid receptor RNA activator 1, and Akt1, all of which have been implicated in experimental ICH pathogenesis. NF-kB transcription factor perpetuates inflammation and is activated by ICH. Finally, there were 108 exons with differential expression between ICH and VRFC in the RNA-seq samples. Eighty of these exons differentiated the majority of ICH from VRFC in a separate subject set.
Conclusions: We provide evidence for DAS in whole blood in ICH, IS and its major causes, suggesting disease specific immune responses which could result in biomarkers. Inclusion of both sexes and a further validation of results in a larger cohort is needed.

Disclosures: C.J. Dykstra-Aiello: None. **G.C. Jickling:** None. **B. Ander:** None. **X. Zhan:** None. **D. Liu:** None. **H. Hull:** None. **M. Orantia:** None. **C. Ho:** None. **F.R. Sharp:** None. **B.S. Stamova:** None.

Poster

793. Ischemia: Human

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 793.25/S5

Topic: C.07. Ischemia

Support: VA Grant I01 BX002985

AHA Grant 15IRG23050015

Title: The role of alpha-synuclein in mediating secondary ischemic brain damage

Authors: *T. KIM, S. MEHTA, B. KAIMAL, K. LYONS, R. VEMUGANTI;
Univ. of Wisconsin - Madison, Madison, WI

Abstract: α-synuclein (α-syn) is a small protein (14.5 kDa) that is abundantly expressed in the adult mammalian brain and predominantly localized in the presynaptic terminals. It is the major component of Lewy bodies, an abnormal protein aggregates, found in chronic neurodegenerative disorders including Parkinson's disease (PD), dementia with Lewy bodies and multiple system atrophy, hence referred to as synucleinopathies. α-syn has been extensively studied for its pathophysiological roles in neurodegenerative disease conditions. However, despite the fact that

acute brain injuries like ischemic stroke share similar molecular mechanisms with chronic neurodegenerative diseases, the scope of research so far has been mainly confined to chronic neurodegenerative diseases particularly in PD. Therefore, we examined whether α-syn also contributes to post-stroke neuronal death and neurological dysfunction. Rodents were subjected to transient middle cerebral artery occlusion (tMCAO) and α-syn induction was silenced with a cocktail of α-syn-specific siRNAs. The levels of α-syn were estimated with qPCR and Western Blots. Post-ischemic motor deficit was evaluated with rotarod, beam walk and adhesive removal test 1 to 7 days after ischemia, and infarct volume was measured on cresyl violet stained brain sections. Cellular changes after ischemia were examined using immunofluorescence staining. Following tMCAO, α-syn levels were significantly up-regulated and phosphorylated at serine-129 in ischemic penumbra. Interestingly, in the ischemic brain non-phosphorylated and phosphorylated α-syn species translocated into the neuronal nuclei. We also observed that silencing α-syn by α-syn siRNA cocktail 2 h prior to tMCAO significantly decreased the infarction and improved the motor function. The neuroprotective effects were still observed when α-syn siRNAs were administered 30 min after the tMCAO. We found that the rate of survival at 7 days after a 90 min tMCAO was remarkably higher in α-syn KO mice (>90%) compared to wild-type control mice (50%). These KO mice also showed significantly smaller infarcts and better motor recovery. Furthermore, α-syn suppression significantly mitigated the post-ischemic pathologic markers including oxidative stress (3-NT), apoptosis (cleaved Caspase-3) and mitochondrial dysfunction (phospho-Drp1). Thus, we presently show that α-syn plays a critical role in neuronal death.

Disclosures: T. Kim: None. **S. Mehta:** None. **B. Kaimal:** None. **K. Lyons:** None. **R. Vemuganti:** None.

Poster

793. Ischemia: Human

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 793.26/S6

Topic: C.07. Ischemia

Title: The functional assessment of edaravone-induced neuroprotection after hypoxic insults

Authors: *T. MORITA[1], S. SHIBUTA[1], J. KOSAKA[2], Y. FUJINO[1];
[1]Osaka Univ. Grad. Sch. of Med., Suita-Shi, Japan; [2]Ctr. for Med. Science, Intl. Univ. of Hlth. and Welfare, Ohtawara, Japan

Abstract: Backgrounds:
There are no reports referring to the functional evaluation of the neuroprotective effect of

edaravone on cortical neurons against hypoxic insults (HI). In this study, we investigated the response to neurotransmitters in rat primary cultured cortical neurons which were protected with edaravone against prolonged HI.

Material and Methods:

Neurons prepared from E17 Wistar rats were used after 10-11 days in culture. Shortly before 24h HI, 50μM edaravone was administrated to the neurons. The degrees of neurotransmitter-induced intracellular calcium ($[Ca^{2+}]i$) elevation were measured using fluorescence measurement systems after HI.

To evaluate the effects of neurotransmitters, acetylcholine (ACh) and L-glutamate (Glu), on primary cultured neurons, the mean maximum change in fluorescence intensity (Fmax) upon addition of neurotransmitter was measured and normalized to the baseline fluorescence obtained before neurotransmitter application (F0). We measured the mean value of Fmax/F0 (height) calculated from the integration of $[Ca^{2+}]i$ response curves of the surviving neurons. A height ratio was calculated as follows: the height of the $[Ca^{2+}]i$ response in an experimental culture divided by the height of the $[Ca^{2+}]i$ response in the control culture.

Data are expressed as the mean ± SEM of height ratios. These ratios were compared to normoxic control without edaravone administration.

Results:

When ACh was used as a neurotramsmitter, the height ratio of hypoxic neurons without edaravone was significantly lower than control (0.47 ± 0.14 vs 1.02 ± 0.02, $P < 0.01$). The height ratio of hypoxic neurons protected with edaravone was significantly higher than the ones without edaravone (0.87 ± 0.09, $P = 0.02$). When Glu was used as a neurotransmitter, a similar tendency was seen, however, there was no significant difference among the groups ($P = 0.07$).

Conclusions:

Edaravone showed a significant neuroprotective effect on neurons against HI, especially the responsiveness to ACh was maintained in surviving neurons.

Keywords:

acetylcholine, calcium imaging, edaravone, hypoxia, L-glutamate, primary culture

Disclosures: **T. Morita:** None. **S. Shibuta:** None. **J. Kosaka:** None. **Y. Fujino:** None.

Poster

793. Ischemia: Human

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 793.27/S7

Topic: C.07. Ischemia

Support: NIH R01NR014181

Title: Impaired cholinergic function following orthopedic surgery

Authors: *H. HUANG[1], L. WAN[1], A. RAJAN[1], N. SCHWAB[2], J. TANNER[2], C. PRICE[2], M. DING[1];
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Abstract: Cognitive decline can occur after major surgeries. In older adults post-operative cognitive dysfunction (POCD) has been reported as heralding longer-term cognitive impairment and dementia. Understanding the neural underpinning of POCD is a key step toward developing predictive biomarkers and effective interventions. Past research has established the importance of acetylcholine in cognition. Decrease in cortical acetylcholine levels, due partly to the neuronal loss in the basal nucleus of Meynert (BNM), leads to cognitive dysfunction. Considering that propofol, a widely used anesthetic, is thought to suppress acetylcholine, we examined BNM-seeded whole brain functional connectivity pre- and post-total knee replacement surgery. Non-demented older adults electing total knee replacement surgery with the surgeon and the propofol protocol were enrolled. Participants completed pre-surgery and post-surgery (within 72 hours post-surgery) resting-state fMRI (3T Siemens Verio). BNM-seed whole-brain cross correlation was computed to assess changes in functional connectivity before and after surgery. Compared to pre-surgery, post-surgery BNM-seeded functional connectivity strength declined in multiple brain regions, including cingulate cortex, dorsal lateral prefrontal cortex (DLPFC), superior temporal lobe (STL), and inferior temporal lobe (ITL). Follow-up assessment of cognitive status and structural and functional brain changes is currently underway.

Disclosures: H. Huang: None. **L. Wan:** None. **A. Rajan:** None. **N. Schwab:** None. **J. Tanner:** None. **C. Price:** None. **M. Ding:** None.

Poster

793. Ischemia: Human

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 793.28/S8

Topic: C.07. Ischemia

Title: Differential regulation of VEGF co-receptors in the hypoxic developing mouse brain in response to exogenous stimulation of the hypoxia-inducible transcription factor (HIF) system

Authors: *R. TROLLMANN, G. BOIE, M. RICHTER, F. BRACKMANN, S. JUNG;
Univ. of Erlangen, Erlangen, Germany

Abstract: Background: Neovasculogenesis due to hypoxic-ischemic injury represents a common maturation-related compensatory mechanism of the hypoxic brain that is mainly regulated by hypoxia-inducible transcription factors (HIF). However, disturbance of early maturational processes of the developing brain including aberrant angiogenesis and disruption of physiological neuronal and glial differentiation and migration have to be considered. We aimed to investigate in vivo effects of prolyl-4-hydroxylase inhibitor (PHI) FG-4497 and recombinant human erythropoietin (rhEPO) on cerebral vasoactive factors and cerebral vasculogenesis in an established mouse model of acute neonatal systemic hypoxia.
Methods: Neonatal C57BL/6NCrl mice (P7) were exposed to systemic hypoxia (8% O2, 6h; hypoxia chamber INVIVO2 400) and treated with FG-4497 (30/60/100 mg/kg, i.p; Fibrogen) or rhEPO (2500/5000 IU/kg, i.p; Roche) 0h, 24h, and 48h post exposure. After 72h of reoxygenation mRNA expression of VEGF-A, VEGFR-1, VEGFR-2, Nrp-1, Nrp-2, ANGPT-1, ANGPT-2, and TIE-2 was quantified by real-time RT-PCR. Cell type and brain region-specific expression pattern were investigated by RNA in situ hybridization. Vascular development was assessed by PECAM-1 immunohistochemistry and 2D reconstruction (Imaris).
Results: PHI and rhEPO treatment significantly induced differential cerebral target gene activation including additive effects on vasoactive targets (ADM, VEGF-A, CXCR4) under global hypoxia. Both treatment regimens significantly increased cortical vessel length and branching but, VEGF-A co-receptor regulation differed significantly. While PHI treatment at once decreased the mRNA level of VEGFR-2 and Nrp-2 ($p<0.01$) and stimulated the mRNA expression of ANGPT-2 ($p<0.01$) compared to controls decreasing the ANGPT-1/ANGPT-2 mRNA ratio ($p<0.05$) that may indicate functionally elevated and disturbed vascular permeability, rhEPO therapy increased the ANGPT-1/ANGPT-2 ratio in a dose-dependent manner suggesting that HIF-independent regulation of ANGPT-1 is associated with functional stabilization of vessel structures.
Conclusions: Differential regulation of VEGF-A co-receptors in response to exogenous activation of the cerebral HIF system implicates modulation of developmental cerebral vasculogenesis and vasomotor control upon global hypoxia by HIF-dependent as well as HIF-independent pathways. Considering possible regenerative effects of rhEPO on cerebral vascular development in the hypoxic developing mouse brain, long-term effects as well as age-specific aspects of endogenous VEGF-A co-receptor regulation are objectives of our ongoing work.

Disclosures: R. Trollmann: None. **G. Boie:** None. **M. Richter:** None. **F. Brackmann:** None. **S. Jung:** None.

Poster

793. Ischemia: Human

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 793.29/S9

Topic: C.07. Ischemia

Support: NIH GRANT NS086929

AHA GRANT 15GRNT25240004

Title: Methylene blue promotes cortical neurogenesis following photothrombotic stroke in rats.

Authors: D. G. L. TUCKER, M. AHMED, Y. DONG, Y. LU, R. WANG, *Q.-G. ZHANG; Augusta Univ., Augusta, GA

Abstract: Ischemic stroke in rodents stimulates neurogenesis in the adult brain and the proliferation of newborn neurons that migrate into the penumbra zone. The present study investigated the effect of methylene blue (MB) on neurogenesis and functional recovery in a photothrombotic (PT) model of ischemic stroke in rats. PT stroke model was induced by photo-activation of Rose Bengal dye in cerebral blood flow by cold fibre light. Rats received intraperitoneal injection of either MB (0.5 mg/kg/day) from day 1 to day 5 after stroke or an equal volume of saline solution as a control. Cell proliferative marker 5-bromodeoxyuridine (BrdU) was injected twice daily (50 mg/kg) from day 2 to day 8 and animals were sacrificed on day 12 after PT induction. We report that MB significantly enhanced cell proliferation and neurogenesis, as evidenced by the increased co-localizations of BrdU/NeuN, BrdU/DCX, BrdU/MAP-2 and BrdU/Ki67 in the peri-infarct zone compared with vehicle controls. MB thus effectively limited infarct volume and improved neurological deficits compared to PT control animals. The effects of MB were accompanied with an attenuated level of reactive gliosis and release of pro-inflammatory cytokines, as well as elevated levels of cytochrome c oxidase activity and ATP production in peri-infarct regions. Our study provides important information that MB has the ability to promote neurogenesis and enhance the newborn-neurons' survival in ischemic brain repair by inhibiting microenvironmental inflammation and increasing mitochondrial function.

Disclosures: D.G.L. Tucker: None. **M. Ahmed:** None. **Y. Dong:** None. **Y. Lu:** None. **R. Wang:** None. **Q. Zhang:** None.

Poster

794. Injury and Trauma I

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 794.01/S10

Topic: C.09. Brain Injury and Trauma

Support: NICHDS (R01 HD061504)

NINDS (K99 NS096116)

U54 EB020403

R01 EB008432

R01 AG040060

NS080655

UCLA BIRC,

Title: Improved group differentiation of adolescent traumatic brain injury using multi-modal registration and automatic multi-atlas tract extraction (automate) toolkit

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Abstract: Traumatic brain injury (TBI) is the leading cause of death and disability in children and adolescents; each year, there are 50,000-90,000 new patients that suffer moderate to severe pediatric TBI in the United States alone. Depending on the severity and the type of impact, these injuries can result in a diverse range of pathologies, including short- and long-term disruptions to white matter (WM) integrity. Using diffusion-weighted imaging (DWI) we can noninvasively examine WM integrity, including possible traumatic axonal injury (TAI). Even so, the lesions and heterogeneity of TBI can affect the accuracy of imaging registration - the alignment of images from different subjects. Here we demonstrate an improvement to our DWI analytic workflow. Using information from three imaging modalities: DWI, T1, and FLAIR, we perform an intra-subject, multimodal registration prior to executing our autoMATE (automatic multi-atlas tract extraction) workflow to extract 3D models of tracts and analyze WM integrity. T1-weighted imaging provided a high spatial resolution anatomical scan. FLAIR (Fluid-Attenuated Inversion

Recovery) was used for improved detection of lesions, and DWI assessed the integrity of WM pathways in the brain. Combining information from these modalities results in more accurately registered DWI images. To compare our results, we used Support Vector Machine (SVM), a learning model to classify our connectivity features, and differentiate connectivity patterns in TBI and normal development. **Table 1** demonstrates improvement to our classification outputs when compared to a single-channel registration with our standard autoMATE template and study specific template. This step further improved the classification accuracy for models based on FA (fractional anisotropy) and RD (radial diffusivity), while the outputs for MD were slightly poorer, but close to those from the intermediate registration. Classification based on axial diffusivity metrics also improved with the multi-modal registration. We hope to use this stepwise improvement to better detect subtle brain changes following pediatric TBI.

Single channel registration / Standard template

	BAC	*Accuracy*	*Sensitivity*	*Specificity*	*F1*
FA	0.7995	0.8039	0.8640	0.7350	0.8222
MD	0.7621	0.7692	0.8525	0.6717	0.7992
RD	0.7823	0.7892	0.8670	0.6975	0.8143
AD	0.7475	0.7580	0.8525	0.6425	0.7920

Single channel registration / Study specific template

	BAC	*Accuracy*	*Sensitivity*	*Specificity*	*F1*
FA	0.8004	0.8116	0.8925	0.7083	0.8435
MD	0.8133	0.8170	0.8450	0.7817	0.8348
RD	0.8100	0.8191	0.8850	0.7350	0.8467
AD	0.7213	0.7402	0.8625	0.5800	0.7854

Multi-modal registration / Study specific template

	BAC	*Accuracy*	*Sensitivity*	*Specificity*	*F1*
FA	0.8079	0.8200	0.9050	0.7108	0.8518
MD	0.8129	0.8168	0.8450	0.7808	0.8343

RD	0.8108	0.8205	0.8900	0.7317	0.8488
AD	0.7325	0.7511	0.8750	0.5900	0.7951

Table 1. Comparison of SVM classification performance, for data computed with the basic, intermediate, and multi-modal registration protocols.

Disclosures: F. Rashid: None. **E.L. Dennis:** None. **J. Villalon-Reina:** None. **G. Prasad:** None. **J. Faskowitz:** None. **T. Babikian:** None. **R. Mink:** None. **C. Babbitt:** None. **J. Johnson:** None. **C. Giza:** None. **R. Asarnow:** None. **P. Thompson:** None.

Poster

794. Injury and Trauma I

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 794.02/S11

Topic: C.09. Brain Injury and Trauma

Support: Canadian Institutes of Health Research Fellowship

Alberta Innovates Health Solutions Clinician Fellowship

Own the Podium Operating Grant

Title: Test-retest reliability of KINARM robot assessments of sensorimotor and cognitive function in elite athletes: towards the assessment of sport-related concussion

Authors: *C. MANG[1], T. D. MAH[1], M. S. COSH[2], S. H. SCOTT[3], B. W. BENSON[2], S. P. DUKELOW[1];
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Abstract: Background: There is a need for improved tools to assess sensorimotor and cognitive deficits after sport-related concussion. Robotic technology allows objective assessment of aspects of sensorimotor and cognitive function that are challenging to evaluate with traditional clinical tools. The purpose of the current work was to evaluate test-retest reliability of robotic assessments (KINARM robot) of reaching, position sense, bimanual motor function, visuospatial skills, attention and decision-making in elite athletes competing in high-speed sports with a risk for concussion.
Methods: Baseline robotic assessments were conducted during the pre-season on 50 healthy,

high-performance athletes (22.2 ± 5.5 years) over three consecutive seasons between 2011 and 2013 (343 ± 55 days). Five robotic tasks (Visually guided reaching, Position matching, Object Hit, Object Hit and Avoid, Trail Making B) were employed, from which 63 parameters that characterize sensorimotor and cognitive function were measured. Test-retest reliability was investigated by determination of intra-class correlation coefficients (ICCs) between seasons 1 and 2 (S1 to S2) and seasons 2 and 3 (S2 to S3). Change in performance on tasks between baseline assessments was also evaluated with multivariate analysis of variance (MANOVA) and where appropriate, post-hoc comparisons within specific task parameters.
Results: ICCs ranged from -.08 to .91 and -.26 to .90 for S1 to S2 and S2 to S3, respectively. ICCs were moderate to good (≥ 0.5) for 46 of 63 parameters (73%) when considering S1 to S2 assessments and for 42 of 63 parameters (66.7%) when considering S2 to S3 assessments. MANOVAs and post-hoc comparisons indicated an improvement in a total of 12 of 63 parameters (19%) measured from 4 of 5 tasks (no changes in performance on Object Hit and Avoid task parameters). All changes in performance were found only when comparing S1 to S2 or S1 to S3. There were no significant differences in task performance on any parameters between S2 and S3.
Conclusion: The results suggest moderate to good test-retest reliability for the majority of task parameters measured from the KINARM robot in elite athletes. Improvements in performance across season to season assessments were observed in relatively few parameters between seasons 1 and 2, and task performance stabilized completely between seasons 2 and 3. Overall, the results suggest that robotic technology can provide a reliable assessment of baseline sensorimotor and cognitive function in elite athletes. Future work will consider the potential use of this information for diagnosis and prognosis of concussion-related neurological deficits.

Disclosures: **C. Mang:** None. **T.D. Mah:** None. **M.S. Cosh:** None. **S.H. Scott:** Other; Dr. Scott is co-founder and chief scientific officer of BKIN Technologies, the company that commercializes the KINARM robotic device.. **B.W. Benson:** None. **S.P. Dukelow:** None.

Poster

794. Injury and Trauma I

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 794.03/S12

Topic: C.09. Brain Injury and Trauma

Title: Characterization of iron deposition changes in cerebral regions of young athletes using susceptibility-weighted imaging

Authors: *X. MAO[1], B. JOHNSON[3], T. M. TALAVAGE[1,2], S. SLOBOUNOV[4];
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Abstract: Introduction: Susceptibility-weighted imaging (SWI) has been shown to be sensitive to the iron in the form of ferritin, hemosiderin, and deoxyhemoglobin (Haacke, EM. et al. 2009), providing the ability to measure iron deposition *in vivo*. Our previous study (Mao, X. et al. 2015) has shown that the magnitude data of SWI can reveal the neurophysiological changes associated with Traumatic Brain Injury (TBI) in high school athletes. Here we use phase-filtered SWI data to assess potential changes in brain health of college-aged football athletes over a single season.
Methods: Eighteen (18) college football athletes (ages 19-23, mean=20.7) participated in imaging around a single competition season. SWI were performed before (*Pre*) and after (*Post*) the season, separated by approximately 5 months. None of these athletes was diagnosed with a head trauma during the season. SWI data were acquired on a 3T Siemens Prisma scanner, using an axial 3D multi-echo pulse sequence (TR =36.0ms; FOV=250x320 acquisition matrix). Acquired images underwent a pre-processing pipeline (see Mao, X. et al. 2015) and were then parcellated into 55 disjoint anatomical regions of interest (ROIs) at a gyrus level (Lancaster, JL. et al. 2000) in MNI152 space. ROI-specific intensity changes across the sessions (i.e. *Post*-*Pre*) were measured for each individual subject, and were compared with the averaged group changes, using the Wilcoxon rank-sum test.
Results: Statistically-significant decreases in SWI signal (e.g., Fig. 1) were observed in 10+ (out of 55) ROIs for 8 of 18 (44%) male football players at *Post*, relative to *Pre*.
Discussion and Conclusion: Hypointensity suggests these ROIs have experienced iron deposition during the season, which would be an expected consequence of vessels damaged by repeated subconcussive exposure. Given that SWI is very sensitive to deposition of iron due to microhemorrhage or leaky vessels, this work further argues that the technique has potential to quantify iron deposition as a biomarker of exposure to neural injury, even in the absence of diagnosable symptoms.

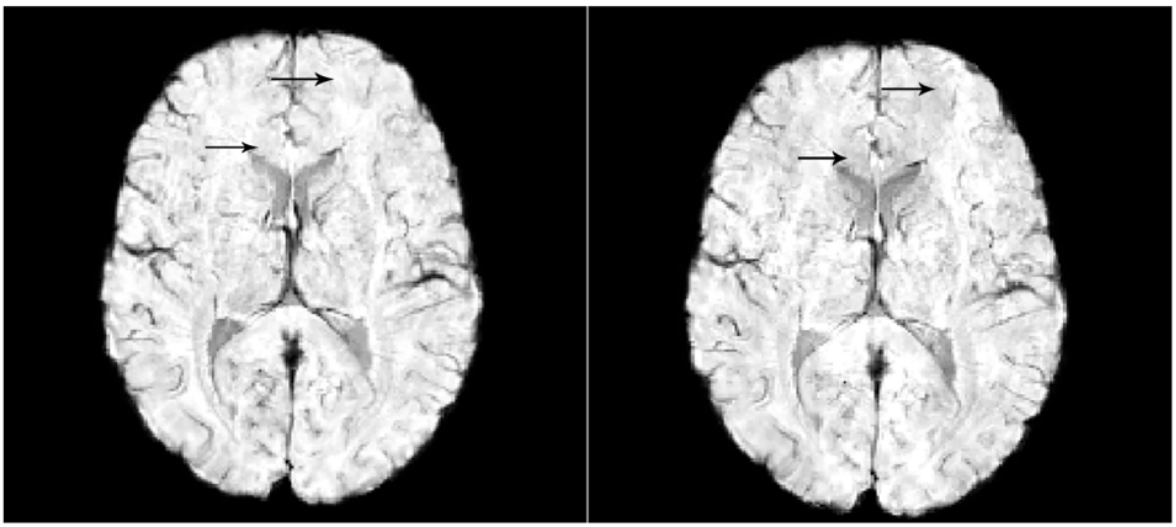

Fig.1 The SWI processed images of *Pre* (left) and *Post* (right) of one specific player in the subject pool. Note the hypointensities (black arrow) are implying the iron deposition changes between the two imaging sessions.

Disclosures: **X. Mao:** None. **B. Johnson:** None. **T.M. Talavage:** None. **S. Slobounov:** None.

Poster

794. Injury and Trauma I

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 794.04/S13

Topic: C.09. Brain Injury and Trauma

Support: I01-CX000715

IK2 CX000864

Title: The neural correlates of loss of consciousness during vector memory.

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Abstract: Background: Traumatic brain injury is the signature injury of military combat personnel and is linked to mental health problems and disability following deployment. Evidence suggests that loss of consciousness (LOC) compared to alteration of consciousness (nLOC) may

confer greater risk for neurocognitive sequelae. Methods: We used functional Magnetic Resonance Imaging (fMRI) to examine the influence of LOC on working memory for spatiotemporal information (i.e., vector memory) in 30 combat veterans with and without a history of LOC. The task consisted of tracking a moving object as it traveled across the screen (a) within view (vector tracking), or (b) out of view (vector memory) toward a visible target. Subjects were asked to press a button at the moment of anticipated impact. Task accuracy was examined for group by condition interactions using ANOVA. Change in brain activity was examined via linear mixed effects modeling with group (LOC v. nLOC), memory (vector memory v. vector tracking), distance (35 or 75% of the screen) entered as fixed factors; subjects were entered as a random factors. Results: Subjects with a history of LOC compared to nLOC performed significantly worse during vector memory relative to vector tracking during the long distance condition (75% of the screen or a longer period of occlusion). Initial results revealed that the contrast of vector memory versus vector tracking revealed greater activity in a network of regions involving the anterior and posterior cingulate, insula, lingual gyrus, caudate, and temporal gyrus. This initial analysis revealed no significant group X memory X distance interaction on patterns of brain activation (clusters $\geq$ 2106 μL, $p \leq .05$). Despite poorer performance, LOC relative to nLOC individuals were able to mount sufficient neural resources to complete vector memory during periods of visual occlusion. Conclusions: Combat veterans with a history of LOC relative to those without demonstrated poorer spatiotemporal, or "vector," memory. Results suggest that a history of LOC may impact the visuospatial skills, attention, and predictive timing needed to track moving objects during extended periods of visual occlusion. These findings may have important implications for safe driving among other everyday skills that rely on spatiotemporal processing.

Disclosures: **A.D. Spadoni:** None. **I.A. Strigo:** None. **A.N. Simmons:** None.

Poster

794. Injury and Trauma I

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 794.05/S14

Topic: C.09. Brain Injury and Trauma

Support: an Industrial Disease Clinical Research Grants (150502-02)

a Grant-in-Aid for Scientific Research in Innovative Areas (23118004) from the Ministry of Education, Culture, Sports, Science, and Technology of Japan

a Grant-in-Aid for Young Scientists B (15K19722)from the Japan Society for the Promotion of Science

a Grant-in-Aid for C (26461766) from the Japan Society for the Promotion of Science

Title: Neural basis of cognitive impairments in patient with diffuse axonal injury

Authors: *S. UBUKATA[1], N. OISHI[2,3], G. SUGIHARA[1], W. YASSIN[1,4], T. ASO[2], H. FUKUYAMA[2,3], T. MURAI[1], K. UEDA[1];
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Abstract: Diffuse axonal injury (DAI), a major form of traumatic brain injury, is characterized diffused white matter disruption due to shearing forces of the brain. DAI is a main cause of neuropsychological sequelae following trauma. However, the neural bases of such sequelae are poorly understood. The aim of the present study was to assess structural neural network using connectome analysis and to examine the relationship between the altered connectivity and cognitive impairments in patients with chronic DAI. Eighteen patients with DAI (13 male, mean age 38.7± 12.9 years), and 18 age- and gender-matched healthy controls underwent neuropsychological assessments and magnetic resonance imaging. Most patients were diagnosed as having a severe TBI. All patients completed the Wechsler Adult Intelligence Scale-III, Wechsler Memory Scale-Revised, Behavioral Assessment of Dysexecutive Syndrome and Trail making test AB. All participants underwent diffusion tensor imaging (DTI), consisting of 64 non-collinear volumes with b = 1500 s/mm^2 and high-resolution T1-weighted three-dimensional magnetization-prepared rapid gradient-echo (3D-MPRAGE). DTI data processing was performed using the programs in FSL. 3D-MPRAGE data were processed using the VBM8 toolbox of SPM to determine individual-spaced volumes of interest. Deterministic fiber tracking was processed by Diffusion Toolkit using FACT algorithm with FA > 0.15 and angle > 60 degrees. Based on previous studies, we focused on the structural connectivity comprising corpus callosum (CC). 85 × 85 connectivity matrices for the metrics including a number of fiber and FA were calculated by an in-house Matlab script with three parts of CC derived from JHU white-matter atlas and 82 regions of AAL atlas. Statistical analyses were performed by the network-based statistic (NBS) with a t-statistic exceeding a threshold of t = 3.1 and a family-wise error-corrected p-value < 0.05 for the size of each resulting component using 5000 permutation tests. First, group comparisons were conducted to identify the abnormal connectivities in DAI relative to controls. Second, correlation analyses between FA and each of the cognitive variables were performed in DAI. Patients showed impairments in processing speed (PS) and memory function. Connectome analysis showed a reduction in number of fibers and FA in the CC in DAI compared with the controls. Significant correlations were found between the PS score and connectivity between the CC and medial prefrontal, posterior medial regions such as the precuneus. These results suggest that a structural brain network including the CC plays a key role in the cognitive impairments in DAI.

Disclosures: **S. Ubukata:** None. **N. Oishi:** None. **G. Sugihara:** None. **W. Yassin:** None. **T. Aso:** None. **H. Fukuyama:** None. **T. Murai:** None. **K. Ueda:** None.

Poster

794. Injury and Trauma I

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 794.06/T1

Topic: C.09. Brain Injury and Trauma

Support: Polish National Science Centre grant DEC-2013/11/B/HS6/01242

Title: 40-Hz auditory steady-state responses in patients with disorders of consciousness: positive correlation between Coma Recovery Scale-Revised results and phase-locking index

Authors: M. BINDER[1], U. GÓRSKA[1], *I. GRISKOVA-BULANOVA[2];
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Abstract: *Objective:* Auditory steady-state response (ASSR) is a frequency-domain EEG activity observed in response to periodic auditory stimulation. These responses were shown to be sensitive to changes in the cortical arousal occurring naturally during sleep (Cohen et al., 1991) and artificially, during the general anesthesia (Plourde, 2006). Following this evidence, we aimed to elucidate whether 40-Hz ASSRs could also be sensitive to the state of patients with disorders of consciousness (DOC) as measured with Coma Recovery Scale-Revised (CRS-R).
Methods: 15 patients with DOC were included (11 males and 4 females; mean age±SD 45.5±15.4). The state of the patients was evaluated with the Polish version of the CRS-R (Giacino et al., 2004). In each patient, CRS-R testing took place within one week from the date of the EEG session. The mean total CRS-R score was 8.5±6.1, range 3-20. The 40 Hz click trains of 500 ms duration were presented 100 times with the interstimulus interval of 700-1000 ms through earphones while subjects remained in a sitting position in their beds or wheelchairs. EEG was recorded using 64-channels Biosemi ActiveTwo system. The off-line processing of EEG data was performed in EEGLAB and ERPWAVELAB for MatLab© (Delorme and Makeig 2004; Mørup et al. 2007). After conventional cleaning procedures, epochs of 900 ms were created starting at 200 ms prior to the stimulus onset and lasting for 700 ms post-stimulus. ASSRs were analyzed from FCz location, showing maximal activity. Mean phase-locking index (PLI) within 38-42Hz window was calculated for 100 ms bins. The correlation between PLI values and CRS-R scores was evaluated using Pearson's correlation coefficient (p-values Bonferroni corrected).
Results and Conclusions: The highest PLIs were observed during 200-300 ms period, corresponding to prior observations on 40-Hz ASSRs (Griskova-Bulanova et al., 2016). The PLI values from the periods of 300-400 ms and 400-500 ms after the stimulus onset, corresponding to the entrainment phase of the response, positively correlated to the CRS-R subscales' scores (Auditory, Visual, Communication; $r>0.7$, $p<0.003$) and the total CRS-R score ($r>0.74$,

$p<0.002$), but there were no correlations between PLI values and Motor, Verbal and Arousal subscales. These results emphasize the role of the integrity of auditory system in determining the level of functioning in DOC patients, corresponding to previous observation with fMRI during resting-state paradigms (Demertzi et al., 2015). Our initial results also suggest possibility to use the ASSR protocol as an objective diagnostic method in DOC patient group.

Disclosures: M. Binder: None. **U. Górska:** None. **I. Griskova-Bulanova:** None.

Poster

794. Injury and Trauma I

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 794.07/T2

Topic: C.09. Brain Injury and Trauma

Support: National Natural Science Foundation of China (81271476) to Feng Li

The 111 Project, China (B13037) to Feng Li

Science and Technology Research Foundation of Guangzhou, China (201300000154) to Feng Li

Title: Leucovorin decreases radiation-induced brain injury in nasopharyngeal carcinoma patients: a retrospective analysis

Authors: Z. LIANG[1,2,3], S. WANG[4], C. WANG[6], S. FENG[5], J. HUANG[1], Y. YANG[1], M. KANG[1], Y. KUANG[1], F. JIA[1], M. XIE[1], C. FIDELIS[1], S. ULLAH[1], *F. M. SESSLER[7], W.-J. GAO[7], Z. CHENG[1,3], F. LI[1];
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Abstract: Radiotherapy in cancer treatment often develop radiation-induced brain injury, also known as radiation encephalopathy (REP). Currently many methods are used to cure REP, but outcomes are limited. To find an effective method of managing REP, we evaluated the protective effect of Calcium leucovorin, a reduced folic acid, on REP in nasopharynx cancer (NPC) patients. The definition of locoregionally advanced NPC followed the staging system of AJCC.

This study included 1080 patients that were diagnosed with NPC with a median follow-up of 8 years (from 2002 to 2014) and survival of 3 years after initial diagnosis. The Leucovorin-Group (Group1) of 163 NPC patients received PFL chemotherapy (cisplatin 80 mg/m², 5-fluorouracil 1000 mg/m²/d, and leucovorin 120 mg/m²) every 3 weeks. The Non-leucovorin-Group (Group2) of 917 patients did not receive leucovorin during the same period. These patients included 262 patients of PF chemotherapy (Group-PF) and 655 patients of other chemotherapy regimens. Data for the two main groups was collected from medical records, including temporal lobe injury, sensorineural hearing loss (SNHL) and other cranial nerves disorders, were evaluated according to MRI, etc. We identified that 11 (6.7%) patients of the Group1 had REP as compared to the 112 (12.2%) in the Group2 (λ^2=4.06, P<0.05). The incidence of REP of the Group1 as compared to the Group2 at 3, 5 and 8 years were 1.2% vs. 3.7%, 2.5% vs.6.9%, 5.5% vs. 9.9%, respectively. The REP occurrence time post-radiotherapy of Group1 was longer than that of Group2 (61.1±7.8 months vs. 50.9 ±4.2 months, p<0.05). Considering the ototoxicity of cisplatin, we then compared the incidence of SNHL in Group1 and Group-PF particularly. The incidence of sensorineural hearing loss (SNHL) in Group1 was much lower than the Group-PF (16.6% vs. 21.4%).The decrease in the incidence and delay of the occurrence time of REP were significantly ameliorated by administration of leucovorin. Subgroup analysis revealed that leucovorin prevented hearing impairment, especially hearing loss in patients underwent cisplatin-based chemotherapy. These findings provide the first evidence that leucovorin has beneficial effects of decreasing radiation-induced brain injury in NPC patients.

Disclosures: **Z. Liang:** None. **S. Wang:** None. **C. Wang:** None. **S. Feng:** None. **J. Huang:** None. **Y. Yang:** None. **M. Kang:** None. **Y. Kuang:** None. **F. Jia:** None. **M. Xie:** None. **C. Fidelis:** None. **S. Ullah:** None. **F.M. Sessler:** None. **W. Gao:** None. **Z. Cheng:** None. **F. Li:** None.

Poster

794. Injury and Trauma I

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 794.08/T3

Topic: C.09. Brain Injury and Trauma

Title: Dynamic virtual environments in the computer assisted rehabilitation environment (CAREN): developing novel assessments for service members with comorbid mild traumatic brain injury and post traumatic stress disorder

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Abstract: For service members (SMs), mission-essential tasks often require dual-tasking skills, which may be impaired by mild traumatic brain injury (mTBI) and posttraumatic stress disorder (PTSD). Conventional dual-task assessments cannot incorporate visual cognitive tasks during gait, are often time-consuming, and are not military-relevant. The Computer Assisted Rehabilitation Environment (CAREN) enables the incorporation of visual cognitive tasks by integrating multi-planar motion and locomotion with interactive virtual environments (VEs). Thus, our objective was to determine the efficacy of military-relevant dual-task assessment for SMs with comorbid mTBI-PTSD. Male SMs (N=37: mTBI-PTSD = 25; uninjured = 12) completed the PTSD Checklist - Military Version (PCL-M) and three CAREN VEs: 1) Balance Balls (BB), requiring weight-shifting; 2) Balance Cubes (BC), requiring step-shifting; and 3) Dual-Tasking Rank Insignia (DTRI), requiring three single-tasks (walking, rank insignia recognition, and rank insignia discrimination) and two dual-tasks combining walking and the rank insignia tasks (i.e. DTRI-Disc and DTRI-Rec). The main outcomes were time for the BB and BC tasks, and dual-task cost (% change in gait speed) and cognitive error (CE; % change in accuracy) for the DTRI tasks. BB time was significantly correlated with BC time ($r = 0.777$; $p < 0.001$), DTRI-Rec cost ($r = 0.374$; $p = 0.025$) and both DTRI-Disc cost ($r = 0.494$; $p = 0.002$) and CE ($r = 0.574$; $p < 0.001$). DTRI-Disc and DTRI-Rec cost, but not CE, were significantly correlated ($r = 0.903$; $p < 0.001$), and DTRI-Disc cost and CE were significantly correlated ($r = 0.480$; $p = 0.003$) such that gait speed increased as accuracy decreased. When controlling for mTBI history, BC time was significantly related to PCL-M score ($\beta = 1.053$, $p = 0.028$), such that SMs endorsing higher PCL-M scores spent more time on the BC task. BB and DTRI outcomes did not vary by PCL-M score. Developing immersive, military-relevant assessments is essential for improving treatment planning and clinical outcomes. Similar to published reports, we found that accuracy was inversely correlated with gait speed when SMs completed a visual discrimination task during ambulation, supporting dual-task assessment in the CAREN. Moreover, consistent with our previous study in SMs with TBI, those endorsing greater PTSD symptoms spent more time step-shifting, regardless of mTBI history, providing further evidence for utilizing the BC task in identifying comorbid mTBI-PTSD. Future research will determine whether multi-tasking assessments that integrate step-shifting with the visual cognitive tasks are more sensitive to group differences.

Disclaimer

Disclosures: **M.M. Onakomaiya:** None. **M.M. Pape:** None. **K.B. Highland:** None. **D.S. Clayborne:** None. **S.E. Kruger:** None.

Poster

794. Injury and Trauma I

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 794.09/T4

Topic: C.09. Brain Injury and Trauma

Support: NSC 102-2314-B-038 -023 -MY3

Title: Day-time sleepiness after mild traumatic brain injury correlates to initial IGF-1 level

Authors: *Y.-H. CHIANG[1], S.-H. TSAI[2], W.-T. CHIU[1], K.-H. LIAO[4], J.-C. WU[1], K.-Y. CHEN[3];
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Abstract: Mild traumatic brain injury (mTBI) is a major public problem that results in several psychiatric problems. The insulin-like growth factor 1 (IGF-1) system is involved in growth and survival signaling in the central nervous system. In addition, IGF-1 has been implicated as a neuroprotective agent in brain injury. The aim of this study is to examine the association between IGF-1 and the disorders of anxiety, depression and sleep among mTBI patients and controls without brain injury. In our observational study, 53 mTBI patients and 116 healthy participants (control group) was evaluated for four psychiatric symptoms and problems, which are anxiety (Beck's anxiety inventory), depression (Beck's depression inventory), daytime sleepiness (Epworth sleepiness scale), and sleep quality (Pittsburgh sleep quality index). The results show significant relationship between IGF-1 and participants' age but not correlated with the weight. Our previous findings showed the IGF-1 level did correlate significantly with these continuous scores, but it was significant when we revealed that IGF-1 was related with the anxiety problem after mTBI. The results of this report show significant relationship between IGF-1 and participants' age, but not correlated with the weight. Finally, our finding suggests that initial IGF-1 level was related with the daytime sleepiness problem one year after mTBI.

Disclosures: **Y. Chiang:** None. **S. Tsai:** None. **W. Chiu:** None. **K. Liao:** None. **J. Wu:** None. **K. Chen:** None.

Poster

794. Injury and Trauma I

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 794.10/T5

Topic: C.09. Brain Injury and Trauma

Support: Mid-Atlantic Mental Illness Research, Education and Clinical Center & W.G. Hefner VAMC

Wake Forest School of Medicine: Translational Science Institute, Department of Neurology, and Center for Biomolecular Imaging

Title: Meg decision-making network differences in veterans with ptsd and tbi.

Authors: *J. R. STAPLETON-KOTLOSKI[1,7], J. A. ROWLAND[7,2], I. MCGOWIN[3], J. V. RAWLEY[4], G. ALBERTO[2], D. W. GODWIN[2,5,6,7], K. TABER[7,8];
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Abstract: In this study we used MEG to investigate differences in brain activity in post 9/11 Veterans with and without PTSD and mTBI during the Iowa Gambling Task (IGT). The IGT is a decision making task that requires individuals to balance immediate rewards against delayed consequences over time. Performance is not strongly predicted by IQ or cognitive abilities. Impairments on the task have been observed in people with higher levels of trait anxiety or who have undergone a stress induction, suggesting that individuals with PTSD may perform poorly on the IGT. There is also overlap between the networks implicated in the IGT by lesion and fMRI studies and areas of volumetric difference observed in PTSD (amygdala and cingulate), providing further evidence for a possible negative impact of PTSD on IGT performance. While the effect of TBI on IGT performance has not been described, the IGT is a relatively complex task that may be sensitive to network dysfunction due to small diffuse injuries. Twenty-four right-handed males (average age 38 yrs) who had completed a comprehensive diagnostic interview were included. Subjects were either diagnosed with PTSD alone (6), mTBI alone (4), PTSD+mTBI (5), or had no Axis I diagnosis (9).
Subjects were scanned with a 275 channel CTF Systems Inc. MEG and data were routinely preprocessed. Win and loss trials were analyzed separately. Based on the power spectra of the event related averages for wins and losses for control subjects, synthetic aperture magnetometry (SAM) was used to beamform activity at 1-8, 8-15, and 15-70 Hz using randomly selected resting state epochs as the contrast. SAM maps exhibited increased desynchronization of frontal and parietal networks in subjects with PTSD for losses at 1-8 Hz in comparison to controls.

Interestingly, subjects with TBI-only had patches of synchronization within overall regions of desynchronization in frontal and parietal networks, and thus showed more total synchronization than subjects with PTSD-only or controls for all loss frequencies. Subjects with PTSD+TBI exhibited stronger levels of dorsal desynchronization at 1-8 and 15-70 Hz for losses in comparison to all groups. Maps for wins were more complex but showed similar dorsal desynchronization patterns for all four groups. These results suggest that distributions of synchronous and desynchronous brain rhythms may differentially vary as a function of PTSD and TBI status.

Disclosures: J.R. Stapleton-Kotloski: None. **J.A. Rowland:** None. **I. Mcgowin:** None. **J.V. Rawley:** None. **G. Alberto:** None. **D.W. Godwin:** None. **K. Taber:** None.

Poster

794. Injury and Trauma I

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 794.11/T6

Topic: C.09. Brain Injury and Trauma

Support: NSERC

Title: The effects of aerobic exercise on corticospinal excitability in high versus low physically active individuals

Authors: *J. EL-SAYES, T. LULIC, H. J. FASSETT, A. J. NELSON;
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Abstract: Regular physical activity can impact cortical function and the propensity for plasticity. Few studies have examined the influence of physical activity level on the propensity for plasticity. Transcranial magnetic stimulation (TMS) can be used to asses short-term plasticity effects and the present study aimed to determine changes in corticospinal excitability that follows aerobic exercise. Additionally, it compared changes in corticospinal excitability after a single session of aerobic exercise in high versus low physically active individuals. Participants included twenty-four young, healthy adults (ages 18 - 30 years) who were divided into two equal groups based on the physical activity scores determined by the Minnesota Leisure-Time Physical Activity Questionnaire: low physical activity (LPA): 708.12 ± 632.89 and high physical activity (HPA): 2149.88. TMS was used to obtain motor evoked potential (MEP) recruitment curves from the first dorsal interosseous (FDI) before and after moderate intensity aerobic exercise that required cycling on a recumbent cycle ergometer for 20 minutes at 50-70% of the age-predicted maximal heart rate. MEP recruitment curves were measured as a function of resting motor

threshold (RMT), and also active motor threshold (AMT) (90-150% RMT/AMT) the required 5-10% of their maximum voluntary contraction of the FDI during MEP acquisition. MEPs were quantified as the peak-to-peak amplitude and recruitment curves were assessed by their slope. Results indicate that in the HPA group, resting MEP peak-to-peak amplitude and the slope of the recruitment curve increases following exercise. MEP recruitment curves and amplitudes were unchanged for the LPA group. These results may suggest that there is a difference in the propensity for neuroplasticity in high versus low physically active individuals. Therefore, it is necessary to consider lifestyle activity when developing and implementing rehabilitation protocols used in clinical populations.

Disclosures: J. El-Sayes: None. **T. Lulic:** None. **H.J. Fassett:** None. **A.J. Nelson:** None.

Poster

794. Injury and Trauma I

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 794.12/T7

Topic: C.09. Brain Injury and Trauma

Support: Gates Foundation OPP1119489

Title: Fetal neuronal exosome miR-9 and its downstream targets BDNF, REST and Synapsin: robust non-invasive maternal biomarkers of ETOH mediated fetal brain injury

Authors: *N. DARBINIAN[1,2], E. J. GOETZL[3], N. MERABOVA[2], E. LAURETTI[2], G. TATEVOSIAN[2], D. MARTIROSYAN[2], L. GOETZL[2,4];
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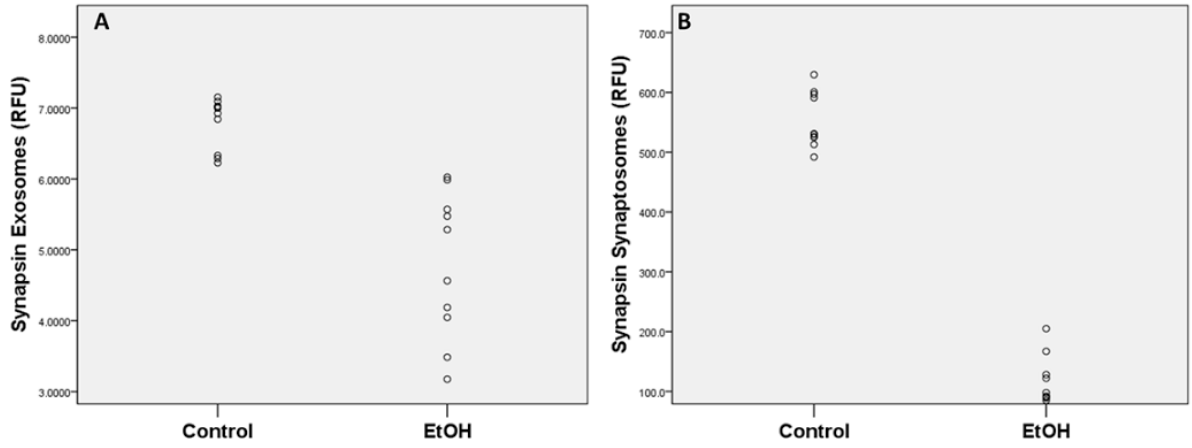
Abstract: **Introduction**: Ethanol (EtOH) can disrupt fetal brain development and formation of synaptic connections but mechanisms elucidated in animal models can be hard to confirm in human models. We hypothesized that altered fetal brain levels of the neuronal regulator microRNA-9 could be detected using our novel non-invasive method: maternal-plasma derived fetal neuronal exosomes (FNEs). **Methods:** We performed a matched case-control study in women at 9 -19 weeks gestation (GA). Heavy EtOH users were compared to unexposed controls matched for fetal sex and GA (10 CNTRL/10 EtOH). Plasma exosomes were precipitated (ExoQuick) and the fetal subset enriched (anti-Contactin-2/TAG1-steptavidin bead absorption). Synaptosomes (SYNPs) were prepared from fetal brain. MiR-9 levels were quantified by qRT-

PCR. Protein levels were assessed by ELISA or q Western blots. **Results**: EtOH was associated with significant down regulation of Mir-9 (FNE, 4.16 fold ↓, $p<0.001$, Brain, 1.2 fold↓, $p=0.004$), which supports a fetal origin for exosomes as Mir-9 is typically upregulated in adults. Similarly, downregulation was observed in Mir-9 downstream double negative feedback targets, REST and BDNF: BDNF FNEs (↓1.2; $p=0.009$), SYNPs (↓1.4; $p=0.04$); REST FNEs (↓1.33; $p=0.04$) SYNPs (↓4.6; $p<0.001$). Brain MiR-9 was strongly correlated with brain BDNF mRNA ($\rho= 0.82$, $p=0.004$). Synaptic injury was robustly associated with EtOH exposure and could be detected non-invasively using FNEs (Figure 1. $p<0.001$ for both) with high correlation between SYNPs and FNEs ($\rho = 0.86$, $p<0.001$). **Conclusions**: Our data suggest that in-utero exposure to EtOH is associated with potentially clinically significant alterations in human fetal brain expression of Mir-9 and downstream genes. Our results also support use of FNEs as a non-invasive approach to confirming mechanisms observed in animal models. FNE results should be correlated with pediatric outcomes to confirm their clinical utility in identifying pregnancies at risk for fetal alcohol syndrome. **Figure 1. Synapsin Expression in FNEs (A) and SYNPs (B) in an In-Vivo Human FAS Model.**



Disclosures: **N. Darbinian:** None. **E.J. Goetzl:** Other; Patent application. **N. Merabova:** None. **E. Lauretti:** None. **G. Tatevosian:** None. **D. Martirosyan:** None. **L. Goetzl:** Other; Patent application.

Poster

794. Injury and Trauma I

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 794.13/T8

Topic: C.09. Brain Injury and Trauma

Support: National Institute of Health Research (UK) grant RP-011-048

Title: Minocycline reduces chronic microglial activation following traumatic brain injury

Authors: *D. J. SHARP, A. JOLLY, J. COLE, P. JENKINS, M. PATEL, A. P. GOLDSTONE, R. GUNN, P. MATTHEWS, G. SCOTT;
Imperial Col. London, London, United Kingdom

Abstract: Objective:
Traumatic brain injury (TBI) can trigger chronic microglial activation, which may be harmful. The antibiotic minocycline is neuroprotective in animal models of TBI and other neurological disorders. An important mechanism is the inhibition of microglial activation. [^{11}C]PBR28 positron emission tomography (PET). binds to the translocator protein up-regulated by activated microglia. Here, we used [^{11}C]PBR28 PET to test the hypotheses: (1) chronic microglial activation is present in patients at least six months after moderate-severe TBI; (2) chronic microglial activation is higher in areas of WM damage that show progressive atrophy; and (3) minocycline reduces chronic microglial activation after TBI.
Methods:
Fifteen patients at least 6 months after a moderate-severe TBI and controls had structural and diffusion MRI, neuropsychological testing and [^{11}C]PBR28 PET. Patients received either minocycline 100mg orally twice daily or no drug (2:1 ratio) for 12 weeks. Patients had follow up at 12 weeks (with PET) and 6 months (without). [^{11}C]PBR28 volume of distribution (V_T) was estimated with the Logan plot, normalized to whole brain mean (distribution volume ratio, DVR) for cross-sectional analysis.
Results:
[^{11}C]PBR28 DVR was increased in cerebral white matter (WM) and thalamus. MRI measures of WM damage were highest in areas of increased [^{11}C]PBR28 binding. These areas with increased microglial activation showed greater longitudinal atrophy. Minocycline treatment was well tolerated and [^{11}C]PBR28 V_T after minocycline was significantly reduced (mean WM ΔV_T=-23.3%, 95% confidence interval -40.9 to -5.6%) compared to no drug. Patients showed impairments of information processing speed and this showed improvement of borderline significance in the minocycline treated group.
Interpretation:
Brain trauma can trigger long-term neurodegenerative processes, including persistent neuroinflammation. Using PET, we demonstrate that microglial activation is associated with progressive white matter (WM) damage, months and years after moderate-severe TBI. For the first time we show that areas associated with high [^{11}C]PBR28 binding showed greater atrophy over time, suggesting a mechanistic link between TBI-induced chronic neuroinflammation and neurodegeneration. In addition, we show that minocycline treatment in TBI patients produced a widespread reduction in [^{11}C]PBR28 binding, providing *in vivo* evidence of a direct effect of minocycline on chronic microglial activation.

Disclosures: **D.J. Sharp:** None. **A. Jolly:** None. **J. Cole:** None. **P. Jenkins:** None. **M. Patel:** None. **A.P. Goldstone:** None. **R. Gunn:** None. **P. Matthews:** None. **G. Scott:** None.

Poster

794. Injury and Trauma I

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 794.14/T9

Topic: C.09. Brain Injury and Trauma

Title: The auditory steady-state response can be a predictable index of conscious outcome in patients with severe head injury in the early stage

Authors: *S.-I. HIRANO;
Osaka Dent. Univ., Osaka, Japan

Abstract: Early diagnosis is important for all patients to provide appropriate treatment. Some electrophysiological examinations have been utilized to estimate the outcome of consciousness disturbance. One of the most influential causes of consciousness disturbance is hypofunction of brainstem reticular formation. Previous studies have suggested that the 40Hz auditory steady-state response (40Hz-ASR) originates in midbrain reticular formation. Hence I used the 40Hz-ASR with the auditory brainstem response (ABR), which reflects the specific ascending activity, to know the brainstem function in patients with severe head injury.
In this prospective study, the usefulness of the 40Hz-ASR as a predictor of consciousness outcome was evaluated. The 40Hz-ASR was examined in 27 patients with severe head injury. All of them were deeply comatose (Glasgow coma scale 3-8). No patient experienced a major complication during the treatment period. The author recorded the 40Hz-ASR and ABR simultaneously, and compared the results to clarify the characteristics and pathophysiological differences of these responses. The author classified the 40Hz-ASR into four groups and the ABR into five groups according to their appearances. The change in patients' consciousness level was noted successively. The author evaluated their condition at discharge following the Glasgow outcome scale, and determined as the final outcome.
The patients who lost waves III and V of the ABR had a poor outcome, and, in general, showed no 40Hz-ASR. In contrast, the ABRs of these patients who showed progressive worsening of 40 Hz-ASRs, were not necessarily disturbed at the same time. The patients who exhibited wave V had low mortality. However, if they showed no 40Hz-ASR during their convalescent stage, the consciousness disturbance persisted and some of the patients became vegetative. The patients who showed good or fair 40Hz-ASR in the acute or sub-acute stage recovered from the coma. Our results suggest that the ABR and the 40 Hz-ASR make original contributors in separate regions, and indicate that the ABR correlated with the vital outcome and the 40Hz-ASR correlated with the consciousness recovery. They might be utilized as indices of the vital risk and consciousness recovery, respectively. Moreover, as the 40Hz-ASR changed before the alteration of the level of consciousness in patients who were improving or worsening, it may serve as a useful tool for early prognostic evaluation of comatose patients. This tendency was not obvious

in the ABR results. The author has obtained Institutional Review Board approval prior to launching this study, and has no COI to declare.

Disclosures: S. Hirano: None.

Poster

794. Injury and Trauma I

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 794.15/T10

Topic: C.09. Brain Injury and Trauma

Support: WRIISC/VA Patient Care Services

Title: Neural and epigenetic contributions to posttraumatic stress symptoms: The influence of hippocampal volume and glucocorticoid receptor gene methylation

Authors: *M. W. MCNERNEY[1,2], T. SHENG[1,2], A. LEE[2], D. LYONS[2], S. SOMAN[3], J. NECHVATAL[1,2], J. HALLMAYER[1,2], R. O'HARA[1,2], W. ASHFORD[1,2], J. YESAVAGE[1,2], M. ADAMSON[4,2];
[1]VA, Palo Alto, CA; [2]Stanford Med. Sch., Palo Alto, CA; [3]Beth Isreal, Boston, MA; [4]DVBIC, Dept. of Defence, Palo Alto, CA

Abstract: Background: Deployed Veterans often experience physical and psychological trauma during combat and exhibit symptoms of posttraumatic stress (PTSD) after service. As the etiology of PTSD symptoms is complex, a better understanding of the underlying biological mechanisms can potentially inform preventative care and treatment. Recent findings from the fields of neuroimaging and epigenetics have offered important insights about potential brain structures and biochemical pathways of modified gene expression associated with PTSD, but a comprehensive model of predictive biomarkers is still lacking. **Methods**: In the current study, we evaluated the potential of an integrated biomarker model that combined neuroimaging and epigenetic measures. Sixty-seven post-deployed Veterans received high resolution structural brain scans and provided saliva samples for DNA extraction. Based on previous literature, we characterized the overall hippocampal volume (using FreeSurfer; adjusted for total intracranial volume) and quantified methylation of the promoter region of the glucocorticoid receptor (GR) gene (DNA pyrosequencing). The patient sample was split into evenly matched discovery (n = 34) and validation (n = 33) subsamples (balanced across all predictor and outcome variables) to enable validation/generalizability analyses. **Results**: In the discovery subsample, we found that total hippocampal volume, GR methylation, and their interaction were indicative of self-reported PTSD symptom severity (adjusted r^2 = .24, p = .02, all |T|s > 2.35; education and history of

traumatic brain injury (TBI) as covariates). History of TBI was also a significant factor (T = 2.26). A confirmatory analysis with the validation subsample indicated that predicted self-report PTSD symptoms were substantially correlated with patients' actual self-reported PTSD symptoms (r = .37, p = .03). **Conclusion**: Our findings suggest that GR methylation and total hippocampal volume contribute to PTSD symptoms. This finding was confirmed using validation analysis with an independent patient sample. Thus, a more comprehensive biomarker model that incorporates measures from different sources and considers their potential interactions will be valuable towards predicting mental health symptoms.

Disclosures: **M.W. McNerney:** None. **T. Sheng:** None. **A. Lee:** None. **D. Lyons:** None. **S. Soman:** None. **J. Nechvatal:** None. **J. Hallmayer:** None. **R. O'Hara:** None. **W. Ashford:** None. **J. Yesavage:** None. **M. Adamson:** None.

Poster

794. Injury and Trauma I

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 794.16/T11

Topic: C.09. Brain Injury and Trauma

Support: CENC W81XWH-13-2-0095

Veterans Affairs I01RX001774

U01NS086659-0

P30AG13846

Title: Preliminary expression profiling of tau-positive cholinergic basal forebrain neurons in the nucleus basalis of Meynert in postmortem chronic traumatic encephalopathy brain: A Chronic Effects of Neurotrauma Consortium Study

Authors: ***E. J. MUFSON**[1], S. E. PEREZ[1], B. HE[1], S. LEE[2], E. PETRKOVA[3], A. C. MCKEE[4], S. D. GINSBERG[2];
[1]Neurobio., Barrow Neurolog. Inst., Phoenix, AZ; [2]Dept. of Psychiatry, Nathan Kline Inst., Orangeburg, NY; [3]Child and Adolescent Psychiatry, New York Univ. Langone Med. Ctr., New York, NY; [4]Neurol. and Pathology, Boston Univ. Sch. Med., Boston, MA

Abstract: Military personnel in the battlefield and athletes in contact sports (e.g., boxing, American football, and hockey) are exposed to mild repetitive traumatic brain injury, which can result in chronic traumatic encephalopathy (CTE). Although in its early stages, the

neuropathology of CTE is characterized by the intracellular accumulation of abnormally phosphorylated tau protein (p-tau), the main constituent of neurofibrillary tangles (NFTs) in the forebrain similar to Alzheimer's disease (AD). Recently, we found that as in AD, the cholinergic neurons within the nucleus basalis of Meynert (nbM) display intracellular tau accumulation and deposition across the pathological stages of CTE. However, molecular mechanisms underlying CTE neurodegeneration are not well understood. Here, we assessed the genetic signature of cholinergic neurons containing the tau pretangle maker pS422 within the nbM obtained from subjects who died with a clinical diagnosis of CTE and received a neuropathological staging assessment of stage II, III, and IV based on NINDS consensus criteria, using laser capture microdissection and custom-designed microarray analysis. Preliminary analysis revealed that between CTE Stages II and III there was a significant upregulation of genes associated with neuropathology and protein aggregation including alpha-synuclein (SNCA), sirtruin 1 (SIRT1) and neprilysin}, NFT formation (MAPK and GSK3B), apoptosis (CASP8, FAS/FASLR), endosomal/lysosomal/autophagy (M6PR, LAMP2, USP1, LIPA, ACP2, and PPT1), RNA and DNA repair and synthesis (RHEB, ERCC1, and DDX1), and neurodevelopment (TSC2, NOTCH-1). By contrast, comparing Stage II to IV, the only significant preliminary gene alteration was the downregulation of the pro-apoptotic gene CASP-7. Comparing Stage III to IV revealed an upregulation of SNCA, JUNB, Protein kinase C epsilon and amyloid-beta precursor protein (APP) genes, each related to AD, as well as downregulation of the inhibitory GABA neurotransmitter transporter, GAT2. These preliminary findings suggest that genes related to protein aggregation, cell survival/death are upregulated during the early pathological stages of CTE along with a late upregulation of the APP gene. Based on these initial findings, drug discovery related to CTE should be directed towards mechanisms of neuron survival rather than focusing solely on amyloid or tau therapies.

Disclosures: **E.J. Mufson:** None. **S.E. Perez:** None. **B. He:** None. **S. Lee:** None. **E. Petrkova:** None. **A.C. McKee:** None. **S.D. Ginsberg:** None.

Poster

794. Injury and Trauma I

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 794.17/T12

Topic: C.09. Brain Injury and Trauma

Support: Brain Scope Inc.

Title: Preventing mild traumatic brain injury in women's soccer: an assessment of the relationship between cerebrovascular reactivity changes and daily loading

Authors: *D. O. SVALDI[1], E. C. MCCUEN[1], J. P. E. MUSIC[2], C. JOSHI[3], E. A. NAUMAN[4], T. M. TALAVAGE[5];
[1]Biomed. Engin., [2]Mechanical Engin., [3]Electrical Engin., [4]Mechanical Engin. Biomed. Engin., [5]Electrical Engin. Biomed. Engin., Purdue Univ., West Lafayette, IN

Abstract: As participation in women's soccer continues to grow, prevention of mild TBI (mTBI) has become a major concern for female athletes. Studies suggest (Len & Neary, 2011) that cerebrovascular deficits play an important role in the neurocognitive sequela associated with mTBI. However, the relationship between head impact exposure and cerebrovascular brain changes associated with mTBI is not well understood. Previous FMRI work (Svaldi et al., 2016) comparing asymptomatic female high school soccer athletes experiencing high cumulative loading to female high school non-collision sport control athletes revealed cerebrovascular reactivity (CVR) decreases in soccer athletes comparable to those observed following mTBI (Gardner et al., 2015; Mutch et al., 2014). Here, a larger dataset is used to assess the effect of relative daily loading on observed neuroimaging changes. Cerebrovascular reactivity (CVR) was measured with FMRI (3T GE Signa HDx) using a breath hold challenge as described in (Svaldi et al., 2016). Soccer athletes were imaged before contact (*Pre)*, within the first (*In1*) and second halves (*In2)* of competition, and 1-2 months after the end of competition (*Post)*. Controls were scanned twice (*Test/Re-test)*, 4-6 weeks apart, during comparable periods of activity. Head acceleration events experienced by soccer athletes were monitored as in (McCuen et al., 2015). The (to-date) cumulative peak translational acceleration (CPTA) was calculated for each soccer athlete at each imaging session only using events exceeding 50g. Soccer athletes were divided into three groups (*HighLoad*, *MidLoad*, *LowLoad*) at each imaging session for two analyses: (1) net loading using CPTA, (2) normalized loading (nCPTA), obtained by dividing CPTA by the number of participation days. At each session, changes in CVR were evaluated as a function of exposure (CPTA, nCPTA) for all soccer athletes *(Total*) and after division into groups. CVR changes between sessions were also evaluated for the control athlete cohort. Control athletes exhibited no change in CVR. Soccer athletes (*Total*) exhibited significant decreases in CVR for at all time-points. Decreases were biased by the intensity of daily loading experienced by the individual athletes, rather than by the absolute total loading experienced to-date. From this we conclude that cumulative load and the amount of time over which this load is accrued are both important in assessing the relationship between head impact exposure and observed cerebrovascular changes. Limiting daily loading maybe useful in preventing sports related mTBI.

Disclosures: D.O. Svaldi: None. **E.C. McCuen:** None. **J.P.E. Music:** None. **C. Joshi:** None. **E.A. Nauman:** None. **T.M. Talavage:** None.

Poster

794. Injury and Trauma I

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 794.18/T13

Topic: C.09. Brain Injury and Trauma

Support: CIHR/NSERC 315705

CIHR 398908

Title: Concussion alters basal cerebral blood flow and reactive capacity: a dual-echo pcasl fMRI study

Authors: *C. I. MARK[1], A. CHAMPAGNE[1], A. BHOGAL[2], I. JOHNSRUDE[3], D. COOK[1]; [1]Ctr. for Neurosci. Studies, Queen's Univ., Kingston, ON, Canada; [2]Radiology, Univ. Med. Ctr. Utrecht, Utrecht, Netherlands; [3]Brain and Mind Institute, Dept. of Psychology, Univ. of Western Ontario, London, ON, Canada

Abstract: Objectives
Existing symptom-based and structural brain imaging methods have been of limited help in outcome prognostication or making return-to-play decisions. A possible explanation for persisting deficits is sustained impairment of cerebrovascular autoregulation. Quantitative functional MRI (qfMRI) and robust gas control provides an opportunity to directly image cerebrovascular physiology and may be a more sensitive modality to investigate the pathophysiology of concussion.
Methods
We complement traditional blood oxygenation-level dependent (BOLD) acquisition with simultaneous cerebral blood flow (CBF) measurements during targeted hypercapnic breathing challenges in varsity athletes during the acute (< 7 days), early (14 days) and late (3 months, 1 year) post-concussion stages. Subjects are scanned on a 32-channel receiver coil [Tim-Trio, Siemens]. Following standard anatomical imaging, and acquisition of a CBF quantification image, the breathing task is performed through a sealed rebreathing circuit (RespirAct^{TM}, Thornhill Research Inc) under Dual-Echo pseudo-Continuous Arterial Spin Labelling (DE-pCASL): A block of 2 min hypercapnia at 10 mmHg increase in end-tidal partial pressure in CO_2 above the subject's resting level, preceded and followed by 2 min at rest, under iso-oxia. In-house data analysis includes motion correction, de-trending, spatial smoothing, slice time correction, re-alignment of MR data with the respiratory traces and registration to MNI space. Block designs are used to model BOLD-CVR and quantitative CBF maps.
Results
Preliminary data on 8 concussed (CI, 3 females) and 10 non-concussed (NC, 5 females) athletes over acute and early recovery time points reveal significant abnormal patterns in BOLD-CVR

(p=0.009), baseline perfusion (p=0.008) and CBF-CVR (p=0.006) subsequent to concussion. A reduction in BOLD-CVR is generally observed 7 days post-concussion; grossly recovering after 14 days, with the greatest differences in the frontal cortex. A closer look at the underlying baseline perfusion maps indicates a hyperemic response 7 days post-injury, which does not resolve to normal level after 3 months. Reduced CBF-CVR is observed throughout all time points.

Conclusion

In this study, indications of impaired cerebrovascular regulation, through changes in BOLD, baseline perfusion and reactive capacity, were observed across athletes in the acute and early recovery stages post-concussion. Sustained impaired CVR, while BOLD is restored to normal levels might be indicative of a rising hypometabolic response; a potential homeostatic safety mechanism of the brain to spare healthy tissue.

Disclosures: C.I. Mark: None. **A. Champagne:** None. **A. Bhogal:** None. **I. Johnsrude:** None. **D. Cook:** None.

Poster

794. Injury and Trauma I

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 794.19/T14

Topic: C.09. Brain Injury and Trauma

Support: NSERC

Title: The influence of aerobic exercise on intracortical circuits in high versus low physically active individuals

Authors: *T. LULIC[1], J. EL-SAYES[2], F. J. HUNTER[2], A. J. NELSON[2];
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Abstract: There is emerging evidence that regular physical activity can influence brain function and plasticity. In general, lower limb cycling has been shown to increase corticospinal excitability and reduce short-intracortical inhibition (SICI) in resting upper limb muscles. In addition, the response to a neuroplasticity protocol has been found to be dictated by previous physical activity levels. However, the exact mechanisms by which physical activity promotes plasticity are unknown. Additionally, it is unknown whether levels of physical activity may influence response to an exercise intervention. Hence, the aim of this study was two-fold: 1) to determine if differences exist in intracortical circuitry in highly physically active and low physically active individuals; and 2) to determine whether the amount of change in intracortical

circuitry following a single session of moderate intensity aerobic exercise is modulated differently in high and low physically active individuals. A total of 24 participants (18-30 years) were divided into low-physically active (LPA) and high-physically active (HPA) group based on Minnesota Leisure-Time Physical Activity Questionnaire (LPA: 708.12 ± 632.89, HPA: 2149.88). Electromyographic recordings were obtained from the right first dorsal interosseous (FDI) muscle. Paired-pulse Transcranial magnetic stimulation (TMS) of the left-hemisphere motor cortex was used to assess short-interval intracortical inhibition (2 ms SICI) and facilitation (10 ms ICF), as well as short intracortical facilitation (1.2 and 2.5 SICF) before and following exercise. Exercise involved 20 minutes of moderate intensity (50-70% age-predicted maximal heart rate) lower limb cycling on a recumbent cycle ergometer. There were no differences in SICI, ICF and SICF before or following exercise between LPA and HPA. However, reductions in SICI and were observed in both groups following exercise. These findings show that a short period of aerobic exercise can transiently reduce inhibition and facilitation in the motor cortex. However, the amount of previous physical activity may not influence baseline measures of intracortical circuitry or the amount of change within the circuits following aerobic exercise. Exercise induced reductions in inhibition have been suggested to provide a favorable environment for plasticity induction, and hence it is important to further explore the effects of chronic exercise on plasticity within motor cortex.

Disclosures: **T. Lulic:** None. **J. El-Sayes:** None. **F.J. Hunter:** None. **A.J. Nelson:** None.

Poster

794. Injury and Trauma I

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 794.20/T15

Topic: C.09. Brain Injury and Trauma

Support: 5 P01 HL 046925-19

5 T32 GM 007337-38

Title: Brain structure in premature infants: liberal vs. restricted red blood cell transfusions

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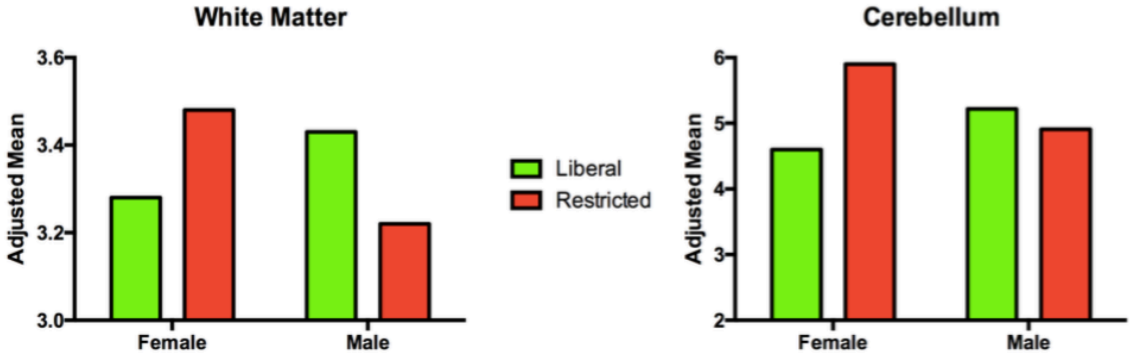
Abstract: **Objective:** To assess the neonatal brain structure changes in preterm infants who received red blood cell transfusion for anemia of prematurity.

Methods: As part of the larger clinical Transfusion of Prematures trial, the neonates are randomly assigned to receive red blood cell transfusions according to one of two paradigms: either liberal or restrictive threshold. It is unknown which transfusion strategy is superior for optimal brain development. To accurately measure neonatal brain volumes, a novel neonate brain atlas was developed. To account for brain growth, all volumetric analyses were corrected for total intracranial volume. Analysis of covariance assessed differences in brain region volumes between neonates (n=15) assigned to liberal or restrictive transfusions, controlling for sex, gestational age and chronological age. As multiple studies established pro-inflammatory profile in neonates who receive transfusions, we included a panel of pro-inflammatory biomarkers. Spearman's rank correlation was used to determine the relationships between maximum serum levels of pro-inflammatory biomarkers and brain growth.

Results: Significant sex-by-group interaction was found. Females assigned to the liberal group had lower volumes of cerebral white matter and cerebellum, whereas, males assigned to the restricted protocol had lower volumes of cerebral white matter. Higher serum concentrations of pro-inflammatory cytokines IL-8 and MCP-1 were associated with lower volumes of cerebral white matter. A lower level of the combination of pro-apoptotic cytokines TNF-α, TNF-β, and a marker of endothelial activation sVCAM-1 was associated with higher volumes of cerebral white matter.

Conclusions: Red blood cell transfusions affected brain development in premature infants assigned to liberal or restrictive transfusion protocols via potential inflammatory pathways. Understanding how different red blood cell transfusion practices impact brain growth may lead to significant clinical impact on the treatment guidelines for anemia of prematurity.



Disclosures: **A.V. Tereshchenko:** None. **A. Metzger:** None. **V. Magnotta:** None. **J. Widness:** None. **P. Nopoulos:** None.

Poster

794. Injury and Trauma I

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 794.21/T16

Topic: C.09. Brain Injury and Trauma

Support: NIH R01 NS082432

The Dana Foundation David Mahoney Neruorimaging Program

Title: Executive dysfunction associated with greater number of lifetime concussions in amateur soccer players

Authors: *L. E. HUNTER[1], M. LIPTON[2];
[2]Radiology, [1]Albert Einstein Col. of Med., Bronx, NY

Abstract: Objectives: Concussion is a common occurrence in soccer that can be caused by collisions as well as heading the ball. While symptoms related to concussion resolve in most people, up to 30% of individuals who suffer a concussion will have chronic impairments that negatively impact their quality of life. Herein, we aim to identify the risk for long -term cognitive deficits due to all causes of recognized concussion in amateur soccer players who have been playing at a similar frequency for an average of twelve years.
Methods: We measured 275 soccer players (mean age 25.8; 202 men, 73 women) enrolled in the Einstein Soccer Study, an ongoing longitudinal study of adult amateur soccer players. History of concussion was captured using a structured questionnaire that asks participants to report the number of lifetime concussions for which they received or were advised to seek medical attention. Executive function, attention, vigilance, working memory, visual learning memory, verbal learning and memory and psychomotor speed were measured using Cogstate, a validated computer based measurement of cognition. We used multivariate linear regressions to examine the association between number of lifetime concussions and cognition in the aforementioned domains. Regressions were adjusted for age, gender, years of education, handedness, race, IQ and total lifetime headings.
Results: 65% of players reported no lifetime concussions, 16% reported 1 lifetime concussion, 10 % reported 2 lifetime concussions, and 9% reported 3-6 lifetime concussions. Number of lifetime concussion was significantly (=1.87, p= 0.021) associated with worse executive function, evidenced by more errors on the Cogstate set-shifting task.
Conclusion: Recognized concussions are associated with executive dysfunction in adult amateur soccer players. Future studies would benefit from investigation of the underlying pathologic mechanisms that subserve cognitive dysfunction.

Disclosures: L.E. Hunter: None. **M. Lipton:** None.

Poster

794. Injury and Trauma I

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 794.22/T17

Topic: C.09. Brain Injury and Trauma

Title: Unsupervised diffusion component analysis in post-traumatic epilepsy

Authors: *D. DUNCAN[1], P. VESPA[3], A. W. TOGA[2];
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Abstract: Introduction: Epileptogenesis is common after traumatic brain injury (TBI), and because much is known about the physical history of post-traumatic epilepsy (PTE), it represents a near-ideal human model in which to study the process of developing seizures. The latency period between the injury and the development of seizures is usually short, with a median latency of one year, making it practical to study epileptogenesis with reasonable follow up periods.
Methods: Using scalp EEG recordings for 29 patients as well as depth EEG recordings for 6 of those patients, the goal of our analysis is to find a way to quantitatively detect seizure onset post trauma. A novel approach based on the diffusion map framework, which is considered to be one of the leading manifold learning methods, is proposed. Diffusion mapping provides dimensionality reduction of the data as well as pattern recognition that can be used to distinguish different states of the patient, such as seizures and non-seizure spikes in the EEG. A new algorithm, Unsupervised Diffusion Component Analysis is developed to construct coordinates that generate efficient geometric representations of the complex structures in the data. The algorithm is an adaptation of diffusion maps and is combined with principal components analysis and other techniques. The extensions lead to efficiency in use, in terms of reduced computational complexity, which have the potential to become useful techniques for practitioners in the field. Furthermore, the algorithm is completely automatic and unsupervised, which could potentially be a useful tool for doctors to identify early features of epileptogenesis after trauma. This method is also adapted to the data to enable the extraction of the underlying brain activity.
Results: Some new, interesting and promising results indicating how the proposed algorithm is used to detect spikes in the EEG data as well as other changes over time is shown.
Discussion: This nonlinear and local network approach has been used to determine if the early occurrences of specific electrical features of epileptogenesis, such as interictal epileptiform activity and morphologic changes in spikes and seizures, during the initial week after TBI predicts the development of PTE.

Disclosures: D. Duncan: None. **P. Vespa:** None. **A.W. Toga:** None.

Poster

794. Injury and Trauma I

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 794.23/T18

Topic: C.09. Brain Injury and Trauma

Support: Tiny Blue Dot Foundation

McDonnell

Title: How do the dynamics of functional brain connectivity change during recovery from traumatic brain injury?

Authors: *J. S. CRONE[1], P. M. VESPA[2], E. E. LUTKENHOFF[2], M. M. MONTI[2];
[1]UCLA, Los Angeles, ; [2]UCLA, Los Angeles, CA

Abstract: After severe injury, the brain reorganizes itself recovering gradually from coma. However, some patients remain in a state of wakefulness without or with only minimal awareness. Studying these patients is essential not only for research of consciousness but also for clinical purposes. Despite extensive work, the mechanisms underlying recovery are not well understood.

To address these problems, previous research in patients has focused on the identification of biological markers for impaired consciousness. However, findings remain divergent in respect to effects on global information integration and specific regions involved. This may partly be due to the fact that these studies were only performed in chronic patients. However, the complex dynamic process of traumatic brain injury and recovery of consciousness is most likely taking place in the first days to weeks. Thus, it is essential to investigate dynamics at an acute stage of injury.

Resting-state functional connectivity of 12 acute patients with severe brain injury were investigated at 2 time points during the acute stage (days after the incidence) and during the chronic stage (6 months after). Spatial group ICA was performed with 100 components to define the nodes of the graphs. For the dynamic connectivity analysis, we used a sliding time-window approach. For each time-window, we obtained a 48 × 48 nodes correlation matrix and calculated connectivity strength. To identify the underlying connectivity states, we implemented the approach by Yu et al. (2015, Neuroimage 107, 345-355) based on the modularity of the correlated nodal connectivity strength. Patients were divided in 2 groups; 7 patients being in a state of unconsciousness at the first assessment and 5 patients being in a state of (minimal) consciousness. Variance in connectivity strength and number of states were compared between groups and within patients.

The results show that there is a significant difference of variance in connectivity strength across time between the acute and the chronic stage (see Fig. 1). Interestingly, the variance at the

chronic stage was much higher for those patients who transitioned from unconsciousness at the initial assessment to a state of consciousness compared to those who were already conscious (see Fig. 2). When comparing the number of brain states, only chronic patients who have been conscious from the initial assessment on and show a higher level of cognitive recovery have a higher number of states (see Fig. 3). This indicates that in severe brain injury a flexible repertoire of functional configurations (brain states) is rather a marker of higher level cognitive functioning than of consciousness per se.

Disclosures: J.S. Crone: None. **P.M. Vespa:** None. **E.E. Lutkenhoff:** None. **M.M. Monti:** None.

Poster

795. Injury and Trauma II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 795.01/U1

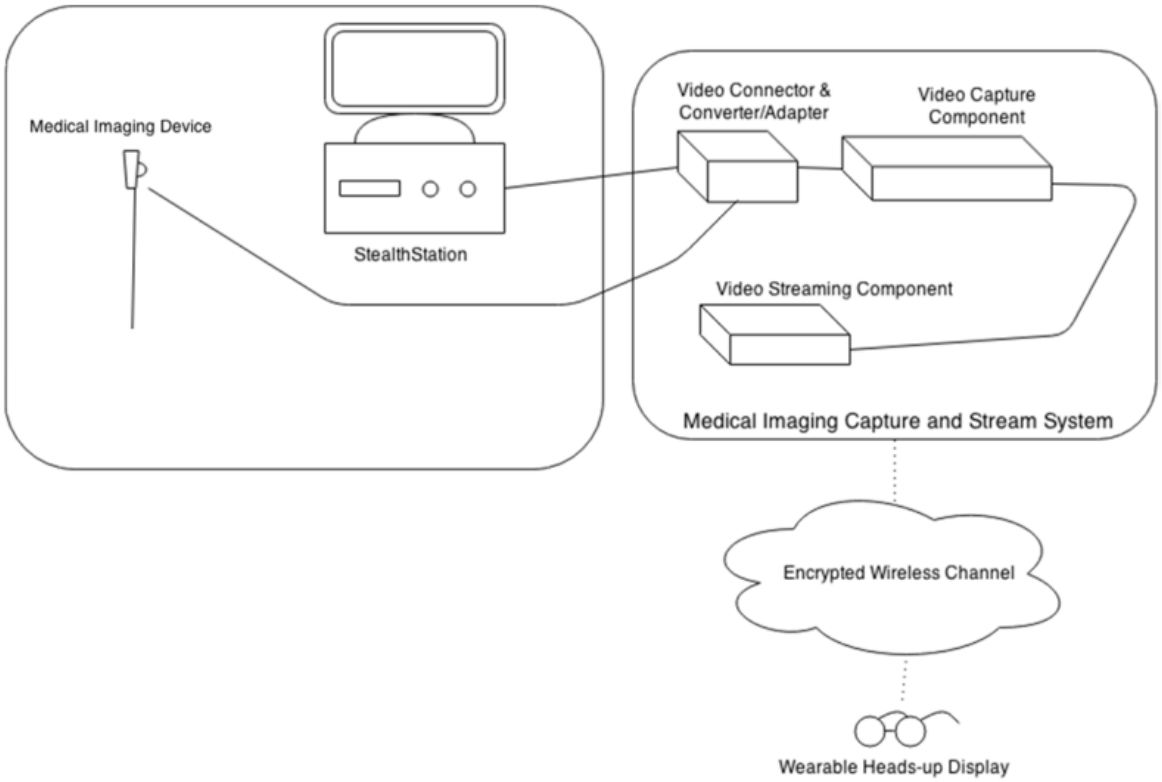
Topic: C.09. Brain Injury and Trauma

Title: Evaluation of a wearable head-up display assisted spine instrumentation system.

Authors: *R. CHEN[1], P. K. HAN[1], P. SI[1], W. D. FREEMAN[2], S. M. PIRRIS[2,3], J. W. YOON[2]; [1]Georgia Inst. of Technol., Atlanta, GA; [2]Mayo Clin., Jacksonville, FL; [3]St Vincent's Spine and Brain Inst., Jacksonville, FL

Abstract: Objective: The primary aim of this study was to determine the safety and feasibility of capturing and streaming neuronavigation images onto a head-up display during spine instrumentation. **Methods:** Using a novel device, neuronavigation images were captured and transferred wirelessly via a password-encrypted network to the head-up display. Medical images from the StealthStation device are captured by a medical imaging capture and stream system, which processes and streams the image onto the head-up display via an encrypted wireless channel (Figure 1). This setup allows physicians to place pedicle screws without having to shift attention away from the patient (Figure 2). Two surgeons used the device intra-operatively in ten patients undergoing spine instrumentation. The surgeons conducted the operations both with and without the head-up display, and screw placement times were recorded. At the end of the procedure, the surgeons completed a survey to gather their opinion of the system. **Results:** 40 pedicle screws were placed using a head-up display. The average screw placement time was shorter when a head-up display was used (4.13 minutes with vs. 4.86 minutes without). The postprocedure survey demonstrated that the surgeons had an overall positive experience using a head-up display. **Conclusion:** A wearable head-up display can benefit current neuronavigation

systems, but larger, outcomes-based trials are needed. An enlarged display and higher processing speed may significantly improve this technology.



Disclosures: **R. Chen:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); MedCyclops. **P.K. Han:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); MedCyclops. **P. Si:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); MedCyclops. **W.D. Freeman:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); MedCyclops. **S.M. Pirris:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); MedCyclops. **J.W. Yoon:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); MedCyclops.

Poster

795. Injury and Trauma II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 795.02/U2

Topic: C.09. Brain Injury and Trauma

Support: Utah NASA Space Grant Consortium

Title: A quantitative motor assessment with normative data for traumatic brain injury

Authors: *P. K. JOHNSON[1], C. J. KINCAID[2], S. D. GRIMSHAW[3], E. D. BIGLER[4], S. K. CHARLES[2];
[1]Physiol. and Developmental Biol., [2]Mechanical Engin., [3]Statistics, [4]Psychology, Brigham Young Univ., Provo, UT

Abstract: Conventional exams to assess motor deficits following a traumatic brain injury (TBI) often rely on subjective observations of the clinician conducting the assessment and tend to fail to detect subtle underlying damage in the brain. Motion capture devices developed primarily for gaming make it possible to record finger and hand movements with great speed and accuracy. We leveraged this technology to create a Quantitative Motor Assessment (QMA) to evaluate movement following a TBI and establish a database of normative measures. Our QMA consists of customized software integrated with a portable, inexpensive motion capture sensor, and five movement tests adapted from conventional tests. The tests include measures of balance, efficiency and regularity of finger oscillation (FO), visually guided movement (VGM), kinetic and postural tremor, and reaction time. We administered the QMA to 104 (53 male and 51 female) healthy individuals, 18-50 years old. In addition, we included grip strength, visuomotor integration, and Halstead-Reitan Finger Tapping Test (FTT) for reference. We converted the

captured raw data to meaningful measures on which we conducted a statistical analysis and established a normative database of unimpaired motor behavior. The normative data were generally stereotyped with the following expected differences. We found differences in the number of taps between men and women on the FO test ($p=.007$) and differences in dysmetria between the dominant and non-dominant hands on the VGM test ($p<.001$). On the balance tests, there were differences between Eyes Open vs. Eyes Closed conditions on both Hard Surface ($p<.001$) and Soft Surface ($p<.001$). There was a high correlation between the amplitude and frequency of FO (right $r = .69$ and left $r = .63$), as well as a negative correlation between the mean number of FO and the frequency of FO ($r = -.72$). In addition to these expected differences, we were surprised to find no correlation (right $r=.23$ and left $r=.36$) between the QMA FO and the traditional FTT, which we interpreted to indicate that the QMA test measures a different attribute than the FTT. Current research focuses on administering this QMA to a TBI population and also acquiring MRI brain scans in order to compare their results to the normative data, and to correlate their QMA abnormalities to abnormalities seen on their scans. We expect that the sensitivity, objectivity, low cost, portability, and ease of use will make the QMA a beneficial and accessible tool to clinicians as well as researchers.

Disclosures: **P.K. Johnson:** None. **C.J. Kincaid:** None. **S.D. Grimshaw:** None. **E.D. Bigler:** None. **S.K. Charles:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Vykon Technologies LLC.

Poster

795. Injury and Trauma II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 795.03/U3

Topic: C.09. Brain Injury and Trauma

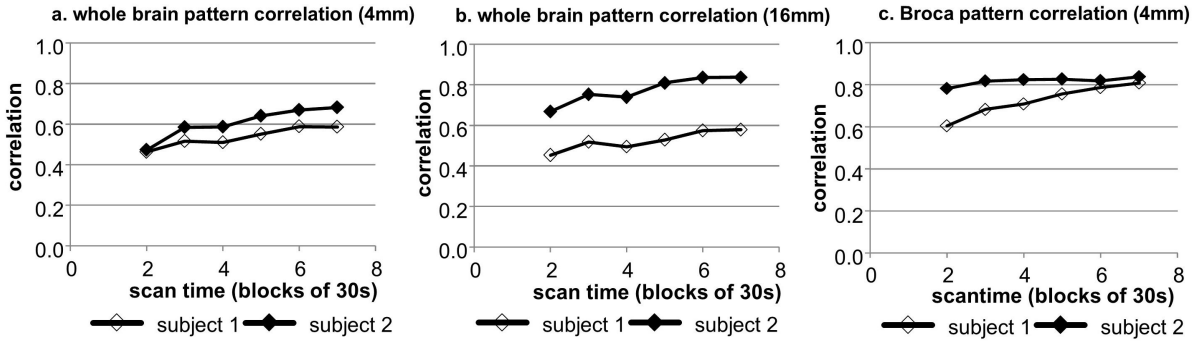
Support: ZonMW 80-84200-98-14211

Title: Estimation of single subject fMRI reproducibility

Authors: *J. M. JANSMA[1], G.-J. RUTTEN[2];
[1]Elisabeth Hosp., Tilburg, Netherlands; [2]Dept. of Neurosurg., Elisabeth Tweesteden Hosp., Tilburg, Netherlands

Abstract: Introduction. There is an increasing demand for clinical use of fMRI, for instance to aid surgical planning. For these applications, it is important to know the single subject fMRI reproducibility. Although many statistical packages can produce single subject statistical maps, that maps do *not* contain information about reproducibility, but about the chance that there was

activation at the time of the scanning session. Additionally, pattern reproducibility may be more relevant for clinical applications than single voxel value reproducibility. In this study, we estimated the effect of scantime, voxel resolution as well as the size of the examined region on pattern reproducibility in two subjects, scanned three and four times with a commonly used clinical fMRI paradigm. Method. Both subjects performed a verb generation task in a block design with seven 30s task blocks alternated with eight 30s rest periods (3T Philips scanner). A GLM was performed to calculate beta values per voxel (for 2, 3, 4, 5, 6 and 7 blocks), at unsmoothed 4 mm as well as a transformed 16 mm resolution. Activation maps were correlated voxel by voxel for each subject, resulting in six values for subject 1 and three for subject 2, per condition. Values were averaged per subject. Results. Whole brain pattern reproducibility appeared to be relatively high for all conditions in both subjects (subject1: 10.45- 0.59; subject 2: 0.47 - 0.84). Effect of scantime was substantial in both subjects (see figure 1a, b). Effect of resolution was also substantial in one subject, but almost non-existent in the other subject (see figure 1a, b). Limiting the region to left Broca did not reduce reproducibility (4mm resolution; subject 1: 0.60 - 0.81; subject 2: 0.78 - 0.84, see figure 1c). Discussion. Our results shows that within subject pattern reproducibility is at a level that appears to be sufficient to produce information that can be used for clinical applications, even in small regions, at a relative high unsmoothed resolution, and for short scantimes. These results are promising for clinical applications of fMRI such as surgical planning.



Disclosures: **J.M. Jansma:** None. **G. Rutten:** None.

Poster

795. Injury and Trauma II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 795.04/U4

Topic: C.09. Brain Injury and Trauma

Support: USAMRMC NINAD MEM-91-2714

Department of Defense the Center for Neuroscience and Regenerative Medicine 300601 8.0160855510005

Title: Disrupted gamma synchrony after mild traumatic brain injury and its link with cerebellar white matter damage

Authors: *C. WANG[1], M. E. COSTANZO[2], D. KEYSER[3], K. BASHIRELAHI[1], D. DARMON[1], D. L. PHAM[5], M. J. ROY[4], P. RAPP[3];
[1]HJF/USUHS, Rockville, MD; [2]HJF/USUHS, Bethesda, MD; [3]Dept. of Military and Emergency Med., USUHS, Bethesda, MD; [4]USUHS, Department of Medicine, MD; [5]Ctr. for Neurosci. and Regenerative Med., The Henry M. Jackson Fndn., Bethesda, MD

Abstract: Mild traumatic brain injury (mTBI) has been associated with disrupted structural connectivity due to induced white matter damage and degeneration. However, little is known about how the breakdown of white matter integrity alters functional neuronal connectivity in the brain after mTBI. To investigate this question, we recorded resting state EEG and diffusion tensor imaging (DTI) from a cohort of military service members recently returned from deployment to Iraq or Afghanistan. A newly developed neural synchronization measure, namely, weighted phase lag index (wPLI), was computed from EEG data and the fractional anisotropy (FA), a measure of white matter integrity, was computed from DTI data. Fifteen service members with a history of mTBI (< 3 years) were compared to twenty-two demographically similar controls who reported no history of head injury. In the EEG analysis we observed that phase synchrony at low-gamma frequency band (25-40 Hz) across scalp regions was significantly decreased in mTBI cases compared with controls. In the DTI analysis we observed that the FA of the inferior cerebellar peduncle was significantly lower in mTBI cases compared with controls. More importantly, we found that these two impaired measurements were significantly correlated across subjects in the mTBI group: lower FA of the inferior cerebellar peduncle was associated with lower phase synchrony at low-gamma frequency. These findings suggest that disrupted synchronization of low-gamma activity across cortical areas is likely to be a characteristic functional pathology after mTBI, and its underlying cause may be the breakdown of cortical-cerebellar circuits due to diffuse axonal injury.

Disclosures: **C. Wang:** None. **M.E. Costanzo:** None. **D. Keyser:** None. **K. Bashirelahi:** None. **D. Darmon:** None. **D.L. Pham:** None. **M.J. Roy:** None. **P. Rapp:** None.

Poster

795. Injury and Trauma II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 795.05/U5

Topic: C.09. Brain Injury and Trauma

Support: NIDILRR-ARRT-H133P130001

Title: Neurocognitive and symptom recovery from sport-related mild traumatic brain injury (mtbi)

Authors: E. ABBASSI[1], H. BRASSEL[1], *A. P. SALVATORE[2];
[1]Rehabil. Sci., Univ. of Texas at El Paso, El Paso, TX; [2]U. of Texas At El Paso, Santa Teresa, NM

Abstract: Introduction: Medical reports suggest sport-related MTBI may result in permanent cognitive and neurological impairments. Frequency of MTBI and a concern about its long-term effects have caused legislative organizations to call for MTBI management programs. The clinical focus is to prevent premature return to play reducing an athlete's risk of receiving another injury. Studies in this field are not consistent regarding recovery duration of MTBI. Some studies show a short recovery time (a few days) whereas others suggest recovery time extends beyond one week of the injury. The main purpose of the present study was to further investigate the recovery duration in MTBI young athletes. **Method:** A computerized neurocognitive test, Immediate Post-concussion Assessment and Cognitive Testing (ImPACT™), was administered to 38 athletes. A pre-injury baseline assessment was conducted and when the athlete sustained an MTBI, post-injury assessments were repeated so that results could be compared. The neurocognitive testing included four composite scores of verbal memory, visual memory, speed of processing, and reaction time. A self-reported list of 22 MTBI symptoms (e.g., headache, nausea, fatigue, sensitivity to noise) captured a total symptom score. The four composite scores and the total symptom score were dependent variables. **Results:** Participants were 17.08 years old (SD = 3.0). The mean time from injury to first, second, and third assessment post-injury was 5, 11, and 18 days, respectively. Repeated-measures ANOVAs were used to determine if mean scores for each of the abovementioned cognitive functions and symptoms differed across the four assessments. Results showed significantly lower scores for all the cognitive functions at the first assessment compared to baseline (all ps < .01); however, scores of the second and third assessments were not significantly different from those of the baseline (all ps > .05). For symptom scores, there was a significantly greater (worse) symptom score at the first assessment compared to baseline (p < .000); difference between symptom scores of the second assessment and baseline was still significant (p = .024), but not symptom scores of the third assessment and baseline (p = .89). **Conclusion:** The present study suggests recovery is

not complete during the first 5 days post-injury. Recovery duration for MTBI symptoms seems to be even longer and extends to the second-week post-injury. MTBI athletes may not recognize the potential risk of MTBI and tend to return to play immediately. However, professionals involved in MTBI management programs should warn athletes against negative consequences of returning to play soon after an injury.

Disclosures: **E. Abbassi:** None. **H. Brassel:** None. **A.P. Salvatore:** None.

Poster

795. Injury and Trauma II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 795.06/U6

Topic: C.09. Brain Injury and Trauma

Support: Roddy-Holden Foundation

Faxon Friends

NIH-Brown Graduate Partnership Program

Title: pyMIND: Open-source, python-based multimodal integrated neural data acquisition for conducting basic science research in neurointensive care units

Authors: *U. AGRAWAL[1,2], A. C. OYALOWO[1,2,4], A. PILLING[3], S. LEE[1,2], W. F. ASAAD[1,5,6,7,2];
[1]Dept. of Neurosci., [2]Brown Inst. for Brain Sci., [3]Alpert Med. Sch., Brown Univ., Providence, RI; [4]Grad. Partnership Program, NIH, Bethesda, MD; [5]Dept. of Neurosurg., Alpert Med. Sch., Providence, RI; [6]Norman Prince Neurosciences Inst., [7]Dept. of Neurosurg., Rhode Island Hosp., Providence, RI

Abstract: Neurointensive care units (NICUs) are responsible for alleviating suffering due to primary brain injury as well as predicting and preventing the onset of secondary brain injury. Patients are continuously monitored, and volumes of physiological data are collected—sometimes in a manner that could rarely be recorded in any other context outside of the NICU (e.g. direct measurements of intracranial pressure via intraventricular catheter). Such access presents a unique opportunity for investigating basic science questions about cerebral physiology following injury that may help to improve the quality of care. However, relatively few patients in NICUs undergo any form of continuous brain monitoring. Furthermore, although vitals data is collected continuously, it is discarded, observed intermittently, or presented independently on paper charts that do not represent how the data streams could be related. To address these

problems, we created pyMIND to integrate the vitals routinely collected in the NICU with electroencephalography (EEG) and near-infrared spectroscopy (NIRS). Specifically, pyMIND is an open-source, Python-based interface that establishes a connection to the existing proprietary medical telemetry devices in NICUs, saves the data in a standardized HDF5 format, and visualizes the data in realtime using Vispy, the open-source, interactive 2D/3D data-visualization Python library. By conducting both hypothesis-driven and machine learning-based analyses, we aim to identify biomarkers that predict adverse events such as seizure or vasospasm. pyMIND is being applied to patients with severe traumatic brain injury and spontaneous subarachnoid hemorrhage. Specifically, we plan to explore how the correlation of primary vitals, decreases in regional oxygen saturation (as recorded by NIRS), and prolonged decreases in spectral power of neural activity (as recorded by EEG) correspond to the event of a delayed cerebral ischemia. Ultimately, pyMIND is a potential tool for conducting basic science research in the NICU and improving patient care in the future.

Disclosures: **U. Agrawal:** None. **A.C. Oyalowo:** None. **A. Pilling:** None. **S. Lee:** None. **W.F. Asaad:** None.

Poster

795. Injury and Trauma II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 795.07/U7

Topic: C.09. Brain Injury and Trauma

Support: VA Grant I01-CX-000816-01

I01-CX-000715-01

Title: Pain susceptibility after trauma: physical, psychological or premorbid

Authors: *I. STRIGO[1,2], A. SPADONI[3,4], S. INSLICHT[2], A. SIMMONS[4];
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Abstract: Background: Combat trauma often results in mild traumatic brain injury(MTBI) and posttraumatic stress disorder(PTSD), both of which dramatically increase vulnerability for chronic pain. We have shown that women with PTSD show dysregulated functional brain activity during experimental pain processing that was related to their level of avoidant symptoms. The aim of this study was to better understand the mechanisms of pain processing in men who sustained MTBI during combat.

Methods: 70 males performed validated experimental pain paradigm administered in two sequential runs during fMRI. 46/70 reported history of MTBI and 26/46 also met criteria for PTSD. Change in brain activity and connectivity to repeated application of painful temperature was examined with the linear mixed effects model with group (Controls(n=24), MTBI(n=20), PTSD(n=26)) and administration (run1, run2), entered as fixed factors, subjects entered as a random factor and depression severity (BDI2) entered as covariates.
Results: Significant group by administration interaction to repeated application of thermal pain was observed within right anterior insula(RAI) where both PTSD and MTBI groups showed decreased activation, while controls participants showed increased activation between administrations. Importantly, change in RAI activation across administrations was significantly and inversely correlated to avoidance symptoms only in those with combat-related PTSD. Furthermore, whereas in the PTSD group overall decoupling between RAI and rostral anterior cingulate predicted insula attenuation overtime, increased fronto-insula coupling overtime predicted insula attenuation in the non-PTSD participants, i.e. MTBI and control groups.
Conclusions: The current study provides evidence for the hypothesis that combat trauma interferes with normal processing of acute pain whereby repeated exposure to even brief painful stimuli results in attenuation of insula activation over time. Furthermore, in those with PTSD, anterior insula shows greatest attenuation in those with the highest level of avoidance. These findings enhance our prior work in which we showed that brain injury without significant psychological symptoms disrupts endogenous pain modulation, suggesting dual dysfunction in pain processing and pain modulatory systems in those suffering from co-morbid MTBI and PTSD. Most strikingly, we found that the degree of childhood trauma, the degree of combat exposure and the severity of brain injury were comparable between the two trauma groups potentially pointing to preexisting pain and PTSD vulnerability mediated by weakened core-control circuits.

Disclosures: I. Strigo: None. **A. Spadoni:** None. **S. Inslicht:** None. **A. Simmons:** None.

Poster

795. Injury and Trauma II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 795.08/U8

Topic: C.09. Brain Injury and Trauma

Title: Magnetoencephalography shows hemisphere compensation in a case of penetrating head injury caused by a metal rod

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Abstract: In August 2012, a 24-year-old construction worker suffered an accident wherein a two meter long, over one inch diameter metal rod penetrated his head through the right frontal hemisphere. A rescue team was called, the patient was transported to the hospital, and a craniotomy was implemented to remove the rod. The patient remained conscious, alert and oriented throughout. The rod was successfully removed leaving a cavity predominantly in the middle frontal gyrus. MRI imaging following the incident showed that 11% of the right hemisphere brain mass was lost in the accident. A later MRI, 6 months after the incident, also noted that the anterior thickness corpus callosum was clearly reduced. The patient was put on anticonvulsant drugs, and the only consequences of the accident were two isolated seizures. No personality, social or behavioral change were noted.
Methods: The patient came to the NYU Center for Neuromagnetism and a set of MEG recordings were performed over three days using a 275-channel (CTF) instrument. Several recordings were made. Here we report the results of one that compared left vs. right movement planning, coordination, and execution. This was included since the injury was close to the dorsolateral prefrontal associative cortex and to the premotor cortex. Finger-Thumb tests, in which he sequentially touched each finger of one hand to the thumb, in random order were implemented. Both hands were tested. (100 sets were carried out; 50 with each hand.)
Preliminary results: No mistakes were made. The patient performed the test with the correct hand every time. Low frequency abnormal brain activity was clearly present near the site of the injury. When the right hand was used, an increase in the abnormal activity in the right side was found. When the task was performed with the left hand, abnormal activity on the site of the injury (right) decreased.
Discussion: These findings indicate the presence of functional compensation for the right hemisphere injury. It was noted that when the left hemisphere was engaged in right hand movement, compensation was lost or reduced and abnormal activity was increased. Contrarily, when sites near the injured area (right side) were engaged in left finger movement, less abnormal activity was recorded. This suggests that inter-hemisphere compensation played a fundamental role in the absence of overt movement deficits after injury.

Disclosures: G. Rabello: None. **K. Walton:** None. **R. Rozental:** Other; ICB, UFRJ. **R.M.C. da Silva Filho:** None. **R. Llinás:** None.

Poster

795. Injury and Trauma II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 795.09/U9

Topic: C.09. Brain Injury and Trauma

Title: A putative panel of PTSD signatures consisting of proteins and differentially methylated probes

Authors: N. CHAKRABORTY[1], R. KUMAR[2], *J. L. MEYERHOFF[3], R. YANG[2], A. GAUTAM[1], S. MUHIE[1], D. ABU AMARA[4], R. YEHUDA[5], F. DOYLE[6], O. WOLKOWITZ[7], S. MELLON[7], C. MARMAR[4], R. HAMMAMIEH[1], M. JETT[1];
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Abstract: Management of PTSD is complicated by the overlapping symptoms of its comorbidities and a diagnosis that relies on self-reporting and a time-consuming psychological evaluation. A strategy of developing unbiased biomarkers for next-generation diagnostics is therefore essential. Herein, we present molecular candidates with potential to be translated into diagnostic applications. The neurodevelopment of PTSD risk has long been explored. Emerging knowledge suggests a significant role of epigenetic plasticity in the development of PTSD pathomechanisms. In this context, we first investigated the expression of targeted proteins, and then we determined the differential methylation of the corresponding genes. A candidate biomarker panel was evaluated by investigating training and test cohorts of PTSD screened from US Operation Iraqi Freedom (OIF) and Operation Enduring Freedom (OEF) veterans. In the training set (to discover potentially predictive relationships), 52 PTSD-positive male veterans of OIF/OEF were matched to 52 controls by age and ethnicity. The independent test set (to assess the strength and utility of the predictive relationship) consisted of age/ethnicity-matched 32 PTSD-positive and 32 PTSD-negative veterans. Veterans with a CAPS score above 40 were identified as PTSD-positive, while those with a score less than 10 were determined to be controls. A 50+ protein panel associated with neurodegeneration was probed with the plasma samples collected from the veterans. Using corrected t-score (cut off 0.05), proteins with significantly altered expression were identified and subsequently validated using the 32/32 test cohort. There were seven proteins which showed similar trends in both test and training sets, and they were duly selected for inclusion in the final panel. In parallel, DNA extracted from the whole blood of the training cohort was bisulfite-converted and probed using a whole genome

methylation array. The differentially methylated probes were annotated to the genes corresponding to the proteins of interest. Targeted bisulfite sequencing validated these preselected regions in both of the test and training sets. Linked with three proteins of interest were three probes (CpG islands) showing differential methylation. PTSD is a multifactorial illness manifested by a number of behavioral and organismal deficiencies. It is essential to develop a multi-omics panel to capture the wide complexity of this illness. Hence, we present a panel of candidate markers consisting of seven proteins. A subset of this panel has additional epigenetic footprints. A more comprehensive investigation with multiple independent cohorts is necessary.

Disclosures: **N. Chakraborty:** None. **R. Kumar:** None. **J.L. Meyerhoff:** None. **R. Yang:** None. **A. Gautam:** None. **S. Muhie:** None. **D. Abu Amara:** None. **R. Yehuda:** None. **F. Doyle:** None. **O. Wolkowitz:** None. **S. Mellon:** None. **C. Marmar:** None. **R. Hammamieh:** None. **M. Jett:** None.

Poster

795. Injury and Trauma II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 795.10/U10

Topic: C.09. Brain Injury and Trauma

Support: DRDC Grant W7719-135182/001/TOR

Title: PTSD and mTBI result in perturbations to magnetoencephalographic resting-state spectral connectivity

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Abstract: Psychological and physical trauma can result in clinical conditions with overlapping symptomology - this makes a differential diagnosis of posttraumatic stress disorder (PTSD) or mild traumatic brain injury (mTBI) difficult. Functional MRI has revealed that PTSD and mTBI might be related to aberrant local patterns of activity, as well as perturbed functional connectivity - i.e. the communication *between* regions - and that this subserves emergent psychological sequelae. Despite this, how trauma impacts *neurophysiological* (as opposed to haemodynamic) mechanisms is unknown, although data suggest trauma alters brain spectral profiles and network topology. Using resting-state magnetoencephalography (MEG), we have shown that electrophysiological coupling between areas in trauma differs in important ways. We compared two clinical groups against two groups of matched controls - soldiers from the Canadian Armed

Forces with combat-related PTSD were contrasted with a combat-exposed, non-PTSD control group of soldiers; and a group of civilians with mTBI were compared to a group of healthy controls. All groups underwent 5 minutes of resting-state acquisition in a 151-channel MEG (CTF Systems). Implementing an atlas-guided 'beamforming' approach, reconstructed time-series from 90 ROIs in cortical and subcortical regions were used to compute resting functional connectivity based on two methods; phase synchrony, defined by the weighted Phase Lag Index (wPLI), and amplitude envelope correlations. Connectivity maps from clinical groups were then contrasted with their respective control groups using the Network-Based Statistic. Elevated connectivity was observed in both trauma groups within and between a number of key regions, particularly those implicated in attention and memory. Most importantly perhaps, these groups were distinguished from each other by the *mechanism* of communication. The PTSD group exhibited fast-wave (high-gamma) phase synchronisation, and the mTBI group were found to differ from controls in low-frequency (delta-through-alpha) amplitude envelope coupling. Hypotheses regarding the mechanistic role of spectrally-mediated, inter-areal communication have posited very distinct functional roles for these oscillatory interactions. They appear to be critical in the dynamic reconfiguration of networks, supporting the integration and segregation of modular brain regions; with efficient interregional communication disturbed in trauma, these perturbations have the potential to describe the clinical symptoms observed in patients and offer accurate discrimination of such conditions.

Disclosures: B. Dunkley: None. **E.W. Pang:** None. **M.J. Taylor:** None.

Poster

795. Injury and Trauma II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 795.11/U11

Topic: C.09. Brain Injury and Trauma

Support: CHRP 205374

Title: Combining diffusion tensor imaging and robotics to assess structural changes and sensorimotor recovery following sport-related concussion

Authors: *A. CHAMPAGNE[1], N. COVERDALE[2], H. BRETZKE[2], C. MARK[2], J. NASHED[2], S. SCOTT[2], D. COOK[2];
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Abstract: Following a concussion, or mild traumatic brain injury (mTBI), individuals experience a broad range of cognitive and motor deficits in the acute post-injury period.

Evidence-based return-to-play guidelines are subjective in nature due to our current inability to properly monitor structural and functional recovery of the injured athlete. A quantitative understanding of the relationship between brain injury and motor deficits could provide objective guidelines for the clinical management of mTBIs. The purpose of this pilot project was to determine whether diffusion tensor imaging (DTI) and robotics could be used to quantify recovery patterns following sport-related concussion.To investigate the structural and behavioral changes following mTBI, we collected imaging and sensorimotor data (using the KINARM^{TM} robot) at two time points (<14 days and 3 months), post-injury. Four injured varsity athletes (20.5±0.6 years, 3M) were recruited following mTBI, while ten non-injured athletes (19.9±2.0 years, 5M) served as controls. To determine structural changes in white matter (WM), we performed a region-of-interest analysis in ten bilateral tracts defined using the John Hopkins University DTI-based WM tractography atlas. The mean fractional anisotropy (FA) for each tract was compared between the acute (<14 days) and follow-up (3 months) time points using a paired t-test. The behavioral changes were examined by selecting parameters from the sensorimotor tasks where the injured groups fell outside of the normative range (5 to 95%). These parameters included the task score and median error score from the Object Hit and Avoid task, which recruits higher executive functions such as attention, rapid motor selection and inhibition. Parameter scores were averaged among the groups and compared to the controls to look for signs of recovery. The imaging results showed a significant increase in FA ($p=0.0035$) within the superior longitudinal fasciculus (SLF) of the acute group when compared to the 3 months follow up. Additionally, the task and median error scores showed improvements at 3 months post-injury as they both closely approached the averaged scores from the controls. After 3 months, injured subjects hence performed better and made fewer errors in the first half of the task compared to when they were initially tested after sustaining a concussion. Although preliminary, these results suggest possible associations between WM changes and deficits in visuospatial processing after mTBI, followed by recovery. This provides exciting potential for the combined use of neuroimaging and cutting-edge robotics to assess recovery after concussion.

Disclosures: **A. Champagne:** None. **N. Coverdale:** None. **H. Bretzke:** None. **C. Mark:** None. **J. Nashed:** None. **S. Scott:** None. **D. Cook:** None.

Poster

795. Injury and Trauma II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 795.12/U12

Topic: C.09. Brain Injury and Trauma

Support: DA06227

DA33684

Title: Striatal dopamine transporter regulation in obesity

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Abstract: Obesity is associated with excessive overeating and preference for palatable, high-fat foods. Increased sensitivity to palatable-food reward drives overeating when accompanied by insufficient inhibitory control. High caloric food and addictive drugs increase dopamine release in brain reward circuits, which mediate their reinforcing effects. The dopamine transporter (DAT) plays a central role in regulating dopamine reward in mesolimbic and nigrostriatal pathways. Studies in rodents demonstrate decreased cell-surface DAT expression in the nucleus accumbens (NAc) and dorsal striatum induced by high-fat diet. We report here quantitative measures of DAT mRNA expression in the substantia nigra (SN) (n=40) and protein in the ventral striatum (n=40) from postmortem human brain sampled from normal weight and obese subjects over a range of body mass indices. Radioligand binding assays using (^{3}H)WIN35,428 demonstrated that DAT binding sites are negatively correlated with BMI in the ventral striatum ($r= -0.47$; $p<0.01$). Dopamine transporter gene expression was significantly decreased in the substantia nigra of obese subjects ($p<0.001$). Dopamine reward deficiency has been suggested to contribute to compensatory overeating of carbohydrates leading to human obesity. Primary food-reward is mediated by dopamine release in the striatum and deficient nucleus accumbens dopamine function contributes to primary food reward and obesity. A shift in the underlying dopaminergic control from ventral to dorsal striatum coincides with the development of habitual behaviors. Our results confirm that human striatal dopamine function is decreased in obesity, which may underlie the compulsive food intake associated with development of habitual overeating. Supported by DA06227 and DA33684.

Disclosures: C. Wu: None. **S.P. Garamszegi:** None. **X. Xie:** None. **D. Mash:** None.

Poster

795. Injury and Trauma II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 795.13/U13

Topic: C.09. Brain Injury and Trauma

Title: Physiological consequences of mild traumatic brain injury in individuals with acute and chronic symptoms

Authors: A. L. YASEN[1], E. K. EDWARDS[1], M. M. LIM[2,3], K. B. WEYMANN[2,3], *A. D. CHRISTIE[1];
[1]Univ. of Oregon, Eugene, OR; [2]VA Portland Hlth. Care Syst., Portland, OR; [3]Oregon Hlth. & Sci. Univ., Portland, OR

Abstract: Chronic symptoms of mild traumatic brain injury (mTBI) are experienced by more than 5 million Americans, yet little is known about the underlying physiology. Although alterations in motor cortex function have been shown acutely following mTBI, such findings have not been extended to individuals with chronic symptoms. The purpose of this study was to examine motor cortex excitability, inhibition, and the associated neurotransmitter concentrations in individuals with acute and chronic symptoms following mTBI. Participants included 7 individuals within 72 hours of an mTBI (21.1±2.4 years; acute), 5 individuals with symptoms lasting more than 3 months (31.0±12.1; chronic) and 12 uninjured individuals (20.9±0.9; control). First, transcranial magnetic stimulation was used to assess intracortical inhibition, via cortical silent period (CSP) duration, and corticospinal excitability, via resting motor threshold (RMT) and motor evoked potential amplitude (MEP). There were no differences across groups in RMT (p=0.13) or CSP duration (p=0.20). However, MEP amplitude was significantly higher in individuals with chronic symptoms compared with controls (p=0.02), and tended to be higher in acutely-injured individuals than controls (p=0.07). Next, concentrations of the excitatory and inhibitory neurotransmitters glutamate and GABA, respectively, were assessed in the primary motor cortex using ^{1}H magnetic resonance spectroscopy (MRS). Both glutamate and GABA concentrations were lower in acutely-injured individuals compared with controls ($p\leq0.001$), and lower in individuals with chronic symptoms than either controls ($p\leq0.001$) or acutely-injured ($p\leq0.05$) individuals. The excitatory-to-inhibitory ratio (EIR) was calculated for MRS measures using the ratio of glutamate:GABA. The EIR was higher in both injured groups compared with controls ($p\leq0.001$), but was not different between the acute and chronic groups (p=0.30). These results suggest a possible imbalance between excitatory and inhibitory neurotransmitters following mTBI, which manifests functionally as a higher net excitability of the motor cortex. Importantly, these physiological consequences appear to be similar in acutely-injured individuals and those suffering from chronic symptoms.

Disclosures: A.L. Yasen: None. **E.K. Edwards:** None. **M.M. Lim:** None. **K.B. Weymann:** None. **A.D. Christie:** None.

Poster

795. Injury and Trauma II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 795.14/U14

Topic: C.09. Brain Injury and Trauma

Support: VA R R&D SPIRE

Title: Pain-related white matter tract deficit in patients with mtbi related persistent headache

Authors: *M. LIM[1], A. KHALAF[1], Z. YANG[1], V. METZGER-SMITH[1], J. CORDERO[1], Y. HE[1], S. SHUKLA[2], L. LIN[1], D. SONG[1], R. LEE[1], G. POLSTON[1], A. TSAI[2], A. LEUNG[2]; [1]UCSD, LA Jolla, CA; [2]VA San Diego Healthcare Syst., La Jolla, CA

Abstract: Introduction: Persistent headache is one of the most prevalent debilitating conditions in patients with mild traumatic brain injury (MTBI). Previous functional imaging studies suggest patients with MTBI suffer from a state of diffuse axonal injury and diminished prefrontal cortical modulation in pain perception [1]. However, the correlation between the structural deficit and impaired pain modulatory function in this patient population is largely unknown. The current study compares the difference in white matter tract fractional anisotropy (FA) between patients with MTBI related headache and healthy controls. **Method:** Diffusion Tensor imaging (DTI) data were acquired in a GE 1.5 T MRI scanner for ~10 minutes for each scan with the following imaging parameters: repetition time = 16.1 sec, TE = minimum, FOV=25.6 cm, 60 oblique slices AC/PC-aligned encompassing the whole brain, and voxel size =2x2x2 mm^3. 54 directions were collected with a b-value of 1000 s/mm^2, and 5 volumes with no-diffusion weighting. All individuals' FA maps were loaded into a non-paired 2-tail T-test to assess the statistical difference between the FA values of the two groups. The resulting significant ($P<0.01$) clusters (>50 voxel cluster threshold) were extracted and their anatomical locations were identified using Johns Hopkins University white matter tractography atlas and confirmed with DTI based white matter atlas provided by the FMRIB Oxford, UK. All analyses were performed in BrainVoyager (Maastricht, Netherland). **Result:** 12 MTBI patients (10 male) with an average age±SD of 35.0±8.0 years old and daily persistent headache intensity greater than 3 on 0-10 numerical rating scale, and an equal number of age and gender matched healthy controls completed the study. The MTBI showed a significant ($P<0.01$. cluster size=139) lower FA in the right anterior thalamic tract near right prefrontal cortex, and left superior longitudinal fasciculus near the left prefrontal cortex. **Conclusion:** The observed white matter tract deficits in regions linking prefrontal cortex and sensory discriminatory regions of pain perception among patients with MTBI are in line with the prefrontal pain modulatory functional deficits found in this patient population.

Disclosures: **M. Lim:** None. **A. Khalaf:** None. **Z. Yang:** None. **V. Metzger-Smith:** None. **J. Cordero:** None. **Y. He:** None. **S. Shukla:** None. **L. Lin:** None. **D. Song:** None. **R. Lee:** None. **G. Polston:** None. **A. Tsai:** None. **A. Leung:** A. Employment/Salary (full or part-time): VA Healthcare System, UC San Diego.

Poster

795. Injury and Trauma II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 795.15/U15

Topic: C.09. Brain Injury and Trauma

Support: Ontario Graduate Scholarship

Title: Electrophysiological markers of variations in perceptual and cognitive processing in coma

Authors: *R. L. MAH, J. F. CONNOLLY, A. E. FOX-ROBICHAUD, C. HAMIELEC; McMaster Univ., Hamilton, ON, Canada

Abstract: Previous work over the last two decades has shown strong positive predictive power of the N1 and mismatch negativity (MMN) ERP components in comatose patients. Beginning with work from Kane et al. (1993, 1996) to studies from Fischer et al. (1999, 2004, 2006), Naccache et al. (2005), and Tzovara et al. (2013), the consensus appears to be that the presence of the N1 and MMN are good predictors of awakening from coma. A common thread with this prior work is the focus on single points in time. Kane et al. used the best response from multiple sessions collected across several days while the patient was still comatose. Fischer et al. and Naccache et al. used only one recording per patient, while Tzovara et al. used two sequential recordings. This approach has served the field well, however it does not offer the opportunity to examine whether variations occur in ERP components with repeated recordings occurring over a 48-hour period. The present study studied whether a waxing and waning of the N1 and MMN occurred in comatose patients who had suffered traumatic brain injuries. We recorded multiple sessions of an auditory oddball mismatch paradigm using tone-length deviants over a period of 48 hours to capture the modulation of the MMN as the patient's level of consciousness changes. Continuous EEG was recorded from 32 sites positioned according to the 10-20 standard. We present a case study of a 29-year old male involved in a motor vehicle collision. He presented with a right parietal subdural hematoma, acute traumatic subarachnoid hemorrhage and diffuse axonal injury, and scored 4/15 on the Glasgow Coma Scale at the initiation of data collection. In total, 17 blocks of data were acquired, each with approximately 30 minutes of active testing with an average inter-block interval of two hours. From these blocks, five showed typical N1 and MMN components, and an additional four blocks showed typical N1 components to the standard tone without the presence of the MMN. Blocks showing typical N1 and MMN activity in the patient were compared to data gathered from healthy controls—N1 and MMN amplitudes were reduced in the patient, however latency was unaffected. The patient had emerged from his coma at the one-month follow up. These data reveal two key points: Electrophysiological markers of early perceptual and pre-attentive processing are not merely observable in coma but appear to wax and wane across a relatively short period of time; and, use of these early responses as

prognostic indicators of the potential for emergence from coma may be less reliable than previously thought. It is possible that poor prognostics for some patients may be more to do with the transient state of the patient at the time of testing.

Disclosures: R.L. Mah: None. **J.F. Connolly:** None. **A.E. Fox-Robichaud:** None. **C. Hamielec:** None.

Poster

795. Injury and Trauma II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 795.16/U16

Topic: C.09. Brain Injury and Trauma

Support: W81XWH-14-1-0320

Title: Mild traumatic brain injury patients recruit compensatory mechanisms to integrate visual information

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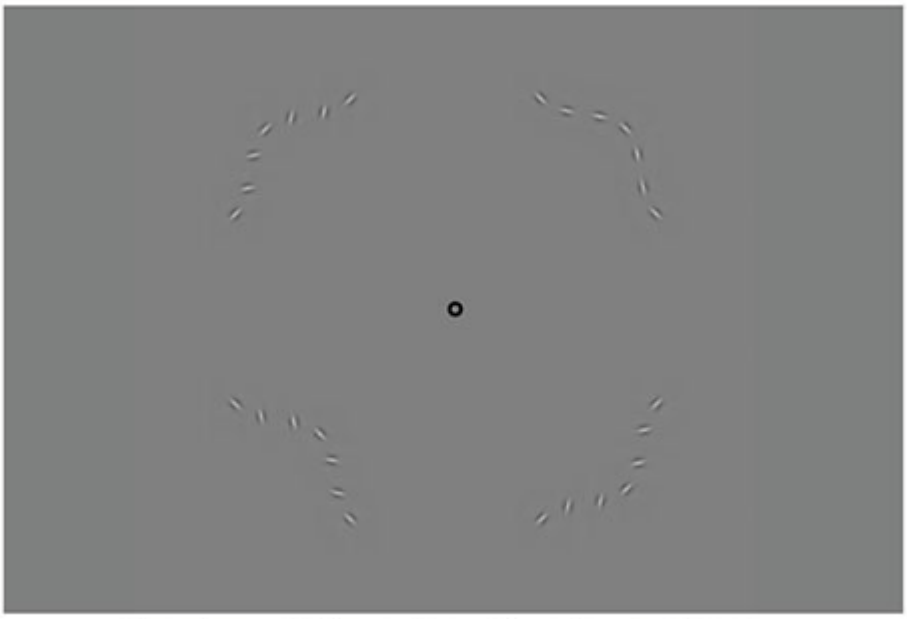
Abstract: Visual disturbances following mild traumatic brain injury (mTBI) are putatively caused by diffuse axonal injury and/or neural loss. Loss of local axonal connectivity in a visual circuit such as V1 would have the anticipated effect of reducing lateral inhibition between columns of neurons representing different orientations at distinct visual field locations. This reduction could make it more difficult for the visual system to deal with a noisy visual image, for example, because local interactions could not disambiguate competing representations. Thus local disruptions of axons would be expected to increase processing errors—increase noise—for tasks requiring integration of orientation across space.Recovering from or compensating for higher internal noise could take one of two forms—either a direct mechanism restores the system to a lower noise level, or the system integrates over a larger range of cortical columns to minimize the influence of the noise. Our newly designed contour integration task specifically enables us to assess visual field defects in terms of internal noise and spatial integration (efficiency). Integration of the stimuli requires processing of the orientation of each Gabor patch in its visual field location, and integrating this information over the visual space occupied by the Gabors forming the contour. In a 4AFC paradigm, participants (mTBI n=50; control n=20) were asked to identify the contour with good continuity from three contours with added orientation noise, each presented in a different visual field quadrant. Curvature thresholds were determined by modulating the amplitude of the curve via a performance dependant staircase. A linear

amplifier model was fitted to estimate the amount of internal noise and spatial integration (efficiency).Results show that while mTBI patients do exhibit higher internal noise, they paradoxically also exhibit higher efficiency in integration. This suggests a simple compensatory mechanism—the integration over a larger amount of retinotopic cortex, in order to overcome the increase in internal noise.



The contours consist in seven Gabor patches resting on a cosine curve.

Here, the good continuation choice is located in the upper right quadrant.

Disclosures: **T. Ruiz:** None. **D. Spiegel:** None. **A. Baldwin:** None. **R. Hess:** None. **R. Farivar-Mohseni:** None.

Poster

795. Injury and Trauma II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 795.17/U17

Topic: C.09. Brain Injury and Trauma

Support: VA Research Service

Title: Alcohol dependence after blast versus non-blast TBI in an OEF/OIF veteran population

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Abstract: OBJECTIVE: To evaluate the prevalence of alcohol dependence in veterans of Operation Enduring Freedom (OEF) and Operation Iraqi Freedom (OIF). Who have had blast versus non-blast traumatic brain injury (TBI) BACKGROUND: One of the signature injuries for veterans deployed in the OEF and OIF conflicts is that of TBI, particularly blast TBI. In addition, alcohol dependence is a relatively frequent sequelae of TBI. METHODS: We conducted a pilot, retrospective chart review of patients with TBI seen at the Poly-Trauma Clinic of the VA Greater Los Angeles Healthcare System. We collected data regarding blast versus non-blast TBI in OEF/OIF veterans. In addition, we collected data regarding alcohol use, which was categorized as positive or negative using the AUDIT-C screen. RESULTS: A total of 737 charts were reviewed. Of these, 375 were identified as OEF/OIF subjects with a confirmed diagnosis of TBI. The racial/ethnicity background of these subjects was 42.9 % Caucasian, 10.9% African-American, 28.5% Hispanic, 4.3% Asian, and 13.4% Other. We found that a mean 64.8% ± 5.1 (n = 243) of subjects had suffered blast-TBI and 35.2% ± 3.6 (n = 132) had non-blast TBI. The mean age of subjects with blast TBI was 32.8 ± 1.2 years, while those with non-blast TBI was 34.4 ± 1.6 years. The prevalence of alcohol dependence following TBI was 27.7% ± 5.4 (n=104). Alcohol dependence was diagnosed in a mean of 25.9% ± 3.0 (n = 63) subjects with blast TBI, and 31.1% ± 3.6 (n = 41) in those with non-blast TBI. The mean AUDIT-C score for male subjects who were positive for alcohol dependence was 6.9 ± 0.5 with blast-TBI, while those for non-blast TBI was 7.5 ± 0.7. CONCLUSION: In this population of OEF/OIF veterans with TBI, alcohol dependence was reported relatively frequently following both blast and non-blast exposure.

Disclosures: B. Aryanfar: None. **K. Panizzon:** None. **A. Papazyan:** None. **C. Spinelli:** None. **A. Shinde:** None. **R. Wallis:** B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution; SK Life Science Pharmaceuticals, GlaxoSmithKline.

Poster

795. Injury and Trauma II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 795.18/U18

Topic: C.09. Brain Injury and Trauma

Support: R01 HD061504

K99 NS096116

U54 EB020403

R01 EB008432

R01 AG040060

R01 NS080655

NS027544

Title: Diverging trajectories in children after traumatic brain injury: predicting outcomes.

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Abstract: Following a moderate/severe traumatic brain injury (msTBI), many patients experience prolonged recoveries. Here we present longitudinal data from a pediatric msTBI cohort, showing that a functional neuroimaging biomarker at 2-5 months post-injury can predict longitudinal changes in white matter (WM) structural integrity. We studied 21 children (16M/5F) with msTBI, assessed 2-5 months post-injury and again 13-19 months post-injury, as well as 20 well-matched healthy control children. We assessed CC function through interhemispheric transfer time (IHTT), measured using event-related potentials (ERPs), and related this to diffusion weighted magnetic resonance imaging (dMRI) measures of WM microstructure. To assess white matter integrity, we used a method developed in our lab, autoMATE (automated multi-atlas tract extraction), to generate along-tract measures of fiber integrity from dMRI data. Half of the TBI patients had significantly slower IHTT at the first time-point (TBI-slow-IHTT, N=11), and half were in the normal range (TBI-normal-IHTT, N=10). These groups did not differ from each other in clinical or demographic variables. The TBI-normal-IHTT group did not differ significantly from healthy controls, either in WM integrity at either assessment or in the longitudinal trajectory of WM integrity between evaluations. In fact, they appear to show signs of recovery of WM integrity longitudinally. In contrast, the WM integrity of the TBI-slow-IHTT group was significantly lower than healthy controls across a large portion of the WM. Longitudinal analyses showed the TBI-slow-IHTT group experienced a progressive decline in WM integrity throughout the brain. We have discovered a biomarker that identifies a subset of

patients with impaired callosal integrity in the first months post-injury who experience widespread continuing and progressive degeneration in the first year post-injury.

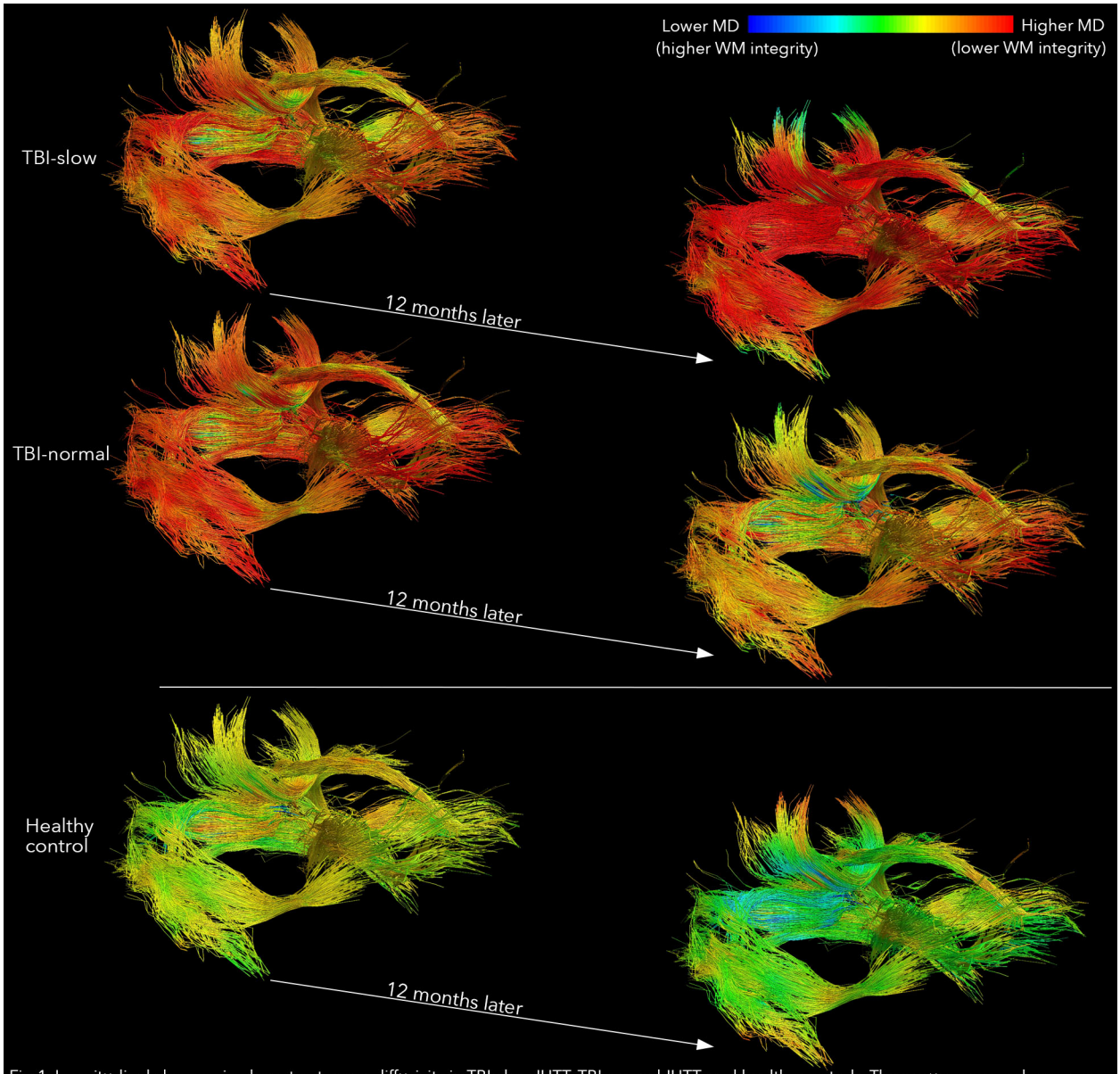

Fig 1. Longitudinal changes in along-tract mean diffusivity in TBI-slow-IHTT, TBI-normal-IHTT, and healthy controls. The group-averaged maps are shown for both time points, across TBI-slow-IHTT (N=11), TBI-normal-IHTT (N=10), and healthy controls (N=20). Approximately 12 months passed between the beginning and ending time point. As indicated in the legend, blue areas have the lowest mean diffusivity (MD) and therefore highest WM integrity, while red areas have the highest MD. The healthy controls show minimal decreases in MD. The TBI-slow-IHTT group shows widespread increases in MD. The TBI-normal-IHTT group shows a mixture.

Disclosures: **E.L. Dennis:** None. **F. Rashid:** None. **M. Ellis:** None. **T. Babikian:** None. **J. Villalon-Reina:** None. **Y. Jin:** None. **A. Olsen:** None. **R. Mink:** None. **C. Babbitt:** None. **J. Johnson:** None. **C. Giza:** None. **P. Thompson:** None. **R. Asarnow:** None.

Poster

795. Injury and Trauma II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 795.19/V1

Topic: C.09. Brain Injury and Trauma

Support: CERC 215063

Title: The relationship between overt responsiveness and white matter abnormalities in patients with disorders of consciousness

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Abstract: The differential diagnosis of disorders of consciousness (DOC) is made on the basis of bedside behavioural scales, such as the Coma Recovery Scale-Revised (CRS-R). The patient's ability to produce discernable behavioural indicators in response to various sensory stimuli determines whether the patient is diagnosed as in a vegetative state (VS) or a minimally conscious state (MCS). The VS is characterized by reflexive responses, while the MCS is characterized by intentional responses. Recent neuroimaging studies have emphasized the problems related to this reliance on external behaviour: if an aware patient was unable to produce overt responses due to a motor dysfunction, they would be misdiagnosed as VS. It has been proposed that damage to motor thalamo-cortical pathways could explain the lack of intentional motor responses after brain injury in an otherwise aware patient. We used diffusion tensor imaging to reconstruct and assess the structural integrity of thalamo-motor tracts in DOC patients and in healthy controls. Patients were grouped into one of two categories: responsive (MCS+ emerging from the MCS) or non-responsive (VS). These groups showed a significant difference in the structural integrity of the thalamo-motor tracts ($F(1,10)=7.086$, $p=.024$), as measured by mean fractional anisotropy (FA). Moreover, FA of these tracts correlated with the patients' CRS-R score ($rho=.847$, $p=.001$ and $rho=.712$, $p=.009$, for left and right respectively). Our results suggest that damage to motor fibres plays a role in the degree of external responsiveness exhibited by DOC patients. The associated reduction in the patients' overt motor performance could be masking their level of awareness, and thus interfering with diagnostic accuracy.

Disclosures: C.A. Stafford: None. **A. Owen:** None. **D. Fernández-Espejo:** None.

Poster

795. Injury and Trauma II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 795.20/V2

Topic: C.09. Brain Injury and Trauma

Support: General Electric-National Football League Head Health Challenge award

X2 Biosystems

Title: Accumulated head trauma predicts longitudinal white matter diffusion alterations in college athletes

Authors: *A. R. ASTURIAS[1], M. CIESLAK[2], L. VOLZ[2], C. GREENE[2], J. D. RALSTON[3], S. T. GRAFTON[2];
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Abstract: Measures of white matter diffusion that characterize myelin integrity have been shown to change in the event of repetitive subconcussive head impact exposures. However, it remains unclear how many head impact exposures, and at what severities, are required to induce either reversible or persistent changes in white matter that are reliably detectable by diffusion imaging. We hypothesized that changes in diffusion would be associated with a cumulative dose of head impacts. Wearable head impact monitors were used to quantify the number and intensity of head impacts accumulated by a group of college athletes throughout a soccer season. In parallel, serial diffusion spectrum (DSI) of white matter were acquired and used to calculate multidimensional anisotropy (MDA). 10 female soccer players were monitored for head impacts throughout a season of collegiate soccer. Head impacts were recorded by X2 Biosystems' xPatch wearable sensors. Linear and rotational accelerations were processed using proprietary algorithms to estimate cumulative impact power. Cumulative impact power was used as a measure of the head trauma accumulated prior to each scan. DSI were acquired at 4 time points; 3 throughout the season and 1 three months post season(pseudo-baseline). 11 matched control DSI datasets were acquired from subjects with low risk for head trauma or history of concussion. DSI was reconstructed with generalized q-sampling imaging, which was then used to calculate MDA. Control distributions of MDA were characterized by the covariance of MDA values across all subjects. Mahalanobis distance was then calculated to determine voxelwise abnormality for each scan. Abnormal was defined by an extreme Mahalanobis distance in groupings of 100 or more adjacent voxels. Recorded impact counts per player ranged from 11 to 82 for the season. Clusters of abnormal voxels were detected in several subjects. The count of abnormal voxels correlated with cumulative head impact power prior to each scanning session. Some abnormal voxel groupings identified within during-season scans were not present in the psuedo-baseline scans.

We observe a relationship between cumulative head trauma load and longitudinal changes in white matter diffusion using high angular resolution DSI imaging. Critically, MDA estimates were also used as an alternative to less sensitive metrics such as fractional anisotropy. This approach, when combined with high performance wearable head impact monitors, demonstrates promise for detecting and characterizing potential sub-concussive head trauma.

Disclosures: **A.R. Asturias:** B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution; Supported by X2 Biosystems and a General Electric-National Football League Head Health Challenge award. **M. Cieslak:** None. **L. Volz:** None. **C. Greene:** None. **J.D. Ralston:** None. **S.T. Grafton:** None.

Poster

795. Injury and Trauma II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 795.21/V3

Topic: C.09. Brain Injury and Trauma

Support: Carvel foundation

K08 NS073796-05 (J.B.C)

R01 HD076436 (K.M.F)

Goldsmith Foundation (D.G)

Title: Sensory connectivity and lesion type predict hand function in children with unilateral spastic cerebral palsy

Authors: *D. GUPTA[1,2], A. BARACHANT[1,2], A. M. GORDON[3], H.-C. KUO[3], J. B. CARMEL[1,2,4], K. M. FRIEL[1,2,4];
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Abstract: The goal of this study was to examine the predictive value of sensory and motor system connectivity and lesion type on hand function in children with unilateral spastic cerebral palsy (USCP). In typically developing children, sensory and motor function are primarily mediated via crossed (contralateral) connections, as opposed to same-sided (ipsilateral)

connections. In children with USCP, an early brain injury often leads to sensory-motor reorganization, where ipsilateral motor connections on the lesioned side are seen to persist. Ipsilateral sensory connections are less common. Given the large scale adaptation in the motor system to unilateral brain injury and smaller scale adaptation in the sensory system, we hypothesized that loss of crossed *sensory* connections would be more predictive of hand function than loss of crossed *motor* connections. In addition, sensory circuits being established early in development have been shown to be more affected by cortical lesions than periventricular (PV) lesions. Thus, we hypothesized that cortical lesions would cause greater hand impairment than PV lesions. 23 children with USCP participated in anatomical, physiological and behavior testing of the sensory and motor systems. Anatomically, lesions were defined using MRI, and principal sensory and motor pathways were reconstructed using DTI. Physiologically, somatosensory evoked potentials (SSEPs) were recorded in response to vibrotactile stimulation of the index fingers; and EMG responses to motor cortex stimulation with TMS were recorded. For behavior, sensory hand function was tested with the Cooper stereognosis test and two-point discrimination; while motor hand function was assessed with the Jebsen-Taylor Test and box and blocks. We found that for the impaired hand, presence of significantly discriminable SSEP in the contralateral hemisphere, and a preserved contralateral sensory tract in DTI were both highly predictive of good hand motor and sensory function (Cohen's kappa agreement between group of subjects with good hand function and testing modality = 0.83 and 0.48 respectively, with kappa > 0.75 being strong agreement, and kappa < 0.40 poor). Lesion type was also predictive of hand function (kappa = 0.47). By contrast, the presence of contralateral motor connections—both physiological from TMS and anatomical from DTI—was less predictive of hand function (kappa = 0.24 and 0.32 respectively). Thus, sensory connectivity is more predictive of hand function in children with USCP than motor connectivity. This indicates that therapies to restore anatomical and physiological sensory connectivity may be important for recovery of sensory-motor function.

Disclosures: D. Gupta: None. **A. Barachant:** None. **A.M. Gordon:** None. **H. Kuo:** None. **J.B. Carmel:** None. **K.M. Friel:** None.

Poster

795. Injury and Trauma II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 795.22/V4

Topic: C.09. Brain Injury and Trauma

Title: Heart rate, minute ventilation, and maximum oxygen uptake in healthy and post-concussed collegiate female athletes

Authors: *D. C. MALLOY[1], S. ADAMS[2];
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Abstract: Background: A sport-related concussion is a form of mild traumatic brain injury (mTBI) with common symptoms such as fatigue, headache, and dizziness that tend to alleviate recovery within seven to ten days. However, neural symptoms can persist anywhere from three to twelve months following onset and can lead to the development of post-concussion syndrome (PCS). There is limited knowledge regarding the effects of an exercise stress test and the respiratory functions in post-concussed (within one year) athletes.**Purpose:** The purpose of this study was to determine if there were differences in heart rate, minute ventilation, and aerobic capacity during exercise on a treadmill in healthy and post-concussed (within one year) collegiate athletes.**Methods:** 14 female athletes, 7 healthy controls and 7 previously concussed, performed a maximal exercise test following a modified Balke protocol with a constant speed of 7.5 mph and an increasing grade each minute on a treadmill ergometer. Self-reported scale measurements were taken prior to and immediately after exercise and metabolic measures were recorded using a portable metabolic cart. Primary outcome measures included heart rate (HR), minute ventilation (VE), and maximum oxygen uptake (VO_2 Max). Linear regression analysis of VO_2 and HR as well as VO_2 and VE with Shapiro-Wilk test was performed. Statistical significance was determined at $p \leq 0.05$.**Results:** The healthy control and post-concussed groups reported the following outcome measures: VO_2 Max (42.8±5.6), HR (191.7±13.3), VE (79.7±7.5) and VO_2 Max (40.1±6.1), HR (180.6±13.7), VE (87.0±8.3) respectively. In the healthy control group, there was a significant linear relationship ($p=0.005$, $R^2=0.821$) between VO_2 and VE, but no significance between VO_2 and HR ($p=0.168$, $R^2=0.342$). In the post-concussed group, there was no significance between VO_2 and VE ($p=0.540$, $R^2=0.079$) or VO_2 and HR ($p=0.698$, $R^2=0.033$). **Conclusion:** This preliminary data indicates that there are noticeable differences between the respiratory functions of healthy and post-concussed (within one year) female collegiate athletes. The post-concussed athletes had variability in VE in relationship to VO_2 Max, whereas healthy athletes had a linear relationship. This suggests that the respiratory control center in post-concussed athletes may not be as efficient during a maximal exercise protocol. A larger participant population is needed to determine the significance of these differences in respiratory function.

Disclosures: D.C. Malloy: None. **S. Adams:** None.

Poster

795. Injury and Trauma II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 795.23/V5

Topic: C.09. Brain Injury and Trauma

Support: NIH Grant 8UL1TR000055

US Army Medical Research and Materiel Command W81XWH-12-1-0004

Defense Health Program under the Department of Defense Broad Agency Announcement for Extramural Medical Research W81XWH-14-1-0561

Title: Role of subconcussive head impacts in pre- and postseason changes in SCAT3 scores

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Abstract: Head impact exposure during routine participation in American football has been associated with cognitive changes in the absence of concussion. Correlating characteristics (number/severity) of head impact exposure with clinical consequences remains important to protect athletes and determine informed exposure limits. To date, characteristics of head impact exposure were outlined for Division I college athletes, but correlation to clinically-meaningful changes was not reported. 205 Division III football athletes participated in this study during the 2013 season. xPatch sensors (X2 Biosystems) adhesively attached to the skin behind the ear collected head impact data during games and practices. Data were downloaded from the sensor at the end of each session. Peak linear acceleration was analyzed for each head impact that exceeded a pre-defined threshold of 10 g. All participating athletes underwent Sport Concussion Assessment Tool 3 (SCAT3) testing for baseline assessments at the beginning of the season. A cohort of 53 athletes repeated the assessments at end of the season. Two enrolled athletes were concussed during the season and removed from the cohort. A total of 22,023 impacts were recorded in the remaining 51 athletes with average resultant peak linear acceleration (PLA) of 26.4 g and a maximum of 165.5 g. To determine a threshold for significant impacts, total number of head impacts above an acceleration threshold during the season was correlated with the difference between pre- and post-season SCAT3 scores using Pearsons correlation. The threshold for significant impacts was varied between 10 and 170 g in 5 g increments and separate correlation analyses were conducted for each threshold level. Significant ($p<0.05$) correlations were identified between SCAT3 scores and PLA ranging from 40 to 130 g with strongest correlation ($R=0.45$) for number of impacts above 75 g. A greater number of significant head impacts was associated with greater SCAT3 changes. This study identified for the first time a positive correlation between the number of significant head impacts and pre- to post-season changes in common postconcussive symptoms in non-injured athletes. Continued analysis of this type may contribute to informed exposure limits (number/severity) to better protect athletes and reduce the risk of concussion symptom burden.

Disclosures: **A. Shah:** None. **B. Stemper:** None. **R. Chiariello:** None. **A. LaRoche:** None. **Y. Wang:** None. **L. Nelson:** None. **M. McCrea:** None.

Poster

795. Injury and Trauma II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 795.24/V6

Topic: C.09. Brain Injury and Trauma

Support: A part of data was provided from ADNI (http://adni.loni.usc.edu)

Title: Comparison of age-related brain atrophy in elderly East Asians and Caucasians

Authors: *H. JANG[1], H. KIM[1], H. LEE[2], K. KIM[1];
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Abstract: Objective: This study investigated whether the age-related brain atrophy rate differs among ethnic groups. Brain volume decreases with increasing age and the severity of brain atrophy rate is a predictor of subsequent neurodegenerative disease like Alzheimer's. Brain is known to be morphologically different across races, especially between Asian and Caucasian populations. Therefore, this study investigated whether the age-related brain volume loss differs between Koreans and Caucasians.
Methods: The data of 96 cognitively normal Koreans (female=48, male=48; mean age=74.97±6.01) from the Korean Longitudinal Study on Cognitive Aging and Dementia (KLOSCAD) and 96 cognitively normal Caucasians (female=48, male=48; mean age=74.90±6.63) from the Alzheimer's Disease Neuroimaging Initiative (ADNI) (http://adni.loni.usc.edu) were selected. Three-dimensional T1-weighted MR images were acquired on 3.0 Tesla scanner. Volumes of total brain, gray matter (GM), white matter (WM), white matter lesions, ventricles, and cerebrospinal fluid were investigated as well as the selected subcortical regions with Freesurfer 3.0.5 (Martinos Imaging Centre) After adjusting the head size in each volume of interest (VOI), the atrophy rates (regression coefficients of age predicting VOI) between two ethnic groups were compared.
Results: Compared to Caucasians, Koreans showed faster atrophy rate in GM volume ($p=0.002$) but slower atrophy rate in total brain ($p=0.044$) and WM volume ($p<0.001$) with age. The ethnic difference in GM atrophy rate was more significant in females ($p=0.016$) than males ($p=0.043$). Interestingly, Korean elderly WM volume showed no significant age-related decline. By sub-analysis in each lobe, the ethnic difference in atrophy rate in female GM was significant only in the frontal lobe ($p=0.033$) whereas that of male GM was significant in broader regions across the frontal ($p=0.025$), parietal ($p=0.022$), and temporal ($p=0.042$) lobes.
Conclusion: According to this study, age-related GM atrophy was faster in Korean, whereas WM atrophy was faster in Caucasians. Environmental and genetic differences, such as higher education attainment in the Caucasian population and higher percent body fat in the East Asian

population, could be possible candidates contributing to the observed differences in GM and WM, respectively. However, factors affecting these ethnic differences need to be directly investigated in future research. The findings from this study implicate that the aging process can be better understood by studying brains of different ethnic groups and that the effective interventions against neurodegeneration might vary across ethnicity.

Disclosures: **H. Jang:** None. **H. Kim:** None. **H. Lee:** None. **K. Kim:** None.

Poster

795. Injury and Trauma II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 795.25/V7

Topic: C.09. Brain Injury and Trauma

Support: H2020 ComaWare

Title: A brain-computer interface for communication with DOC patients

Authors: ***C. GUGER**[1], B. ALLISON[2];
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Abstract: Brain-computer interfaces are often used for control, rehabilitation, spelling, but an emerging application is assessment of patients with disorders of consciousness (DOC). DOC patients have varying levels of cognitive activity, with categories such as vegetative state (VS) and minimally consciousness state (MCS). For the physician or family members, it is difficult to know which cognitive functions are left. But it is crucial to learn whether patients can understand conversations or can even communicate.
The current study screened patients in the VS, MCS+, MCS- state as well as ALS patients that are completely locked-in. The system works with (i) auditory P300, (ii) vibro-tactile P300 with 2 tactors (VT2) and (iii) vibro-tactile with 3 tactors (VT3). In (i) and (ii), odd-ball paradigms are presented to the patient for 4-8 minutes, and the patient has to actively count either deviant auditory stimuli or deviant vibro-tactile stimuli. In (iii), the patient has one tactor on the left hand, one tactor on the right hand and one on a neutral midline location. The person has to count either the stimuli on the left or right hand to produce a corresponding P300 response. Then, the evoked potentials are calculated and statistically analyzed. Additionally, brain-computer interface (BCI) algorithms are trained on the data to provide an objective measure of classification accuracy. In the next step, questions can be asked to the patient, who can answer by counting the stimuli on the right hand to say YES and on the left hand to say NO. An

interesting case participated in an assessment recently. The patient was diagnosed as MCS and performed the auditory evoked potential, the vibro-tactile 2 tactor and the vibro-tactile 3 tactor experiment with 100 % classification accuracy, each. The evoked potentials of all three experiments showed clear P300 responses with a significant difference between target and non-target stimuli. The auditory experiment needed 20 deviant stimuli to reach 100 % accuracy. The VT2 protocol was especially effective, leading to 100% classification accuracy after only three trials. The VT3 protocol also led to 100 % accuracy after only 15 stimuli showing that the patient very likely could communicate. Next, the communication mode was used to answer questions. In the example above, the assessment results appeared comparable to a healthy control person, which was very important information about the patient for his family. The system can assess DOC patients and help us understand if they can do standardized cognitive tasks. More data will be collected to identify how many patients can use the system for communication.

Disclosures: C. Guger: None. **B. Allison:** None.

Poster

795. Injury and Trauma II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 795.26/V8

Topic: C.09. Brain Injury and Trauma

Support: I01-CX-000715

Title: Differentiation of emotional trauma and loss of consciousness through examination of cortical thickness

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Abstract: Background: Trauma experienced by combat veterans often includes both emotional and physical components. This has led to difficulty in the dissociation of Post traumatic Stress Disorder (PTSD) from post concussive symptoms. We have found that a key determinant of the impact of Traumatic Brain Injury (TBI) is whether an Loss of Consciousness (LOC) was experienced. Here we look to see if cortical thickness data was related to the LOC status or PTSD status in a sample of concussed combat veterans. Methods: Cortical thickness was calculated in a sample of 60 TBI veterans comprised of similarly sized samples of PTSD+/LOC+, PTSD-/LOC+,PTSD+/LOC-, and PTSD-/LOC- using Advanced Normalization Tools (ANTs). Results: There was a significant effect of LOC on cortical thickness, specifically

the bilateral inferior frontal and superior temporal lobes showed a significant reduction in cortical thickness in both LOC groups. PTSD did not show any marked difference in these regions. Conclusions: The initial data appears to suggest that LOC has significant effects on cortical thickness in combat exposed mild TBI regardless of the presence or absence of PTSD. This suggests that while damage may not be observable on a single subject clinical observation of T1 images that there is marked changes in brain regions associated with concussive injury.

Disclosures: A. Simmons: None. **A.D. Spadoni:** None. **R. Klaming:** None. **I. Strigo:** None.

Poster

795. Injury and Trauma II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 795.27/V9

Topic: C.09. Brain Injury and Trauma

Support: Navy BUMED

VA HSR&D

Marine Corp funding

Title: Interactions between COMTval158met polymorphism and trauma history in Active-Duty Marines: a role in the development of PTSD

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Abstract: Background and objectives: Posttraumatic stress disorder (PTSD) affects 7-8% of the American population and is even higher in military veterans. The catechol-*O*-methyltransferase (COMT) enzyme is implicated in the catabolism of dopamine and plays a key role in cortical signaling. The COMTval158met polymorphism has been associated with a greater risk of neuropsychiatric disorders, including PTSD. Our objectives were to investigate (1) whether COMTval158met polymorphism interacts with PTSD diagnosis to impair fear response and extinction, and (2) whether COMTval158Met genotype modifies combat exposure effects on fear responding in Marines and Navy Corpsmen.
Methods: Participants completed the Clinician-Administered PTSD Scale (CAPS), the Life-Event Checklist (LEC), Childhood Trauma Questionnaire (CTQ) and Deployment Risk and

Resilience Inventory-2 (DRRI-2) before (n = 714) and after (n = 452) deployment to Afghanistan. Fear acquisition and extinction were assessed at each visit using fear-potentiated startle.
Results: Before deployment, Met/Met carriers diagnosed with PTSD displayed significantly greater fear-potentiated startle to the CS- (safety signal) during acquisition and extinction compared to Met/Val and Val/Val carriers. Childhood trauma significantly modified this association, as only Met/Met carriers with PTSD that endorsed childhood trauma had a higher fear-potentiated response to the CS- during extinction compared to the same carriers that did not endorse childhood trauma. After deployment, we found that an elevated fear-potentiated response to the CS+ (danger signal) was found only in Met/Met carriers reporting a high combat exposure score, independently of their PTSD diagnosis, compared to the same carriers with low combat exposure score, confirming a genotype × trauma interaction.
Conclusions: These findings replicate previous studies showing that the Met/Met carriers with PTSD are more likely to show increased fear responding compared to Val/Val carriers with PTSD, and extend this finding to show that this association is modulated by early life exposure. Importantly, Met/Met carriers also exhibit increased fear responding after combat trauma, regardless of PTSD diagnosis, suggesting some acute loss of fear regulation after trauma in Met/Met carriers as a whole. These results support also the key role of gene-environment interactions in the development of psychiatric disorders, including PTSD. Further work will be necessary to understand the mechanisms underlying the modulation of cortical signaling by the COMTval158met polymorphism and fear extinction memory impairments in PTSD pathophysiology.

Disclosures: J. Deslauriers: None. **D.T. Acheson:** None. **M.A. Geyer:** None. **D.G. Baker:** None. **C. Nievergelt:** None. **V.B. Risbrough:** B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution; VA Merit Award BX002558-01. C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Johnson & Johnson.

Poster

796. Extrastriate Cortex I

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 796.01/V10

Topic: D.06. Vision

Support: NIH Grant R01 EY106184

NIH Grant R01 EY022090

McDonnell Center for Systems Neuroscience

Title: Modular connectivity between amygdala and the ventral visual stream.

Authors: *A. M. MEIER[1], Q. WANG[2], A. BURKHALTER[1];
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Abstract: Visual information informs an organism about emotionally salient objects, such as predators, food, and mates. Salient cues are processed in the amygdala, which integrates input from many sensory modalities to drive behavioral responses. In primates, the amygdala reciprocally connects with the ventral 'what' visual cortical stream specialized for object discrimination and not the dorsal 'where' stream specialized for visuomotor guidance (Baizer et al, 1993; Freese and Amaral, 2005). Here we examined the reciprocal connectivity between amygdala and different areas of mouse visual cortex. To study projections to the amygdala, we injected BDA, an anterograde tracer, into each of ten visual areas. Injection sites were identified using callosal projections labeled with bisbenzimide, enabling parcellation of visual cortex into distinct areas (Wang and Burkhalter, 2007). We found that all ventral stream extrastriate areas project to the lateral amygdala. Dorsal stream and V1 provide few projections to the amygdala. Postrhinal cortex (POR) provides the strongest input and is the only area that also projects to basolateral amygdala (BLA). We next studied projections of the amygdala to ventral stream areas by anterograde viral tracing from the BLA and lateral amygdala. We found that the amygdala provides input to layer 1 of posterior ventral stream areas including POR and the Posterior area (P). Few amygdala inputs to layer 4 were found, resembling cortico-cortical feedback projections. Previous work found modularity in primary visual cortex delineated by expression of type 2 muscarinic acetylcholine receptor (M2), and that these separate modules possess distinct visual tuning properties and connectivity (Ji et al, 2015). We thus stained tissue with an antibody against M2 in order to examine possible modularity of projections from amygdala. Amygdala projections to POR and P avoided M2+ patches, targeting M2- 'interpatches' instead. Third, we determined the origins of projections from the amygdala to POR by injecting the retrograde tracer DY into POR. We found that the lateral amygdala, but not BLA project to POR. In summary, the amygdala is selectively and reciprocally connected to the ventral visual stream, suggesting a role of the ventral stream in processing affectively salient objects. Additionally, amygdala feedback to posterior ventral stream areas avoids M2+ clusters, indicating a possible modular organization of affective stimulus processing related to visuomotor guidance.

Disclosures: **A.M. Meier:** None. **Q. Wang:** None. **A. Burkhalter:** None.

Poster

796. Extrastriate Cortex I

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 796.02/V11

Topic: D.06. Vision

Support: Whitehall 2014-5-18

NSF BCS143221

NEI R01EY026924

Title: Maintenance of spatial information modulates beta rhythms within MT cortex

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Abstract: Psychophysical experiments have shown that remembering a location enhances visual discrimination performance at that location. Findings in our lab indicate that neurons in extrastriate visual areas receive a strong top-down signal from prefrontal cortex during the maintenance of spatial information. Although delay-period activity is very weak or non-existent in these visual areas, their sensitivity to incoming visual signals is enhanced during spatial memory maintenance. One possible explanation for this increase in sensitivity to visual input without an increase in baseline firing rate is that the top-down signal provides a sub-threshold modulation. Since the local field potentials (LFPs) are believed to reflect the level of input to an area, we sought to determine whether, and in what frequencies, extrastriate LFPs are modulated during spatial memory maintenance. For this purpose, we recorded neuronal spiking and LFP signals in the middle temporal (MT) area of rhesus monkeys performing a memory-guided saccade task. In this task, the target was presented for one second; the monkey had to remember the target location during a 1.5-2 second blank delay, and then saccade to the remembered location when the fixation point disappeared. Linear array electrodes were used to simultaneously record the activity of multiple MT neurons and LFPs. We measured the power density function (PSD) of the LFPs at each recording site prior to target presentation, during target presentation, and during the memory period. The PSDs were normalized based on the PSD prior to target presentation. The beta (15-30 Hz) power significantly increased during the memory period. Evaluating the temporal relationship between spikes and LFP signals revealed a significant increase in the locking between spikes and the phase of ongoing beta oscillations

during the memory period. We also found that the beta power during the memory period predicted the upcoming saccade accuracy and the reaction time: trials with higher beta power had more precise and faster saccadic responses. These findings provide a mechanistic insight into how the maintenance of spatial information contributes to enhanced sensory processing, potentially underlying the behavioral effects of spatial working memory.

Disclosures: Z. Bahmani Dehkordi: None. **M. Daliri:** None. **Y. Merrikhi:** None. **M. Parsa:** None. **B. Noudoost:** None.

Poster

796. Extrastriate Cortex I

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 796.03/V12

Topic: D.06. Vision

Support: NIH grant - MH 93567

Title: Differential expression of the m1 acetylcholine receptor by inhibitory neurons in macaque MT and LIP indicates distinct neuromodulatory compartments in cortex

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Abstract: Chemical signaling between neurons has generally been viewed as a simple relationship in which an action potential in the presynaptic neuron leads to signal transduction in the postsynaptic neuron. However, diffuse regulation by neuromodulatory systems that signal, at least in part, via volume transmission may violate many aspects of the tightly coupled relationship assumed to be true for classical synaptic transmission. Various features of the local cortical circuit, including axonal density, tissue tortuosity, receptor localization, and signal termination mechanisms introduce variability to non-synaptic transmission. These anatomical and functional characteristics form local cortical sub-compartments between which modulatory signals can vary considerably. In the present study, we explore one aspect of these compartments by comparing cholinergic receptor expression by inhibitory neurons across cortical areas. Dual immunofluorescence labeling was used to identify neurons expressing the muscarinic acetylcholine receptor m1 (m1AChR) and gamma-Aminobutryric acid (GABA) in the middle temporal area (MT) and the lateral intraparietal area (LIP) of the macaque. We found a larger proportion of m1AChR-expressing neurons to be immunoreactive for GABA (GABA-ir) in MT than in LIP. Our results indicate, at least in terms of m1AChR expression by inhibitory neurons, that MT and LIP represent distinct neuromodulatory compartments. Previously, in macaque

visual areas V1 and V2, the proportion of m1AChR-expressing neurons that is GABA-ir was found to be larger in V1 than in V2. Together, these results indicate differential targeting of inhibitory and excitatory neurons by the cholinergic system across visual areas, and support the hypothesis that macaque cortex is divided into distinct neuromodulatory compartments based on features of the local circuit.

Disclosures: **J.J. Coppola:** None. **A.A. Disney:** None.

Poster

796. Extrastriate Cortex I

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 796.04/V13

Topic: D.06. Vision

Support: NIDA grant R21DA024293

Title: Understanding the relationship between specific spatial abilities and map reading skills using fMRI

Authors: A. J. BIES, *M. E. SERENO;
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Abstract: Map reading is a common human activity, yet there is little research on the underlying cognitive abilities and neural processes used during map reading. This study uses functional magnetic resonance imaging (fMRI) to evaluate the relationship between different spatial abilities (as specified by psychometric tests) and map readings tasks. We investigated the neural basis of two previously identified spatial abilities (spatial scanning and spatial relations) and two map reading tasks (shortest path and left/right turn decisions) which are hypothesized to rely on the two different spatial abilities. Spatial scanning involves the ability to quickly and accurately survey a spatial pattern to identify a path through it while spatial relations is the ability to rapidly perceive and manipulate simple patterns (e.g., mentally rotating an object). The results show striking similarities in activation patterns from the spatial scanning and shortest-path tasks, suggesting that the spatial scanning ability contributes to this particular map reading exercise. Activity patterns in the spatial relations and left/right turn decision tasks had significant differences (e.g., there was activation in the parahippocampal place area (PPA) and retrosplenial cortex for the left/right turn map task but not the spatial relations task), suggesting that participants are not mentally rotating maps to complete this task. In fact, there was significant activity in several areas known to be important for scene processing and navigation (such as the PPA and retrosplenial cortex) during both map tasks and the spatial scanning task but not the

spatial relations (mental rotation) task. We conclude that using a map not only requires spatial scanning skills but also a more recently defined spatial ability of spatial orientation or perspective taking.

Disclosures: **A.J. Bies:** None. **M.E. Sereno:** None.

Poster

796. Extrastriate Cortex I

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 796.05/V14

Topic: D.06. Vision

Support: Dan and Martina Lewis Biophotonics Fellowship

Gatsby Charitable Foundation

The Fiona and Sanjay Jha Chair in Neuroscience

Canadian Institutes of Health Research

NIH Grant 5T32EY20503-5

Title: Spontaneous cortical waves in area MT of the awake marmoset

Authors: ***Z. W. DAVIS**[1], L. MULLER[1], T. J. SEJNOWSKI[1], J. MARTINEZ-TRUJILLO[2], J. REYNOLDS[1];
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Abstract: Traveling waves are a ubiquitous property of cortical dynamics. They have been observed across species, in multiple cortical areas, under anesthesia and in the awake state, in spontaneous activity and following sensory stimulation. Cortical waves can be revealed using spike- or stimulus-triggered averaging of neural signals. To examine the properties of cortical waves, such as their patterns of propagation, velocities, and frequency of occurrence, individual waves need to be detected. We implanted a Utah array over area MT of a common marmoset (Callithrix jacchus), which lies on the cortical surface, and recorded spiking and local field potentials as the animal sat in front of a computer monitor. We then used a recently developed phase-based approach to detect and measure the spatiotemporal profiles of individual traveling waves. With this method, waves were detected in ongoing activity of several local field potential (LFP) frequency bands. We reasoned that if traveling waves propagate via fixed anatomical pathways, spatiotemporal patterns of activity should be repeatable. However, if the functional

properties of these pathways vary with network state, waves could vary across sensory conditions. To test this, we measured the spatiotemporal properties of waves in two luminance conditions. We found that waves follow stereotyped spatial profiles and that the profile of observed wave directions was preserved across luminance conditions. However, the speed of waves increased systematically with luminance. These results demonstrate that discrete cortical waves are present in the spontaneous activity of Area MT in the awake marmoset, that individual waves can be readily detected, and that wave velocity, but not direction, varies with luminance.

Disclosures: Z.W. Davis: None. **L. Muller:** None. **T.J. Sejnowski:** None. **J. Martinez-Trujillo:** None. **J. Reynolds:** None.

Poster

796. Extrastriate Cortex I

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 796.06/V15

Topic: D.06. Vision

Support: MEXT/JSPS KAKENHI: 15K18357, 25830012, 15H01437, 16H01637

Title: Response sparseness for natural movies in macaque V1 and V4 estimated by 2-photon calcium imaging

Authors: *K. IKEZOE[1,2], T. FUKAZAWA[2], S. NISHIMOTO[2], S. MITA[2], I. FUJITA[2]; [1]Dept. of Physiology, Div. of Med., Univ. of Yamanashi, Chuo, Yamanashi, Japan; [2]Grad. Sch. of Frontier Biosciences, Ctr. for Information and Neural Networks (CiNet), Osaka Univ. and Natl. Inst. of Information and Communications Technol., Suita, Osaka, Japan

Abstract: Every sensory event evokes responses in a population of neurons across brain areas. Barlow (1972) previously proposed that as we ascend in the hierarchy of the mammalian visual cortical pathway, “a relatively small population of neurons are active, and each says a lot when it is active.” We tested this hypothesis via estimating the response sparseness in the primary visual cortex (V1) and a mid-tier cortex (V4) along the ventral visual pathway of monkeys using 2-photon calcium imaging techniques.
We loaded neurons with calcium indicator (Cal-520 AM) in layer 2 or 3 of V1 and V4 and then recorded fluorescence signals from individual neurons during the presentation of a natural movie to two monkeys (*Macaca fascicularis*) under analgesic and immobilized condition. The movie was 3 minutes long, composed of short clips, and presented 10 times. The refresh rate of the movie was 24 Hz. We estimated firing rates of neurons using deconvolution techniques from fluorescence signals sampled at 30 Hz. We analyzed 1857 V1 neurons and 1833 V4 neurons that

responded reliably across the 10 repeated trials. From the response matrix of video frames vs. neuron identities, we computed lifetime sparseness (LS) for each neuron and population sparseness (PS) for each video frame of the movie. LS indicates what fraction of video frames elicits responses in a given neuron, and PS indicates what fraction of neurons responds to a given video frame. Both LS and PS vary from 0 (equal responses to many stimuli or among neurons) to 1 (strong responses to limited stimuli or in particular neurons).
LS was smaller in V4 than in V1 (V1: 0.41, V4: 0.35; Wilcoxon rank-sum test, $p < 0.01$). Similarly, PS was smaller in V4 than in V1 (V1: 0.41, V4: 0.38; $p < 0.01$). Generally, PS becomes smaller for a neural population among which signal correlation, the similarity of response patterns to video frames, is high. However, the signal correlation between neurons was higher in V1 than in V4 (V1: 0.07, V4: 0.03; $p < 0.01$). Therefore, the difference in signal correlation cannot account for the difference in PSs. Instead, PS in each imaged site was correlated with LS in V1 and V4 (V1: $r = 0.84$, $p < 0.01$; V4: $r = 0.84$, $p < 0.01$, Spearman's rank correlation).
Thus, V4 neurons responded more broadly to natural scenes than V1 neurons, and the fraction of active neurons for natural scenes become larger in V4 than in V1. These results do not support Barlow's hypothesis.

Disclosures: **K. Ikezoe:** None. **T. Fukazawa:** None. **S. Nishimoto:** None. **S. Mita:** None. **I. Fujita:** None.

Poster

796. Extrastriate Cortex I

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 796.07/V16

Topic: D.06. Vision

Support: Alfred P Sloan Foundation

Whitehall Foundation

Brain Research Foundation

NEI EY023371

NSF IOS 145704

Title: Model of MT spike count variability accounts for state-dependent tuning disparities

Authors: *J. LOMBARDO, M. MACELLAIO, B. LIU, S. E. PALMER, L. C. OSBORNE;
Univ. of Chicago, Chicago, IL

Abstract: Sensory neurons have variable responses to repeated presentations of the same stimulus. The structure of this trial-to-trial variability within a population directly affects the ability to decode stimulus identity. We compared the spike-count variability of *macaque* MT neurons in both the awake and anesthetized state, finding a state-dependence of variability and variability tuning. In the anesthetized state, the data is well modeled by a Poisson process with variable multiplicative gain. This model predicts a variance to mean ratio, or Fano factor (FF), that is strictly increasing with spike count. However, in the awake state, inverted Fano factor tuning is observed, with decreasing FF at higher spike counts at preferred directions of motion. We developed a unified model of spike count variability that captures the U-shaped Fano factor tuning observed in the awake state, as well as the super-Poisson variability observed in the anesthetized state. In our model, the state-dependent FF tuning changes are mediated by a switch from a low-gain state in the awake state to a higher gain state when anesthetized.

Disclosures: J. Lombardo: None. **M. Macellaio:** None. **B. Liu:** None. **S.E. Palmer:** None. **L.C. Osborne:** None.

Poster

796. Extrastriate Cortex I

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 796.08/V17

Topic: D.06. Vision

Support: NIH Grant DC008794

NIH Grant EY022338

Title: Functional topography of the cortical inputs to layer 1 neurons of medial secondary visual cortex in mice

Authors: *Y.-W. LAM, S. SHERMAN;
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Abstract: Layer 1 of the neocortex consists mainly of the apical tufts of pyramidal neurons and horizontally oriented axons from"matrix" thalamic neurons and other cortical areas. It also contains sparsely scattered GABAergic neurons that innervate cells of lower layers. We studied the topography of the cortical input to layer 1 neurons using laser-scanning photostimulation in coronal slices from brains of Balb/c mice. Layer 1 neurons of the medial secondary visual cortex

were identified in slices as the cells sparsely distributed above the well-packed somata of the layer 2/3 and recorded in voltage-clamp mode held at -45 mV. The slices were then perfused with ACSF containing nitroindoliny-caged-glutamate and stimulated with a UV laser (355 nm wavelength). Photostimulation of cortical layers 2 to 6 evoked responses in about 50% of the recorded neurons. Half of these responses consisted solely of EPSCs and the remainder had a mixture of EPSCs and IPSCSs. We did not see much evidence of local GABAergic input to these cells, suggesting that local connections among these layer 1 cells are sparse at best. Our results suggest that layer 1 neurons receive monosynaptic and polysynaptic inputs from neurons in lower layers within the same region of neocortex, further suggesting that these cells integrate converging inputs from thalamus, other cortical areas, and local inputs.

Disclosures: Y. Lam: None. **S. Sherman:** None.

Poster

796. Extrastriate Cortex I

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 796.09/V18

Topic: D.06. Vision

Support: the Korea Research Institute of Standards and Science (KRISS)

the Ministry of Culture, Sports and Tourism (MCST) and the Korea Creative Content Agency (KOCCA) in the Culture Technology (CT) Research & Development Program 2015

Title: Stereoscopic depth may increase cognitive responses within visual comfortable zone

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Abstract: Stereoscopic three-dimensional contents including 3D movies, 3D TV, head mounted display (HMD), and augmented reality have become popular in recent days. Although excessive stereoscopic depth images can cause visual fatigue and discomfort, proper 3D images can increase sense of realism and viewing experience. In this paper, we hypothesized ‘cognitive zone’ exists within visual comfortable zone. Stereoscopic depth may increase cognitive responses in the brain and is saturated within the visual comfortable zone. In this reasoning, we investigated cognitive responses for four different stereoscopic depth levels within the comfort zone. Simultaneous EEG/MEG acquisition technique was introduced to collect the cognitive

responses of eight participants. We defined subject-specific retinal disparities and designed a single trial-based stereoscopic viewing experimental paradigm. In the single trial analysis, we observed that as depth level increased from 1 to 3, there was a time-locked increase in the N200 component in MEG and the P300 component in EEG on the occipital and the parietal areas, respectively. Averaged retinal disparity of depth level 3 was -0.34 ± 0.036. After 3D depth exceeded the depth level 3, the amplitude of cognitive responses decreased. From these findings, it is expected that cognitive response is likely to be saturated in the visual comfort zone, while depth perceptual load may increase as depth level increases.

Disclosures: **H. Cho:** None. **M. Kang:** None. **S. Ahn:** None. **M. Kwon:** None. **J. Choi:** None. **S.C. Jun:** None.

Poster

796. Extrastriate Cortex I

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 796.10/W1

Topic: D.06. Vision

Support: NSERC

Canada Research Chair Program

Title: Transsaccadic integration of spatial frequency information in an fMRIa paradigm

Authors: *B.-R. BALTARETU[1], B. T. DUNKLEY[2], J. D. CRAWFORD[1];
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Abstract: To date, the neural correlates of feature information integration across saccades (i.e., transsaccadic integration, TSI) are relatively unknown. Using fMRI adaptation, we found that right inferior parietal lobule (IPL; specifically, SMG) and extrastriate cortex (putative V4) are sensitive to objet orientation in a space-fixed reference frame (Dunkley et al., submitted). Here, we used fMRIa to uncover the cortical correlates of spatial frequency in a space-fixed reference frame. Functional data were collected across 11 participants while they observed a vertical grating of a given spatial frequency in the center of the screen, followed by a grating at the same ('Repeat' condition) or different ('Novel' condition) spatial frequency. Participants were required to either fixate in the same position (Fixation task) or to make a saccade to the opposite fixation point (Saccade task). Participants were instructed to decide via a 2AFC task if the subsequent grating was repeated or novel. The Saccade task produced specific, significant ($p<0.05$) summation (repeated > novel; repetition enhancement, RE) in frontal cortex and

adaptation (novel > repeated; repetition suppression, RS) in occipito-parietal areas. The Fixation task produced specific, significant ($p<0.05$) summation (RE) in an extensive occipito-parieto-frontal cluster of areas. We also conducted a region-of-interest analysis to explain parietal and occipital areas found to be involved in transsaccadic memory of object features (Prime et al., 2008; Malik et al., 2015). This indicated regions of significant Novel vs. Repeat effects in several additional parietal and occipital areas, possibly explaining our previous TMS results. Overall, TSI of spatial frequency produced a similar pattern of cortical activation as the pattern for TSI of object orientation in our previous study (although details differed), suggesting a general role for occipital-parietal cortex in spatiotopic TSI of low-level object features.

Disclosures: **B. Baltaretu:** None. **B.T. Dunkley:** None. **J.D. Crawford:** None.

Poster

796. Extrastriate Cortex I

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 796.11/W2

Topic: D.06. Vision

Support: JSPS Grant-in-aid for JSPS Fellows

Title: Diffusion properties of human visual white matter correlate with stereoacuity

Authors: *H. OISHI[1,2], H. TAKEMURA[2,1,3], S. C. AOKI[2,1], I. FUJITA[2,1], K. AMANO[2,1]; [1]Grad. Sch. of Frontier Biosci., Osaka Univ., Osaka, Japan; [2]Ctr. for Information and Neural Networks (CiNet), Natl. Inst. of Information and Communications Technology, and Osaka Univ., Osaka, Japan; [3]Japan Society for the Promotion of Sci., Tokyo, Japan

Abstract: Binocular disparity is an important cue for depth perception. Disparity-sensitive fMRI responses have been reported in a variety of visual cortical regions (Tsao et al., 2003), suggesting that the disparity information is transferred among several areas throughout white matter pathways. Human psychophysical studies identified substantial individual differences in sensitivity for detecting disparity (stereoacuity; Zaroff et al., 2003; Hess et al., 2015). Here we examined how the structural properties of visual white matter pathways are related with the individual difference in streoacuity by combining psychophysics and diffusion-weighted Magnetic Resonance Imaging (dMRI).We measured disparity discrimination threshold for 19 participants with normal or corrected-to-normal vision (age 20-37, mean: 25.1). Completely stereoblind participants were screened out in a prior test. We used circular patches of dynamic random-dot stereograms, each consisting of a center disk and a surrounding annulus. We changed binocular disparity of the disk across trials while keeping the annulus always at 0

disparity. The participant's task was to determine whether the disk appeared in front of or behind the annulus. We observed substantial individual differences in performance of this task, and classified participants into two groups: high- (N=10; median threshold: 0.014 deg) and low-performance (N=9; median threshold: 0.073 deg) groups. We also collected dMRI data using a 3T MRI scanner (2 mm isotropic voxels, 64 angular directions) from the same 19 participants. For dMRI data analysis, we used probabilistic tractography to identify the major visual white matter pathways, optic radiation (OR), the forceps major, and the vertical occipital fasciculus (VOF). For each group of participants, we then calculated Fractional Anisotropy (FA) along these pathways in order to evaluate the structural properties of each pathway. We found a significant difference of the FA in the central portion along the right VOF between the high-performance and low-performance participant groups. Moreover, FA along the right VOF was negatively correlated with disparity discrimination threshold across participants ($R=-0.795$; $p<0.001$). In contrast, FA did not exhibit any inter-group difference or correlation with stereoacuity along the OR and forceps major. The VOF is known as a pathway to link dorsal and ventral visual cortex (Yeatman et al., 2014; Takemura et al., 2015). Our results indicate that the stereoacuity reflects the structural properties on the pathway involving with dorsal-ventral communication, rather than the early visual pathways such as the OR.

Disclosures: **H. Oishi:** None. **H. Takemura:** None. **S.C. Aoki:** None. **I. Fujita:** None. **K. Amano:** None.

Poster

796. Extrastriate Cortex I

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 796.12/W3

Topic: D.06. Vision

Support: NIH Grant R01 EY016184

NIH Grant R01 EY022090

McDonnell Center for Systems Neuroscience

Title: Laminar patterns of interareal axonal projections reveal a hierarchical organization of mouse visual cortical areas.

Authors: *R. D'SOUZA[1], Q. WANG[1,2], A. MEIER[1], A. BURKHALTER[1];
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Abstract: Upon receiving thalamic input, primary visual cortex (V1) sends signals to extrastriate cortical areas, which themselves connect with each other and with V1 with varying strengths. Visual processing is thought to be hierarchical, wherein signals are sent from V1 to increasingly higher areas depending upon the relevant features of visual stimuli, even while each area is targeted by multiple areas. Cortico-cortical connections can be broadly classified as being feedforward (FF) if they send information deeper into the cortex, feedback (FB) if they provide descending inputs from higher to lower areas, or lateral if they connect areas at equal levels of a processing hierarchy. A critical step in understanding how computations within such a distributed processing system leads to visual perception and function requires the identification of the cortical hierarchy, if any, through which signals flow. Using anatomical criteria of interareal axonal projections, the structural hierarchical organization of the cortical visual system has been proposed in primates (Felleman and Van Essen, 1991) and rats (Coogan and Burkhalter, 1993). Because the mouse has emerged as a widely used model for studying cortical circuits and function, due to its genetic tractability, we aimed to identify a multilevel hierarchy through which mouse visual cortical areas communicate. To do this, the anterograde tracer, biotinylated dextran amine (BDA), was injected into each of ten identified visual areas, and axonal termination patterns in each of the other nine areas were examined. The areas were identified by their locations relative to landmarks formed by retrogradely-labelled callosally projecting neurons, which were imaged *in situ* before the brain was coronally sectioned. Projections from V1 to higher areas tended to selectively target layers 2 to 4 (L2-4) while only weakly terminating in L1. On the contrary, FB projections to V1 strongly targeted L1, while preferentially avoiding L2-4. We therefore used the ratio of the density of axonal terminations in L2-4 to that in L1 (‘density ratio’, DR) as a measure for quantifying the hierarchy of connections, and generated a 10x10 matrix of DRs of over 85 interareal pathways. The DR for each area to each of the nine targets was averaged, and the average DR was compared between areas for statistical significance. The analyses revealed at least five hierarchical levels through which visual areas interconnect, with V1 at the bottom, and the postrhinal (POR) and anteromedial (AM) areas at the top of the hierarchy. By further dividing the areas into the dorsal and ventral streams (Wang et al., 2012), we propose the hierarchical organization of each stream.

Disclosures: **R. D'Souza:** None. **Q. Wang:** None. **A. Meier:** None. **A. Burkhalter:** None.

Poster

796. Extrastriate Cortex I

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 796.13/W4

Topic: D.06. Vision

Support: National Eye Institute Grant 1R15EY023834

Title: Steady-state signatures of visual short-term plasticity and perceptual filling-in

Authors: *S. M. LONG, M. A. GANNON, M. M. GARDNER, N. A. PARKS;
Psychological Sci., Univ. of Arkansas, Fayetteville, AR

Abstract: An artificial scotoma is a stimulus-induced analog of retinal deafference; created by superimposing a circumscribed area of uniform luminance on a dynamically altering white noise background. When viewed for several seconds, an artificial scotoma fades from awareness, becoming perceptually filled-in by the dynamic background stimulus. Single-cell work in non-human primates has previously described a phenomenon called 'climbing activity' in which activity of cells within scotoma representations of extrastriate cortex increase responsiveness over time and become responsive to dynamic background stimuli beyond the boundaries of their classical receptive fields (De Weerd, Gattass, Desimone, and Ungerleider, 1995). Here, we used steady-state visual evoked potentials (SSVEPs) to provide an index of climbing activity in human extrastriate cortex and examine its relationship to the perceptual filling-in of an artificial scotoma. EEG was recorded from observers, while they viewed an artificial scotoma display consisting of a six degree mid-gray disc superimposed upon a dynamic background of small white dots for a period of 18 seconds. The dynamic background of this display refreshed at rates of 5 Hz, 10 Hz, or 20 Hz and observers indicated by button press when the scotoma disc began to become filled-in by the background. Time-frequency analyses of SSVEPs were used to examine temporal modulations in spectral EEG power at the dynamic background's driving frequency leading up to the observers' report of perceptual filling-in. Consistent with climbing activity in extrastriate cortex, spectral power at the SSVEP's driving frequency increased in the seconds preceding the report of perceptual filling-in. Climbing activity indexed by the SSVEP further correlated with observers' mean fill-in time of the artificial scotoma disc. These findings provide an index of climbing activity and provide further evidence that the perceptual filling-in of an artificial scotoma is mediated by invading activity originating beyond the scotoma's classical retinotopic boundaries.

Disclosures: S.M. Long: None. **M.A. Gannon:** None. **M.M. Gardner:** None. **N.A. Parks:** None.

Poster

796. Extrastriate Cortex I

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 796.14/W5

Topic: D.06. Vision

Support: JST/PRESTO

DFG

Title: Selective flow of sensory-motor information in the reciprocal connectivity in mouse frontoparietal cortex

Authors: ***T. SATO**[1], T. K. SATO[2], M. HASEGAWA[1], T. ITOKAZU[1], R. KIMURA[1]; [1]Ctr. For Integrative Neurosci., Tuebingen, Germany; [2]Technische Univ. München, Munich, Germany

Abstract: Cortical areas are intertwined with networks of reciprocal long-range connectivity. However, the circuit logic underlying such connectivity is still unclear. Here we report a simple rule on the reciprocal connectivity between sensory and motor areas in mice. Using a newly developed eye movement task, combined with two-photon calcium imaging, electrical stimulation, and anatomical tracing, we identified a motor area that controls eye movements in the medial prefrontal cortex ($mPFC_{eye}$). $mPFC_{eye}$ encodes not only motor command signal, but also visual information that instructed the eye movements. Unexpectedly, dual encoding was also found in visual areas in the parietal cortex ($V_{parietal}$) where we found reciprocal connectivity with $mPFC_{eye}$. Primary visual cortex, in contrast, shows only visual encoding. Remarkable similarity and strong reciprocal connectivity between $mPFC_{eye}$ and $V_{parietal}$ apparently implied little functional segregation of the two. However, segregated information flow was uncovered by axonal calcium imaging: $mPFC_{eye}$ preferentially sends motor information to $V_{parietal}$, whereas $V_{parietal}$ visual information to $mPFC_{eye}$. We speculate that long-range reciprocal connectivity acts as a selective filter which prevents reverberant loops, leading to efficient sensory-motor interactions.

Disclosures: **T. Sato:** None. **T.K. Sato:** None. **M. Hasegawa:** None. **T. Itokazu:** None. **R. Kimura:** None.

Poster

796. Extrastriate Cortex I

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 796.15/W6

Topic: D.06. Vision

Support: Wellcome Trust 095669

Wellcome Trust 095668

Title: Space and choice in mouse parietal cortex during virtual navigation

Authors: *M. KRUMIN, K. D. HARRIS, M. CARANDINI;
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Abstract: Posterior parietal cortex (PPC) is a nexus of sensory and motor areas. In primates it is believed to perform operations such as coordinate transformations and decision making. In rat PPC, some experiments revealed decision signals, but others revealed signals related to navigation. Can these two views be reconciled? To address these questions we trained mice on a virtual reality task that involves both decision-making and navigation. The mice traversed a virtual corridor with a vertical grating painted on one of the side walls. They were rewarded for reporting the position of the grating by either turning right or left at the end of the corridor. Their success rates increased with increasing grating contrast. The animals typically indicated their choices early: trajectories leading to left and right turns diverged well ahead of the end of the corridor.While the mice performed the task, we used 2-photon calcium imaging to record populations of neurons in PPC. Most cells showed activity that was correlated with the animal's choice: they preferentially fired during trials ending in a specific choice. In addition, these cells fired reliably during a specific period during the trial, forming a sequential activation, as different cells fired during different periods (Harvey et al. Nature, 2012). As a consequence, the animal's choice could be predicted from activity of these cells, including well before the animal turned at the end of the corridor. An alternative analysis revealed that the activity of PPC neurons was strongly modulated by the mouse's virtual position along the corridor (z) and virtual head direction (θ). Many of the cells had localized 'space fields' in these coordinates, and this z-θ model gave a prediction of each neuron's activity with explained variance of up to 89% (21±16% for all active cells). These space fields could occur at any location in z-θ coordinates, and indeed the neurons recorded in a single session typically tiled the T-maze.Neural activity was also modulated by other sensory or behavioural parameters, e.g. the visual stimulus, or the motor actions of the mouse. However, for the majority of the cells the space fields accounted for the largest fraction of the neural responses.These results suggest that mouse PPC can play a key role in visually guided behavior. Neural activity showed strong modulation by multiple behaviorally relevant features of the acquired task. These features include not only position in the environment and, possibly, the traces of perceptual decisions, but also virtual heading angle, motor actions, and visual stimulus - all of which are an inherent part of this complex behavior.

Disclosures: **M. Krumin:** None. **K.D. Harris:** None. **M. Carandini:** None.

Poster

796. Extrastriate Cortex I

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 796.16/W7

Topic: D.06. Vision

Support: NSF CRCNS grant IIS-1309725

R01 EY018839

Title: Clustering V4 neurons based on their responses to simple shapes

Authors: R. EGHBALI, A. PASUPATHY, *W. BAIR;
Biol. Structure, Univ. of Washington, Seattle, WA

Abstract: The ventral pathway of the primate visual system is involved in form processing and object recognition, but only the early stages of this pathway are well understood. While most neurons in the primary visual cortex are tuned for orientation and spatial frequency, cells in area V4, an intermediate stage along this pathway, appear to be selective for more complex visual patterns and have been more difficult to characterize. V4 neurons have been shown to respond to aspects of shape, texture and color, and it is likely that additional important axes of representation remain to be discovered. In many past studies attempting to understand V4, the stimulus design and analysis were driven by a specific underlying hypothesis and model. To avoid inherent pitfalls in this approach, and discover novel encoding dimensions, we take a more model-free approach to reanalyze responses of V4 neurons to the set of simple shapes (PC2001) introduced by Pasupathy & Connor (2001). We focus on two main questions: Do V4 neurons fall within clusters in terms of how they respond to the shape set? and, What do the V4 responses tell us about the shape set, i.e., do the shapes cluster in terms of the responses they evoke across the population of neurons? The PC2001 stimulus set provides a unique opportunity to understand V4 encoding because nearly the same set of 370 stimuli (51 shapes at up to 8 rotations) have been presented in several studies of well-isolated single units in macaque V4 over many years. We accumulated data from 3 studies (6 animals) for a total of 272 neurons. We defined a rotation-invariant metric between pairs of cells based on their responses to the shape set such that cells with shape preferences that are rotated version of each other will be separated by a very small distance. Using multiple clustering methods, we found 4 major clusters that included ~20% of the cells. We determined how well the cells within each cluster were fit by published models for V4 - the angular-position and curvature (APC) model and the spectral receptive field (SRF) model - and we examined how well the clusters could be distinguished in APC and SRF parameter space. For each cluster, we also found a subset of shapes that played a significant role in distinguishing that cluster from the rest of the neurons. Overall, our clustering identified novel categories of units that were not distinguished based on the parameters of existing models (APC

and SRF), and we were able to identify clear intuitive dimensions, e.g., tuning for stimulus area and isoperimetric quotient, which did distinguish these clusters. These clusters offer important hints for the design of novel stimuli to better understand shape encoding in mid-level vision.

Disclosures: **R. Eghbali:** None. **A. Pasupathy:** None. **W. Bair:** None.

Poster

796. Extrastriate Cortex I

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 796.17/W8

Topic: D.06. Vision

Support: NEI grant R01EY018839

P51 grant OD010425

Vision Core grant P30EY01730

Title: Primate prefrontal cortex and the representation of partially occluded shapes

Authors: A. FYALL[1], H. CHOI[2], E. T. SHEA-BROWN[3], *A. K. PASUPATHY[2];
[1]Univ. of Washington, Seattle, WA; [2]Biol. Structure, [3]Univ. Washington, Seattle, WA

Abstract: How the primate brain successfully recognizes occluded objects is an enduring puzzle in Systems Neuroscience. Despite dramatic advances in deep learning algorithms, recognition under occlusion continues to stump artificial vision systems. Feedback signals from higher cortices, an oft omitted component in artificial systems, have been hypothesized to underlie the success of the primate brain but this claim has not been physiologically tested. Here we show that neurons in the primate prefrontal cortex, a high level cortical region implicated in the executive control of behavior, exhibit stronger and more selective responses to occluded than unoccluded shapes during the performance of a shape discrimination task under occlusion. This is unlike visual area, V4, where responses decline with increasing occlusion levels. While the earliest transients in V4 decline with increasing levels of occlusion, we demonstrate that many neurons exhibit a second transient that emerges after the onset of PFC responses and, like in PFC, show a stronger modulation for occluded stimuli. These results, replicated by a simple two-layer V4-PFC network model, suggest that PFC inputs could be utilized to selectively boost responses of some V4 neurons to occluded shapes thereby increasing their selectivity and facilitating better discrimination under occlusion.

Disclosures: **A. Fyall:** None. **H. Choi:** None. **E.T. Shea-Brown:** None. **A.K. Pasupathy:** None.

Poster

796. Extrastriate Cortex I

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 796.18/W9

Topic: D.06. Vision

Support: NEI grant R01EY018839

Vision Core grant P30EY01730

P51 grant OD010425

Title: Neural responses in the inferior temporal cortex to partially occluded and occluding stimuli

Authors: ***T. NAMIMA**, A. PASUPATHY;
Dept. of Biol. Structure, Univ. of Washington, Seattle, WA

Abstract: Image segmentation - the process by which scenes are segmented into component objects - is a fundamental aspect of vision and a cornerstone of scene understanding; its neural basis, however, is largely unknown. Partial occlusions pose a special challenge to segmentation because, unlike non-overlapping stimuli, they require the parsing of overlapping contours and regions and/or the grouping of noncontiguous regions. To begin to understand how partially occluded stimuli are segmented in the primate brain, we studied the responses of single neurons in IT cortex to shape stimuli subjected to increasing levels of occlusion. We asked whether IT responses are consistent with a segmented representation whereby responses of each neuron are dictated by either the occluded or the occluding stimulus, but not both.
We recorded from 52 well-isolated, single IT neurons as animals were engaged on a sequential shape discrimination task. On each trial, two stimuli were presented in sequence and the animal had to report whether the stimuli were the same or different with a rightward or leftward saccade, respectively. The second stimulus in the sequence was occluded with randomly positioned dots; occlusion levels were titrated by varying occlude dot. Some neurons (10/52, 19%) showed strong responses to unoccluded stimuli and responses declined with increasing levels of occlusion. These neurons behaved quite like those in IT cortex during passive fixation (Kovacs et al., 1995) and their responses were consistent with a direct encoding of the raw (unsegmented) image. Most IT neurons (37/52, 71%), however, showed weak responses to unoccluded shape stimuli

and stronger responses under occlusion, independent of the shape of the occluded stimulus. These results support the idea that many IT neurons encode just the occluding stimuli supporting a segmented representation.

Disclosures: **T. Namima:** None. **A. Pasupathy:** None.

Poster

797. Mouse Visual Cortex

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 797.01/W10

Topic: D.06. Vision

Title: Generation of a mesoscale connectome of the mouse visual system using individual functional maps for viral targeting

Authors: ***P. A. GROBLEWSKI**, A. BERNARD, A. CETIN, C. FARRELL, D. FENG, M. GARRETT, N. GAUDREAULT, K. E. HIROKAWA, A. HO, T. KEENAN, A. KRIEDBERG, Y. LI, F. LONG, V. MALDONADO, S. MIHALAS, L. NG, J. PHILLIPS, T. SIUDA, C. THOMPSON, W. WAKEMAN, C. KOCH, H. ZENG, J. A. HARRIS;
Allen Inst. For Brain Sci., Seattle, WA

Abstract: The purpose of the Next Generation Connectivity project is to create a comprehensive mesoscale connectome that maps the inputs to, and outputs from, the mouse visual system with cortical layer and cell type specificity. This project extends the findings of the existing Allen Mouse Brain Connectivity Atlas by adding components that improve precision, increase specificity, and enhance characterization of mouse visual circuitry. Specifically, the aims of Next Generation Connectivity are to generate 1) an inter-areal retrograde projectome, 2) an inter-areal and cell type-specific projectome using axonal and synaptic labeling, 3) a target-defined inter-areal and cell type-specific anterograde projectome, and 4) an inter-areal and cell type-specific retrograde trans-synaptic connectome. Here we describe the use of intrinsic-signal-imaging (ISI) to obtain retinotopic and sign maps of the visual cortex in individual mice to precisely guide injections of fluorescent anterograde and retrograde viral tracers into specific locations within primary and higher visual areas. Briefly, mice are first implanted with a headframe that allows for through-skull ISI of the visual cortex while mice view a periodic drifting bar stimulus covering the entire field of view — the resulting maps are then used to guide tracer injections using a custom suite of integrated software and hardware. Using high-throughput 2P serial imaging, coronal sections of the injected brain are generated, viral infection sites are then annotated and all brains are registered to the 3D common coordinate framework (CCF) through our informatics data processing pipeline. Individual ISI maps are then overlaid onto the CCF

using surface vasculature patterns. The steps of this workflow, from the initial surgery to final ISI map overlay, require a common registration system that allows for precise alignment of the mouse brain across all experimental and analysis platforms. Lastly, to showcase the results of this project workflow we will present preliminary Next Generation Connectivity datasets that are currently available through our public data portal (www.brain-map.org).

Disclosures: **P.A. Groblewski:** None. **A. Bernard:** None. **A. Cetin:** None. **C. Farrell:** None. **D. Feng:** None. **M. Garrett:** None. **N. Gaudreault:** None. **K.E. Hirokawa:** None. **A. Ho:** None. **T. Keenan:** None. **A. Kriedberg:** None. **Y. Li:** None. **F. Long:** None. **V. Maldonado:** None. **S. Mihalas:** None. **L. Ng:** None. **J. Phillips:** None. **T. Siuda:** None. **C. Thompson:** None. **W. Wakeman:** None. **C. Koch:** None. **H. Zeng:** None. **J.A. Harris:** None.

Poster

797. Mouse Visual Cortex

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 797.02/W11

Topic: D.06. Vision

Title: The structure of population coding and fluctuations in mouse visual cortex.

Authors: ***G. K. OCKER**, S. DE VRIES, R. AYER, J. SIEGLE, D. DENMAN, J. LECOQ, R. C. REID, M. A. BUICE;
Allen Inst. for Brain Sci., Seattle, WA

Abstract: The Cortical Activity Map Project contains 2P calcium imaging from simultaneously recorded populations of hundreds of neurons in awake mice. Its recordings together span layers 2-5 in areas V1 and the secondary areas LM, AL and PM and are in response to both synthetic and naturalistic stimuli. This dataset offers a powerful new tool for examining population coding in the mouse visual system. The structure of fluctuations in population activity and the relationships between those fluctuations and neurons' stimulus preferences can have powerful effects on population coding. To assess information processing across visual areas and layers, we examine how well different stimuli can be decoded by correlation-based and correlation-ignorant decoders. We then examine how coding performance in different visual areas relates to the structure of fluctuations in the populations' activity.

Disclosures: **G.K. Ocker:** None. **S. de Vries:** None. **R. Ayer:** None. **J. Siegle:** None. **D. Denman:** None. **J. Lecoq:** None. **R.C. Reid:** None. **M.A. Buice:** None.

Poster

797. Mouse Visual Cortex

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 797.03/W12

Topic: D.06. Vision

Title: Characterization of calcium events and spiking activity *In vivo* and their relationship in multiple cell types using transgenic mouse lines

Authors: *U. KNOBLICH, J. WATERS, C. REID, C. KOCH, H. ZENG, L. LI;
Allen Inst. for Brain Sci., Seattle, WA

Abstract: Two-photon (2-p) calcium imaging using genetically encoded calcium indicators (GECIs) has been widely adopted to monitor the activity of groups of neurons. However, the relationship between calcium events and spiking activity is not yet fully understood, making it difficult to link these studies to the large body of existing knowledge about neuronal firing. This spike-to-calcium transfer function depends on several factors, including the particular GECI, the cell type it is expressed in (due to differences in ion channels and intrinsic calcium dynamics), its expression level, and the behavioral state of the animal (due to changes in calcium dynamics, e.g. by neuromodulators). Previous studies have largely relied on virus injections to deliver GECIs into the cells of interest, creating another source of variability due to differential uptake and expression of the virus.
Transgenic mouse lines provide a way to achieve more uniform expression of GECIs in a specifically targeted population of cells, enabling a more straightforward comparison of activity across cells and animals. Using our newly developed intersectional transgenic mouse lines expressing GCaMP6f or GCaMP6s in a Cre-dependent manner, we examine the statistics of spontaneous and stimulus-evoked calcium events across the target layer 2/3 population in primary visual cortex, and their dependence on the state of the animal. In addition, we perform concurrent 2-p calcium imaging and 2-p targeted cell-attached recordings in the same neurons to simultaneously measure spiking and calcium activity to directly characterize their transfer function. These results will be beneficial for interpreting existing as well as future calcium imaging data such as the output of the Cortical Activity Map Project at the Institute.

Disclosures: **U. Knoblich:** None. **J. Waters:** None. **C. Reid:** None. **C. Koch:** None. **H. Zeng:** None. **L. Li:** None.

Poster

797. Mouse Visual Cortex

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 797.04/X1

Topic: D.06. Vision

Title: Functional characterization of visual responses in the Cortical Activity Map

Authors: *S. E. DEVRIES, M. GARRETT, G. K. OCKER, M. A. BUICE, J. LECOQ, A. BERNARD, D. FENG, L. NG, S. OLSEN, C. REID, H. ZENG, C. KOCH;
Allen Inst. For Brain Sci., Seattle, WA

Abstract: In order to explore how features of the sensory environment are represented by cortical circuits, the Allen Institute for Brain Science has recently released the first survey of neural activity in the living brain, the ALLEN Cortical Activity Map. Using high-throughput 2-photon calcium imaging, we have systematically recorded the visual responses of neurons in the awake mouse cortex, generating a dataset that spans multiple visual areas, cortical layers, and Cre lines. Using transgenically expressed GCaMP6 under the control of specific Cre drivers, we captured the responses from specific neuron populations to a wide range of visual stimuli, both synthetic and natural, designed to efficiently capture the visual response properties of cortical neurons. Neurons are individually characterized by their spatial receptive field structure, their temporal dynamics, and their orientation, spatial and temporal frequency tuning. Further, responses to natural images and movies serve to compare the spatial and temporal response properties to activity in a more naturalistic context. This is an extremely rich dataset for exploring cortical computations involved in visual information processing. Here, we examine how these visual response properties are transformed across different cortical layers and visual areas. Further, we evaluate how naturalistic stimulus statistics alter the spatial and temporal processing of visual stimuli throughout the mouse's visual pathway, highlighting non-linear processes in the cortical circuit.

Disclosures: S.E. DeVries: None. **M. Garrett:** None. **G.K. Ocker:** None. **M.A. Buice:** None. **J. Lecoq:** None. **A. Bernard:** None. **D. Feng:** None. **L. Ng:** None. **S. Olsen:** None. **C. Reid:** None. **H. Zeng:** None. **C. Koch:** None.

Poster

797. Mouse Visual Cortex

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 797.05/X2

Topic: D.06. Vision

Title: The common coordinate framework: a 3d mouse brain atlas delineated by multi-modality references

Authors: *Q. WANG, J. A. HARRIS, Y. LI, J. ROYALL, P. LESNAR, S.-L. DING, B. FACER, K. HIROKAWA, A. HO, S. SUNKIN, A. BERNARD, C. KOCH, H. ZENG, L. NG; Allen Inst. for Brain Sci., Seattle, WA

Abstract: Brain atlases are essential tools for neuroscience research. Conventional mouse brain atlases built in 2D format from coronal and sagittal sections such as "*The Mouse Brain in Stereotaxic Coordinates*" (Paxinos and Franklin, 2001) and the *Allen References Atlas* (Dong, 2008). These 2D atlases have been widely used in the field but cannot simply transform to an accurate 3D brain atlas due to imperfect alignment among the images caused by the tissue processing procedure. In order to integrate, visualize and analyze multi-modal big data, it is necessary to build a high resolution 3D mouse brain atlas. In the present study, we first built an average 3D template from the block-face images of 1675 adult laboratory mouse (C57BL/6J and transgenic mice) brains with 10 micron isotropic resolution. This high resolution average template allowed us to see more than 100 cortical and subcortical structures without any further staining. These visible structures were drawn in 3D space with the 3D drawing tool ITK-SNAP. Next, to delineate structures that were not immediately visible on the average template we registered, using local and global alignment, additional data to the average template, including, 1) five reference data sets, 2) connectivity data from the Allen Mouse Connectivity Atlas, and, 3) block-face scanned brain images from 30 transgenic mouse lines. Using these data sets, a total of 43 cortical areas, and their subdivisions, were reconstructed from surface views using a curved cortical coordinate system in the Common Coordinate Framework (CCF). For example, by overlaying the virtual callosal connections made from more than 100 injections throughout the contralateral cortical areas and visuotopic maps made from 26 injections in the primary visual area with the average template, 9 higher visual areas were delineated in this 3D space. Each delineated higher visual area has its own unique shape and size on the surface views. Three and six more visual areas were reconstructed in our 3D atlas compared to what is available in the Dong's Atlas and the Paxinos and Franklin's atlas, respectively. In addition, 187 subcortical gray matter structures, and 82 white matter structures were reconstructed in 3D space. Some of these structures have not been previously annotated in other atlases. For example, the lateral geniculate nucleus was further subdivided into shell, core and ipsilateral retina projection zones based on both the transgenic data and retina projection data from the Allen Mouse Connectivity Atlas.

With accurately reconstructed cortical and subcortical structures in 3D space, the CCF provides a foundation for integrating, analyzing and visualizing multi-modal big data.

Disclosures: **Q. Wang:** None. **J.A. Harris:** None. **Y. Li:** None. **J. Royall:** None. **P. Lesnar:** None. **S. Ding:** None. **B. Facer:** None. **K. Hirokawa:** None. **A. Ho:** None. **S. Sunkin:** None. **A. Bernard:** None. **C. Koch:** None. **H. Zeng:** None. **L. Ng:** None.

Poster

797. Mouse Visual Cortex

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 797.06/X3

Topic: D.06. Vision

Title: Spike-free inference from calcium imaging.

Authors: ***K. Q. LEPAGE**[1], U. KNOBLICH[2], L. LI[2], R. IYER[2], S. MIHALAS[2], C. ANASTASSIOU[2], M. A. BUICE[2];
[1]Allen Inst. For Brain Sci., Seattle, WA; [2]Allen Inst. for Brain Sci., Seattle, WA

Abstract: As a portion of the Cortical Activity Map (CAM) Project, a major initiative at the Allen Institute for Brain Science, head fixed adult mice are shown both artificial and natural visual stimuli while high-throughput 2-photon calcium imaging data are recorded from the mouse visual cortex to assess stimulus processing across cortical layers, cortical areas, and Cre lines. In addition to this effort, to assess the accuracy of statistical inference cell-attached electrophysiological (ephys) data are collected simultaneously with two-photon calcium imaging (ophys). This latter experiment reveals, particularly when imaging at the lower magnification required to cover the mouse cortex, that a large number of spikes are not represented by the fluorescence signal, and conversely, an upward transient in the fluorescence signal does not always correspond with
the occurrence of a neuron action potential. Despite considerable methodological effort, it remains a challenge to associate fluorescence signal with neural spiking. In this work, a three-part approach is taken to estimate neural receptive-fields and filters: (i) generalized linear models of spiking are estimated directly from flu-orescence signal without direct knowledge of spike times, (ii) methods of estimation make explicit use of the calcium moments to facilitate (iii) the incorporation of calcium models derived from the joint ephys/ophys experiment. Finally, the quality of this approach is assessed through the use of large-scale, biophysically detailed simulations. These simulations account for realistic cellular and somatic Ca-transients, and emulate a patch of cortical tissue using single-neuron models of mouse V1 taken from the Allen Institute Cell Types data base, with observation-consistent rules of inter-neural connectivity.

Disclosures: **K.Q. Lepage:** None. **U. Knoblich:** None. **L. Li:** None. **R. Iyer:** None. **S. Mihalas:** None. **C. Anastassiou:** None. **M.A. Buice:** None.

Poster

797. Mouse Visual Cortex

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 797.07/X4

Topic: D.06. Vision

Title: Standardizing optical recording of neural activity for large scale data generation and analysis

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Abstract: The Allen Institute for Brain Science is conducting in-depth surveys of the mouse visual system to better understand the components and computations of the mammalian brain. In particular the **ALLEN Cortical Activity Map** project is a survey of cellular visual responses across multiple brain areas, cortical layers and neuronal populations. We used two photon calcium imaging to simultaneously record from a large number of cortical neurons while an awake mouse was watching a set of standardized visual stimuli. To restrict to specific neuronal sub-populations, we also surveyed a number of different transgenic mice expressing the calcium indicator Gcamp6f against 4 different cre reporters line in the layer 2/3, layer 4 and layer 5. Standardizing data collection, data curation and data analysis is a key component of a survey. Here we present our efforts to normalize data collection across multiple two photon instruments, operators and live animals. In particular, we describe how we balanced automation of both data collection and data curation with standardized operating procedure (SOPs). In addition, as any systems neuroscience experiment, we needed to synchronize and monitor a large number of data streams: two photon movies, visual stimulation movies, eye tracking movies, animal body movies as well as numerous associated meta-data. To that end, we built an automatic reporting system that monitor more than 100 parameters across all data streams recorded during each experiment. We eventually converged to a subset of parameters that allowed us to track individual experiments efficiently. Experimental bias in data curation is another key issue in systems neuroscience. Traditionally, as these experiment are technically challenging, most studies have relied on a low number of animals and experiments to report their findings. Here we

leverage our large dataset (353 experiments) to explore how our criteria for data curation affected visually evoked responses.
Overall, our current platform allowed to collect as many as 50 experiments per week without any backlog in data curation. For this survey, we recorded more than 40,000 neurons in 35 animals across 17 locations (area, layer, and cre-line). This dataset provides a unique opportunity to relate visually evoked activity across 4 different visual areas: V1, AL, LM, PM and will be extended in future data releases.

Disclosures: **J. Lecoq:** None. **K. Roll:** None. **P. Hargrave:** None. **J. Larkin:** None. **C. White:** None. **S. Cross:** None. **F. Griffin:** None. **S. Caldejon:** None. **T. Nguyen:** None. **S. de Vries:** None. **G. Ocker:** None. **M. Buice:** None. **D. Sullivan:** None. **T. Siuda:** None. **T. Keenan:** None. **W. Wakeman:** None. **J. Perkins:** None. **D. Williams:** None. **C. Farrell:** None. **J. Phillips:** None. **C. Koch:** None. **H. Zeng:** None. **A. Bernard:** None.

Poster

797. Mouse Visual Cortex

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 797.08/X5

Topic: D.06. Vision

Support: Allen Institute for Brain Science

Title: The ALLEN Cortical Activity Map: A survey of visually evoked cellular responses in mouse

Authors: ***A. BERNARD**, N. BOWLES, M. BUICE, S. CALDEJON, S. CROSS, C. FARRELL, D. FENG, M. GARRETT, N. GAUDREAULT, F. GRIFFIN, P. GROBLEWSKI, P. HARGRAVE, A. HO, T. KEENAN, A. KRIEDBERG, J. LARKIN, J. LECOQ, L. NG, G. OCKER, S. OLSEN, J. PERKINS, J. PHILLIPS, R. C. REID, K. ROLL, C. SLAUGHTERBECK, S. DE VRIES, W. WAKEMAN, C. WHITE, D. WILLIAMS, C. KOCH; Allen Inst. for Brain Sci., Seattle, WA

Abstract: The Cortical Activity Map project is a physiological survey of neural activity in the visual cortex during sensory stimulation in awake behaving mice. By systematically measuring visual responses from neurons sampled from selected brain areas, cortical layers, and Cre lines harboring cell-specific activity reporters (GCAMP6), a rich dataset has been created. This serves as a resource for quantitative exploration of the functional properties that underlie coding of sensory stimuli through the visual pathway, at both the single-cell and population level. Experimental results from standardized image acquisition, combined with models of cortical

computation, have been generated using a robust, scalable laboratory methodology and neuroinformatics processing workflow. Unionized data formats facilitate visualization and accessibility of data, that is open to the community via the ALLEN Brain Atlas web portal. The project product includes primary sources of data derived from reflectance-based intrinsic signal imaging (ISI) and single neuron response properties measured by 2-photon calcium imaging, accompanied by metadata capturing animal state during engaged or passive visual stimuli. The cellular responses to a wide array of visual stimuli are presented in a novel organization that permits aggregated analysis of single and group populations as a comprehensive survey of visual activity. Anatomical registration of data into a common coordinate framework utilized by other standardized, high density datasets allows for exploration of relationships across anatomical, connectional and genetic axes. Expansion of this dataset is ongoing, and will ultimately include simultaneous activity measurements in response to visual stimuli, sampled from genetically defined cell types in multiple anatomically relevant areas, compounded with behavioral task engagement. Together, the data and its cross-modal integration will provide a community resource to elucidate how distinct features of the visual world are encoded.

Disclosures: **A. Bernard:** None. **N. Bowles:** None. **M. Buice:** None. **S. Caldejon:** None. **S. Cross:** None. **C. Farrell:** None. **D. Feng:** None. **M. Garrett:** None. **N. Gaudreault:** None. **F. Griffin:** None. **P. Groblewski:** None. **P. Hargrave:** None. **A. Ho:** None. **T. Keenan:** None. **A. Kriedberg:** None. **J. Larkin:** None. **J. Lecoq:** None. **L. Ng:** None. **G. Ocker:** None. **S. Olsen:** None. **J. Perkins:** None. **J. Phillips:** None. **R.C. Reid:** None. **K. Roll:** None. **C. Slaughterbeck:** None. **S. de Vries:** None. **W. Wakeman:** None. **C. White:** None. **D. Williams:** None. **C. Koch:** None.

Poster

797. Mouse Visual Cortex

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 797.09/X6

Topic: D.06. Vision

Support: Paul and Jody Allen

Title: Development of customized instrumentation for standardized, high-throughput *In vivo* imaging and analysis.

Authors: ***T. M. KEENAN**, J. PERKINS, D. SULLIVAN, T. SIUDA, R. DIETZMAN, D. WILLIAMS, P. HARGRAVE, C. SLAUGHTERBECK, P. GROBLEWSKI, J. LECOQ, N. GAUDREAULT, C. FARRELL;
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Abstract: The Allen Institute for Brain Science is pursuing a multi-methodological approach to understanding brain function and how it is engendered through molecular mechanisms, morphology, local and long-range connectivity, and neural coding. The upcoming Cortical Activity Map (CAM) product elaborates the coding of visual information within primary and higher-order mouse visual cortex using in vivo single cell responses to diverse visual stimuli in different cell types, layers, and functional regions. When paired with a visual system-focused connectivity atlas created through the Next Generation Connectivity (NGC) project, the neuroscience community can more effectively explore how different forms of visual information are interpreted and parsed within the mouse visual system.
The generation of coding and connectivity data that can be effectively compared and subsequently correlated with other data modalities being pursued at the Allen Institute requires the development of an integrated suite of tools, imaging instruments, and cross-platform systems. Here we detail the design and implementation of those tools, instruments, and systems and how they have enabled efficient, large-scale data collection with novel levels of standardization and statistical reproducibility.

Disclosures: **T.M. Keenan:** None. **J. Perkins:** None. **D. Sullivan:** None. **T. Siuda:** None. **R. Dietzman:** None. **D. Williams:** None. **P. Hargrave:** None. **C. Slaughterbeck:** None. **P. Groblewski:** None. **J. Lecoq:** None. **N. Gaudreault:** None. **C. Farrell:** None.

Poster

797. Mouse Visual Cortex

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 797.10/X7

Topic: D.06. Vision

Title: Cascade Models of Cortical Activity Map based on structural connectivity

Authors: *R. IYER, N. S. GRADDIS, S. DE VRIES, J. A. HARRIS, M. A. BUICE, S. MIHALAS;
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Abstract: It is traditional for models in vision to link the activity of the neuron to the visual stimulus presented. However, as many cortical neurons are several synapses away from the visual input, how to express and parameterize all these transformations into a simple model remains unsolved. We have developed a cascade model of V1 neurons in mouse visual cortex which is based on priors of separation of the visual inputs into predetermined ON and OFF channels, which allows us to combine two linear-nonlinear stages. This model resulted in an improvement in the capacity of the model to explain the activity of individual neurons, but it

makes little use of the structural knowledge, and there is an expectation that each additional stage introduces a nonlinearity. At the Allen Institute for Brain Science, we recently performed measurements of the mesoscopic structural connectivity of the mouse brain (ALLEN Mouse Brain Connectivity Atlas). We combine the data from the inter-regional connectivity model constructed from this data with prior data from the literature to generate a set of hypotheses as to the most likely sources of feedforward information from the other populations. Recent unprecedented measurements of *in vivo* activity in the ALLEN Cortical Activity Map allows us to map activity at a large number of intermediate stages in mouse visual pathways. To characterize the responses we compare two strategies: In the first strategy the responses of neurons for each population are linked directly to the stimulus input. This is realized using either a standard generalized linear model, or by employing a two stage cascade model. We characterize the responses and generate a set of filters using this method. In the second strategy, we characterize subsequent populations (e.g. L2/3 in V1) using the generalized linear or cascade model of the previous population. Such a strategy will potentially allow us to climb on the structurally defined hierarchy of the visual cortex, building one stage at a time as the data from the Cortical Activity Map pipeline becomes available. This will allow us to analyze the similarities between the structural hierarchies and changes in neuronal code.

Disclosures: **R. Iyer:** None. **N.S. Graddis:** None. **S. de Vries:** None. **J.A. Harris:** None. **M.A. Buice:** None. **S. Mihalas:** None.

Poster

797. Mouse Visual Cortex

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 797.11/X8

Topic: D.06. Vision

Title: Highly conserved functional boundaries of the visual cortex are observed using standardized methods for intrinsic signal imaging in a broad survey of the mouse visual cortex

Authors: ***N. GAUDREAULT**, S. CALDEJON, F. GRIFFIN, E. KENJI LEE, M. GARRETT, J. ZHUANG, P. GROBLEWSKI, K. HIROKAWA, J. HARRIS, W. WAKEMAN, F. LONG, L. NG, C. SLAUGHTERBECK, T. KEENAN, C. FARREL, J. PHILLIPS, H. ZENG, A. BERNARD;
Allen Inst., Seattle, WA

Abstract: The Allen Institute for Brain Science is conducting in-depth surveys of the mouse visual system, to better understand the components and computations of the mammalian brain. To evaluate the functional topography of the mouse visual cortex we developed a standardized

imaging platform that provides highly reproducible cortical maps. We used intrinsic signal imaging (ISI) to measure the changes in hemodynamic response to visual stimuli to generate maps of functionally defined visual areas. These maps were subsequently used to target specific visual areas in mice that were part of larger surveys to evaluate brain structure and function. Our recent efforts to expend the ALLEN Mouse Brain Connectivity project utilized ISI-derived retinotopic and sign maps to target injections of anterograde or retrograde viral tracers into functionally identified locations within primary and higher visual cortical areas. The Cortical Activity Map project is a survey of visual responses at the cellular level, and utilized the ISI-derived cortical maps to guide 2-photon calcium imaging experiments in functionally receptive retinotopic locations in primary and higher visual areas. To achieve standardized data acquisition across all experimental platforms, mice were fitted with a custom head frame designed to ensure accurate spatial registration within and between imaging systems. Retinotopic maps were generated in response to a visual display of drifting bar stimuli containing flickering checkerboards, swept along the four cardinal directions, under light anesthesia. Cortical area boundaries were delineated using an automated segmentation algorithm, and maps curated based on stringent criteria to ensure data quality. Over 400 ISI image sets were acquired, from over a dozen transgenic mouse lines. Based on this vast amount of standardized data, we compared visual area organization across multiple experimental variables, including surgical preparation, early adult development in male and female animals, and across multiple transgenic lines. Using metrics extracted from the segmented maps we characterized the variability in number of identifiable visual areas, boundary position, area size and visual field coverage for primary and higher visual areas. Overall we found highly reproducible topography of specific visual fields across multiple experimental conditions and Cre lines, with some notable differences. The ISI map data that was generated for these surveys has been evaluated for quality standards, quantitatively standardized, informatically processed for display in a spatially annotated 3D common coordinate framework, and is now made publically available.

Disclosures: **N. Gaudreault:** None. **S. Caldejon:** None. **F. Griffin:** None. **E. Kenji Lee:** None. **M. Garrett:** None. **J. Zhuang:** None. **P. Groblewski:** None. **K. Hirokawa:** None. **J. Harris:** None. **W. Wakeman:** None. **F. Long:** None. **L. Ng:** None. **C. Slaughterbeck:** None. **T. Keenan:** None. **C. Farrel:** None. **J. Phillips:** None. **H. Zeng:** None. **A. Bernard:** None.

Poster

797. Mouse Visual Cortex

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 797.12/X9

Topic: D.06. Vision

Title: The Allen Cortical Activity Map Data Portal: Interactive navigation and visualization of evoked cellular responses in the mouse visual cortex

Authors: D. FENG[1], W. WAKEMAN[1], *C. KOCH[2], L. KUAN[1], Y. LI[1], F. LONG[1], K. GODFREY[1], T. FLISS[1], N. SJOQUIST[1], F. LEE[1], T. DOLBEARE[1], A. SODT[1], M. CHAPIN[1], C. BARBER[1], S. SHI[1], C. LAU[1], C. THOMPSON[1], S. DE VRIES[1], M. GARRETT[1], M. BUICE[1], A. BERNARD[1], M. HAWRYLYCZ[1], C. REID[1], J. PHILLIPS[1], H. ZENG[1], L. NG[1]; [1]Allen Inst. for Brain Sci., Seattle, WA; [2]Allen Inst. For Brain Sci., Seattle, WA

Abstract: The Allen Institute for Brain Science has embarked on a major new project to study mouse cortical activity during sensory stimulation and behavior. This study systematically measures visual responses in different cortical areas using two-photon calcium imaging of GCaMP6-labeled neurons targeted using Cre driver lines.
We present here the Allen Cortical Activity Map Data Portal, a data resource for understanding and modeling, coding and processing of visual information by characterizing single cell visual response properties such as orientation, spatial and temporal frequency tuning, temporal dynamics and spatial receptive structure and how they correlate with cortical areas, layers and Cre-lines. The use of common Cre-lines and registration to the Allen Common Coordinate Framework permits the integration of information from the Allen Mouse Connectivity Atlas and the Allen Cell Types Database towards understanding how the components of the cortex (circuits and cell types) give rise to functional visual response properties.
All data, including tools for search and analysis, is freely available via the Allen Brain Atlas data portal (brain-map.org). Raw and time series data can be downloaded through the Allen Brain Atlas API in Neurodata without Borders (NWB) format. Additionally, the accompanying Allen SDK provides example source code and functions to foster community use and analysis of this dataset.

Disclosures: D. Feng: None. **W. Wakeman:** None. **C. Koch:** None. **L. Kuan:** None. **Y. Li:** None. **F. Long:** None. **K. Godfrey:** None. **T. Fliss:** None. **N. Sjoquist:** None. **F. Lee:** None. **T. Dolbeare:** None. **A. Sodt:** None. **M. Chapin:** None. **C. Barber:** None. **S. Shi:** None. **C. Lau:** None. **C. Thompson:** None. **S. de Vries:** None. **M. Garrett:** None. **M. Buice:** None. **A. Bernard:** None. **M. Hawrylycz:** None. **C. Reid:** None. **J. Phillips:** None. **H. Zeng:** None. **L. Ng:** None.

Poster

797. Mouse Visual Cortex

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 797.13/X10

Topic: D.06. Vision

Title: Developmental origin of the function & circuits organization in the mouse visual cortex

Authors: *Y. LI[1], Y. DAN[2];
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Abstract: Recently, a clonal-functional relationship has been established in the mouse visual cortex (V1), such that clonally related neurons ("sister cells") shared similar orientation preference despite apparent "salt-and-pepper" organization of rodent V1 (Li et al 2012; Ohtsuki et al 2012). Interestingly, the functional similarity between sister cells observed in Ohtsuki et al (2012) was weaker than Li et al (2012), suggesting that cell lineage might not the only determinant of response selectivity. Li et al (2012) found great similarity in animals that were imaged shortly after eye opening (postnatal days 12-17 [P12-17]), whereas Ohtsuki et al (2012) observed more diversity in preference in older animals (P49-62), indicating the possible impact of visual experience. However, several differences in methodology make it difficult in reconciling the results from these two studies. For example, the embryonic stage when the progenitors were labeled is different. In addition, the number of labeled cells per clone cluster is also different: The study by Li et al study, using in utero injection of GFP-expressing retrovirus at late stages of neurogenesis (E14-16), usually labeled a small number of neurons cluster per clone (<10 in most cases). The study by Ohtsuki et al, using a Cre-driver mouse line to label sister cells, can labeled ~600 cells derived from a common progenitor cell at the beginning of the neurogenesis (~E11). In order to explore the role of experience in specifying response properties of clonally related V1 neurons, we made in utero injection of GFP-expressing retrovirus at earlier embryonic stage (E11-12) & compared the functional similarity of orientation preference in sister cells between different age groups. Injection of retrovirus at earlier stage resulted in labeling a larger size of clones. Our goal is to use two-photon calcium imaging & in vivo circuit mapping method in order to understand the functional significance of circuits reorganization among sister cells in V1 & clarity the extent to which visual experience impact the patterns of connections & response properties that are specified by cell lineage.

Disclosures: **Y. Li:** None. **Y. Dan:** None.

Poster

797. Mouse Visual Cortex

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 797.14/X11

Topic: D.06. Vision

Support: EPSRC grant EP/F500351/

Wellcome Trust Grant 095669

Wellcome Trust Grant 095668

Title: Dependence on visual features, running speed and virtual speed across the mouse visual cortex

Authors: *E. M. DIAMANTI, A. B. SALEEM, K. D. HARRIS, M. CARANDINI;
Univ. Col. London, London, United Kingdom

Abstract: During navigation based on visual cues, the activity of neurons in mouse primary visual cortex (V1) is influenced by at least three factors: (1) the visual features of the environment; (2) the visual speed generated by self-motion, and (3) the animal's running speed. It remains unknown, however, whether the weighing of these three factors differs across V1, and whether it is different in higher visual areas.

To answer this question we placed mice in a virtual reality environment and measured calcium signals from broad portions of visual cortex using widefield imaging and two-photon microscopy. Transgenic mice expressing GCaMP6f in cortical pyramidal cells were head-fixed and free to run on a linear treadmill. We tested three conditions. In the first condition ("closed-loop") animals traversed a virtual corridor containing four prominent visual landmarks, and the speed of the corridor (virtual speed) matched the animal's running speed. In the second condition ("open-loop") we replayed previous sessions to the animal regardless of its behavior. In the third condition we measured responses in the dark.

Widefield imaging data showed that the dependence of visual responses on virtual speed differed between V1 regions devoted to the upper and lower visual field. In closed-loop, responses in upper-field V1 regions were more strongly modulated by speed than lower-field V1 regions. To assess whether the effect of speed was mediated by running or virtual speed, we turned to the open-loop condition. Activity in upper-field V1 regions was strongly modulated by running speed and minimally affected by virtual speed. The effect of running speed was prominent even in the dark, where it strongly modulated responses all across the visual field.

Preliminary analysis of single-neuron responses in V1 and higher visual areas using two-photon microscopy shows that responses of up to 50% of recorded neurons are well predicted by the position of visual landmarks and speed. We are investigating whether single neurons in different regions of V1 and higher visual areas also differ in the way they combine visual with non-visual features.

Our data suggest that when a mouse moves through an environment with visual cues, responses in V1 are modulated differentially, depending on receptive field location.

Disclosures: **E.M. Diamanti:** None. **A.B. Saleem:** None. **K.D. Harris:** None. **M. Carandini:** None.

Poster

797. Mouse Visual Cortex

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 797.15/X12

Topic: D.06. Vision

Support: NIH Grant 2T32HD007348-26

Title: Serotonergic modulation of visual response properties in awake mouse primary visual cortex

Authors: *A. MICHAIEL, C. NIELL;
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Abstract: The neurophysiological mechanisms underlying aberrant sensory processing observed in schizophrenia and psychosis are poorly understood. The serotonin $5HT_{2A}$ receptor has been implicated in these psychopathologies and is thought to underlie symptoms such as sensory hallucination. Additionally, administration of $5HT_{2A}$ agonists causes sensory hallucinations. However, the neuromodulatory effects of serotonin on visual processing at the level of single neurons and populations of neurons is poorly understood. Using single-unit extracellular recordings with multi-site silicon probes in awake mouse primary visual cortex (V1), we characterized changes in cortical dynamics across layers in response to pharmacological manipulation of serotonin $5HT_{2A}$ receptors. Additionally, using optogenetic tagging, we identified neurons expressing the $5HT_{2A}$ receptor, allowing us to characterize response features of this neural subpopulation, as well as to separate the direct effects on $5HT_{2A}$ expressing neurons from indirect effects on downstream neurons. The hallucinogenic $5HT_{2A}$ agonist, DOI (2,5-Dimethoxy-4-iodoamphetamine), yielded bidirectional changes in firing rates, layer-specific changes in response properties, and decreases in correlated activity across populations of neurons. Co-administration of ketanserin, a $5HT_{2A}$ antagonist, with DOI abolished these changes. Ketanserin alone had little effect on neural activity in V1. Our data shows that activation of $5HT_{2A}$ receptors modulates visual processing at the level of single neurons and across populations of neurons.

Disclosures: **A. Michaiel:** None. **C. Niell:** None.

Poster

797. Mouse Visual Cortex

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 797.16/X13

Topic: D.06. Vision

Support: Picower Institute Innovation Fund

NIH R01 EY007023

Title: Dissecting functional organization of mouse visual cortex

Authors: ***M. HU**[1], R. V. RIKHYE[1], M. J. GOARD[2], M. SUR[1];
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Abstract: Although it is known that mice have roughly ten distinct visual areas, the specific function of each area and interactions between areas remain poorly understood. In this study, we used both wide-field and single-cell calcium imaging from awake, head-fixed mice, which transgenically expressed GCaMP6f, to functionally segment the entire visual cortex. First, to identify the gross organization of the visual areas, we performed retinotopic mapping using a custom-built wide-field epi-fluorescence microscope. Next, we characterized the responses of neurons within each segmented area to drifting gratings with various directions and spatial temporal frequencies. Within V1, we found a gradient of bias of averaged peak orientation (from vertical to horizontal orientations) along binocular to monocular axis. We also found systematic variations in averaged peak spatial and temporal frequencies along the same axis. The averaged peak temporal frequency in area LM exhibit a similar distribution (a mirror of V1) in visual space, indicating its role as the second visual area along the feedforward visual pathway. These results suggest that the different visual areas are sensitive to different visual features. To further test this hypothesis, we perturbed either the phase or the amplitude content of natural movies. The phase spectrum of natural movies contains information about salient image features, such as edges; whereas the amplitude spectrum contains low-level information, such as luminance. Interestingly, we found that medial regions (such as medial posterior part of V1 and posterior part of PM) were more selective to phase, while lateral regions (such as lateral anterior part of V1 and AL) were more selective to the amplitude spectrum. Together, our results reveal that mouse visual cortex has organized representation of different visual features, which is globally extended through an entire set of areas. This distribution may already present in V1 and further elaborated in different higher visual areas.

Disclosures: **M. Hu:** None. **R.V. Rikhye:** None. **M.J. Goard:** None. **M. Sur:** None.

Poster

797. Mouse Visual Cortex

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 797.17/X14

Topic: D.06. Vision

Support: NIH Grant 1F32EY023906-01A1

NIH Grant EY022577

NIH Grant MH063912

Gatsby Charitable Foundation

Title: Functional diversity of VIP interneurons in mouse primary visual cortex

Authors: *E. RICHLER, E. M. CALLAWAY;
Salk Inst. SNL-C, La Jolla, CA

Abstract: Activity in the cerebral cortex is in continuous balance between inhibition and excitation. Many subtypes of inhibitory interneurons exist, each with unique roles in cortical function. Almost all interneurons can be classified based on their expression of one of the three major non-overlapping neural markers parvalbumin, somatostatin, and the 5HT3a receptor. Further subdivisions are possible based on additional molecular markers, function, and morphology. Vasoactive intestinal peptide (VIP) expressing interneurons, which represent one such subdivision within the 5HT3aR group, have been recently found to mediate cortical disinhibition, and to play a role in state-dependent neural activity in the cortex. However, there is evidence to indicate that VIP neurons do not comprise a uniform group, and it is unclear if all VIP neurons behave similarly. Here we address this by studying whether the recently observed effect of locomotion on VIP neurons differs based on factors such as cortical depth and additional neural markers. We are using VIP-Cre mice and Cre-dependent AAV vectors to target GcaMP6 expression to VIP neurons across cortical layers of mouse V1. Using in vivo calcium imaging we have found that locomotion affects the activity of nearly all VIP neurons, but that these effects vary. Most VIP neurons show increased activity with locomotion, but a few show a decrease, and there appears to be a layer bias in the magnitudes of the increases. We are also conducting immunostaining post hoc to identify VIP neurons that express other neural markers such as calretinin. Taken together, these experiments will reveal and stratify functional diversity among VIP interneurons.

Disclosures: E. Richler: None. **E.M. Callaway:** None.

Poster

797. Mouse Visual Cortex

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 797.18/X15

Topic: D.06. Vision

Support: NIH Grant EY022577

NIH Grant MH063912

Gatsby Charitable Foundation

Title: Functional *In vivo* connectivity of Vasoactive Intestinal Peptide expressing inhibitory interneuron subtypes in mouse visual cortex

Authors: *A. GARG[1,2], A. E. CASALE[1], E. M. CALLAWAY[1];
[1]Salk Inst. For Biol. Studies, LA Jolla, CA; [2]Neurosciences Grad. Program, UCSD, La Jolla, CA

Abstract: Knowing the characteristics and connectivity patterns of different cell types, and their functional impacts *in vivo* is necessary for understanding functional cortical circuits. Inhibitory GABAergic neurons play an important role in increasing the functional capabilities and diversity of cortical circuits. A subset of these neurons expressing vasoactive intestinal peptide (VIP) is recruited during specific behavior in mice, such as running. These cells preferentially inhibit somatostatin (SOM)-expressing neurons in mouse neocortical layer 2/3 of the primary visual cortex (V1). Previous *in vitro* work from our lab has demonstrated that VIP neurons can be separated into two distinct subsets based on their expression of calretinin (CR): VIP+/CR+ and VIP+/CR-. Each of these subsets preferentially targets different neurons. VIP+/CR+ neurons, which make up approximately 40% of the VIP-expressing population, target SOM+ cells.
We aim to study the effects of activation of these two subsets of neurons *in vivo* in order to better understand the circuit mechanisms at play. To address this question, we utilized Flp and Cre mouse lines (CR-Cre/VIP-Flp) and an intersectional adeno-associated virus (AAV) that expresses Channelrhodopsin-2 (ChR-2) under the control of Flp and Cre recombinases. After separating the VIP neuron population into VIP+/CR+ and VIP+/CR- subpopulations, we performed extracellular electrophysiological recordings in V1 of awake, behaving mice using silicon high-density electrode arrays. Due to the role of VIP and SOM-expressing neurons in orientation tuning and surround suppression, mice were shown several different visual stimuli, including gratings of differing orientations, size, and spatial frequency. Neuronal responses were sorted into clusters and responses were separated by cortical depth to investigate whether any of the functional circuit effects are layer-dependent.

Disclosures: **A. Garg:** None. **A.E. Casale:** None. **E.M. Callaway:** None.

Poster

797. Mouse Visual Cortex

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 797.19/X16

Topic: D.06. Vision

Support: Grant-in-Aid for Challenging Exploratory Research 25560197

Grant-in-Aid for Scientific Research (B) 25282130

Grant-in-Aid for JSPS Fellows 13J01314

Title: Response profiles of a neuronal population excited by intracortical microstimulations in the mouse visual cortex

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[1]Grad. Sch. of Engin., [2]Global Ctr. for Med. Engin. and Informatics, Osaka Univ., Osaka, Japan

Abstract: An intracortical visual prosthesis, which is one of the possible approaches for restoring vision in blind patients, is based on the observations that electrical stimulation applied into visual cortices evoked light perceptions in the patients in accord with the retinotopy. However, previous studies on human and monkey suggested that the minimum stimulus intensities evoking the light perception were unpredictable; sometimes repetitive stimulus current pulses of only a few microamperes in amplitude were enough, but sometimes the amplitude of several tens of microamperes was needed. In order to study if the electrical stimulation can reliably excite the cortical neurons, we recorded populational neuronal responses induced by microstimulation (200-μs biphasic pulse; 5-80 μA/phase) with an in-line multi-channel electrode (Ir-Ox tips; 10-30 kΩ at 1 kHz; MicroProbes, MD, US) inserted in the primary visual cortex (250 μm deep from the surface) of the C57/BL6 mice (n = 5) by utilizing a voltage-sensitive dye imaging technique. We quantified the stimulus-induced excitatory responses with the Naka-Rushton function: $R_{max}I^n/(I_{50}{}^n+I^n)$; where the response amplitude is described as a function of the stimulus intensity 'I', the maximum response amplitude 'R_{max}', the stimulus intensity that induces half-maximum response amplitude 'I_{50}', and the slope constant 'n'. We found that measurable responses were able to be induced by only 10 or 20 μA/phase of the "single-pulse" stimulus, and its peak amplitude was fitted by the Naka-Rushton function with I_{50} = 22/15-25 μA/phase and n = 3.0/2.5-3.4 (median/1st-3rd quantiles, n = 10), suggesting that the neuronal excitation is reliable and the stimulus threshold can be lower than the perceptual one. When the stimuli were simultaneously applied through 300-μm-separated tips of the electrode, the response at the in-between point was equal to, or smaller than, the linear summation of the responses induced by the single-electrode stimulation, even in the rising phase of the response at which a

synaptic inhibition did not take place. Our findings will provide essential information for characterizing the cortical activation pattern induced by multi-site microstimulation, and thus for understanding the phosphene perception in visual prostheses.

Disclosures: **N. Suematsu:** None. **K. Takatani:** None. **Y. Hayashida:** None. **Y. Okazaki:** None. **T. Yagi:** None.

Poster

797. Mouse Visual Cortex

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 797.20/X17

Topic: D.06. Vision

Support: NIH EY-018322

NIH EY-023871

Title: Spatial clustering of tuning in mouse primary visual cortex

Authors: ***D. L. RINGACH**[1], P. J. MINEAULT[2], E. TRING[2], N. D. OLIVAS[3], P. GARCIA-JUNCO-CLEMENTE[3], J. T. TRACHTENBERG[3];
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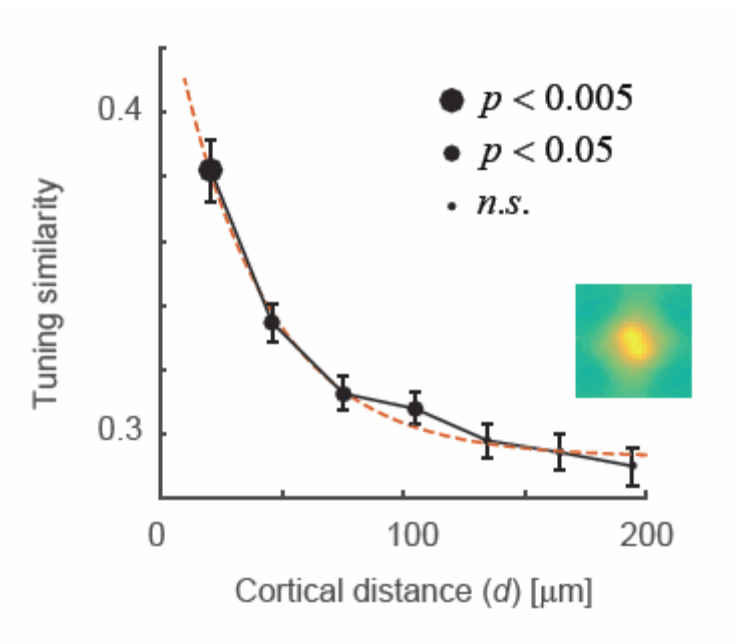
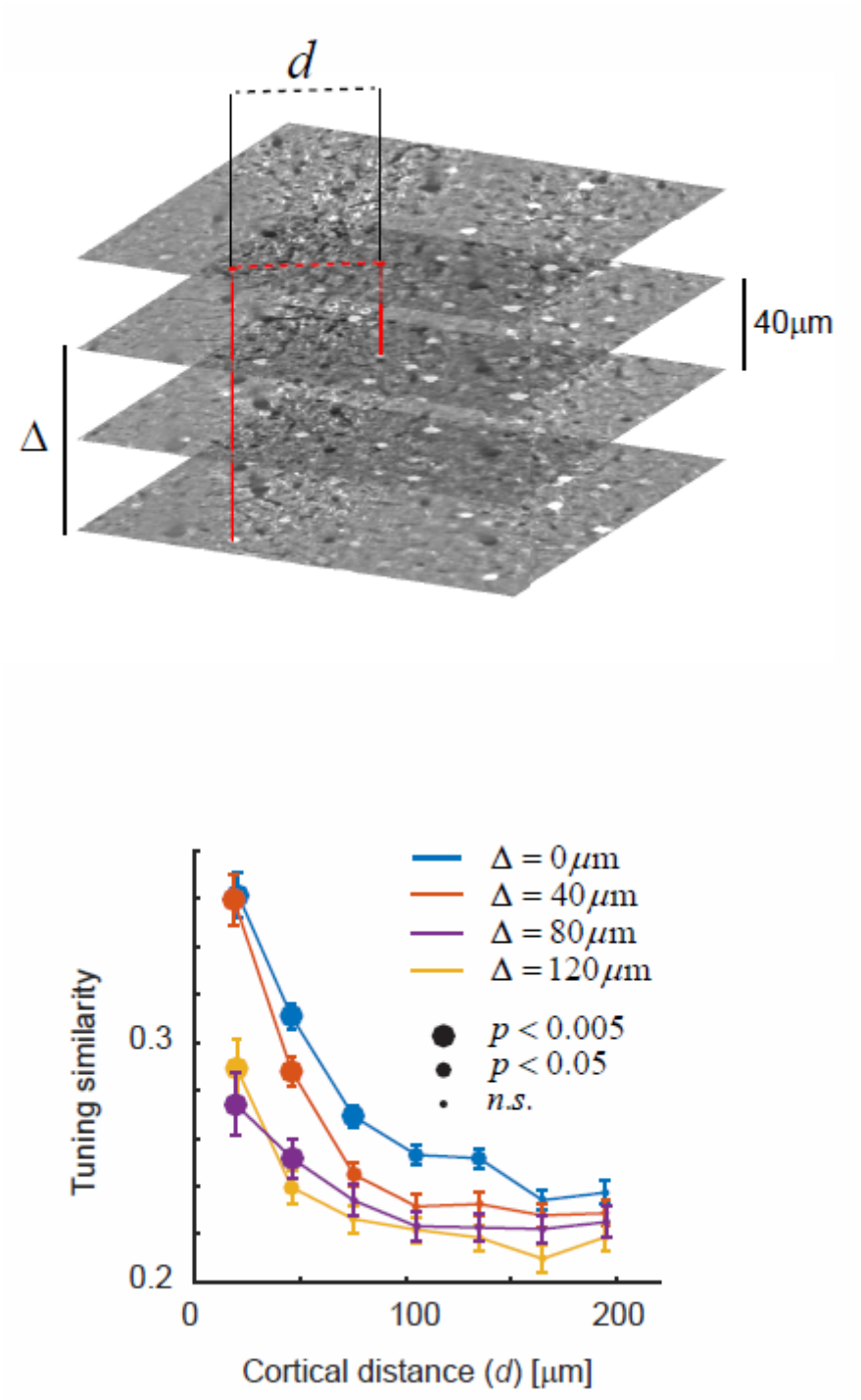
Abstract: The primary visual cortex of higher mammals is organized into two-dimensional maps, where the preference of cells for stimulus parameters is arranged regularly on the cortical surface. In contrast, the preference of neurons in the rodent appear to be arranged randomly, in what is termed a salt-and-pepper map. Here we revisited the spatial organization of receptive fields in mouse primary visual cortex by measuring the joint tuning of pyramidal neurons in the orientation and spatial frequency domain. We found that the similarity of tuning decreases as a function of cortical distance, revealing a weak but statistically significant spatial clustering. Clustering was also observed across different cortical depths, consistent with a columnar organization. Thus, mouse visual cortex is not strictly a salt-and-pepper map. At least on a local scale, it resembles a degraded version of the organization seen in higher mammals, hinting at a possible common origin.


0.4
0.3
Tuning similarity
$p < 0.005$
$p < 0.05$
$n.s.$
0
100
200
Cortical distance (d) [μm]



Disclosures: **D.L. Ringach:** None. **P.J. Mineault:** None. **E. Tring:** None. **N.D. Olivas:** None. **P. Garcia-Junco-Clemente:** None. **J.T. Trachtenberg:** None.

Poster

797. Mouse Visual Cortex

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 797.21/X18

Topic: D.06. Vision

Support: HFSP

NIH Grant EY025102

Title: Common adaptive dynamics in somatosensory and visual cortex of mice

Authors: *N. J. PRIEBE[1], Y. KATZ[2], B. LI[3], I. LAMPL[2];
[1]Univ. Texas, Austin, Austin, TX; [2]Weizmann Inst. Of Sci., Rehovot, Israel; [3]UT Austin, Austin, TX

Abstract: In our natural environment, the intensity of sensory stimuli vary greatly - over several orders of magnitude - surpassing the dynamic range of neurons. Yet our sensory systems are able to convey sufficient information to guide appropriate behaviors. Sensory neurons accomplish by dynamically adjusting their operating points in the face of changing contexts. We take a comparative approach to uncover the dynamics of sensory adaptation across the neocortex by studying the responses to brief (20 ms), discrete stimuli in somatosensory cortex (S1, whisker deflection) and visual cortex (V1, light flash). To reveal the timecourse of adaptation we performed whole cell recordings in S1 and V1 while presenting these brief stimuli at different frequencies. Low frequency sensory stimulation, less than 2 Hz, evokes complex, biphasic responses lasting up to 500 ms. As stimulation frequency increased the response duration to a single stimulus becomes faster and the amplitude was dramatically attenuated. Both S1 and V1 responses decline dramatically average, such that the response to a single stimulus at 10 Hz is only 12% of the response at 0.5 Hz. We also uncovered a large, frequency-dependent response at the end of the sensory stimulation. The peak of the "off" response occurs between 250 and 800 ms following the end of the stimulation. The latency of the off response appears to be related to the amount of adaptation expressed in individual neurons. To determine whether this off response might occur to detect changes in input statistics we played 10 Hz stimulus trains in which one or two of the stimuli were absent. These "oddball" stimulus conditions evoked large response in sensory neurons to the stimulus absence, similar to the response we observe at the end of high frequency stimulation. As both V1 and S1 neurons were characterized by the off and oddball responses, these responses may be reflect a general adaptive process to signal changes in our environment instead of the actual environment.

Disclosures: **N.J. Priebe:** None. **Y. Katz:** None. **B. Li:** None. **I. Lampl:** None.

Poster

797. Mouse Visual Cortex

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 797.22/Y1

Topic: D.06. Vision

Support: Wellcome Trust

ERC

MRC

BBSRC

Title: All-optical interrogation of functional connectivity in mouse visual cortex

Authors: *L. E. RUSSELL, A. M. PACKER, H. W. P. DALGLEISH, M. HAUSSER; Wolfson Inst. for Biomed. Res., Univ. Col. London, London, United Kingdom

Abstract: Visual cortex neurons sharing similar receptive fields are more likely to form monosynaptic connections, creating highly interconnected sub-networks (Ko et al 2011). This organisation of preferential connections forms a functional network architecture that could enable pattern completion of degraded or weak input. To make causal links between connectivity and activity patterns during pattern completion, the ability to simultaneously manipulate and record the activity of multiple neurons with cellular resolution in vivo is critical. Recently we developed a new strategy for performing simultaneous two-photon optogenetic activation and calcium imaging by co-expressing C1V1, a red-shifted opsin and GCaMP6, a genetically encoded calcium indicator (Packer et al 2015). A spatial light modulator allows multiple user-selected neurons to be targeted for spatiotemporally precise optogenetic activation, while simultaneous fast calcium imaging provides high-resolution network-wide readout of the manipulation. Here we present a number of enhancements we have made to this toolkit that further increase its utility in probing functional connectivity in mouse visual cortex. First, we determine interneuron subtype identity by transgenic expression of an additional fluorescent marker. Next, through the use of custom chronic optical windows, we enable pharmacological intervention during all-optical experiments. After functionally characterising the network, ensembles of similarly, or randomly, orientation-tuned cells are selected for controlled photostimulation and the local network response is recorded while delivering sub-optimal visual stimuli to mice in various behavioural states. This approach enables us to probe the functional connectivity, and in particular the potential for pattern completion, of layer 2/3 mouse visual cortex.

Disclosures: **L.E. Russell:** None. **A.M. Packer:** None. **H.W.P. Dalgleish:** None. **M. Hausser:** None.

Poster

797. Mouse Visual Cortex

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 797.23/Y2

Topic: D.06. Vision

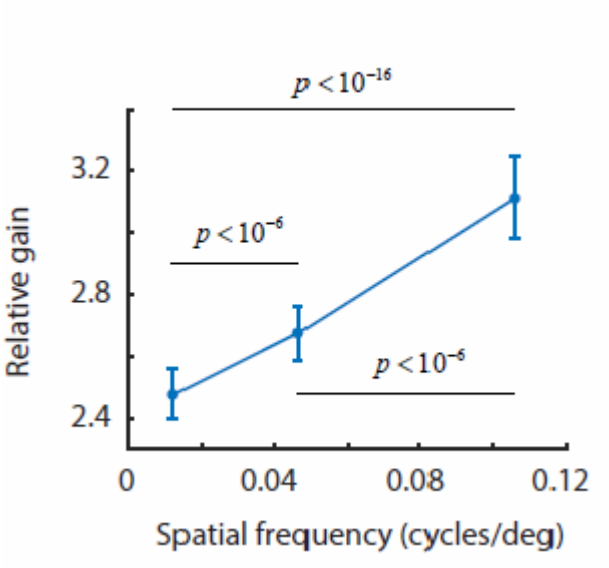
Support: NIH EY-018322

NIH EY-023871

Title: Enhanced spatial resolution during locomotion and heightened attention in mouse primary visual cortex

Authors: ***P. J. MINEAULT**[1], E. TRING[1], J. T. TRACHTENBERG[2], D. L. RINGACH[2]; [1]Neurobio., UCLA, Los Angeles, CA; [2]UCLA Neurobio., Los Angeles, CA

Abstract: We do not fully understand how behavioral state modulates the processing and transmission of sensory signals. Here we studied the representation of the retinal image in mice that spontaneously switched between a state of rest and a constricted pupil, and one of active locomotion and a dilated pupil, indicative of heightened attention. We measured the selectivity of neurons in primary visual cortex for orientation and spatial frequency, as well as their response gain, in these two behavioral states. Consistent with prior studies, we found that preferred orientation and spatial frequency remained invariant across states, while response gain increased during locomotion relative to rest. Surprisingly, relative gain, defined as the ratio between the gain during locomotion and the gain during rest, was not uniform across the population. Cells tuned to high spatial frequencies showed larger relative gain compared to those tuned to lower spatial frequencies. The preferential enhancement of high spatial frequency information was also reflected in our ability to decode the stimulus from population activity. Finally, we show that changes in gain originate from shifts in the operating point of neurons along a spiking nonlinearity as a function of behavioral state. Differences in the relative gain experienced by neurons with high and low spatial frequencies are due to corresponding differences in how these cells shift their operating points between behavioral states.



Disclosures: **P.J. Mineault:** None. **E. Tring:** None. **J.T. Trachtenberg:** None. **D.L. Ringach:** None.

Poster

797. Mouse Visual Cortex

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 797.24/Y3

Topic: D.06. Vision

Support: Fonds Wetenschappelijk Onderzoek (grant G0A3913N and postdoctoral fellowship to D.K.)

Title: Neural adaptation and position tolerance increase along a putative ventral visual pathway in rats

Authors: ***D. KALIUKHOVICH**[1], H. OP DE BEECK[2];
[1]Fac. of Psychology and Educational Sci., [2]Lab. voor Biologische Psychologie, KU Leuven, Leuven, Belgium

Abstract: Most neuroscience techniques target rodents as the primary animal model to study neural circuits. By contrast, primates are seemingly exclusively used to study higher-order perception and, in particular, vision. Recent studies demonstrated commonalities between the visual systems of rats and primates. Here we further test these commonalities and, specifically,

examine how neural adaptation and position tolerance change along a putative ventral visual pathways in rats (Vermaercke et al., 2014). Based on the literature in primates, an increase for both was expected. To test this, we recorded multi-unit extracellular spiking activity in primary visual cortex (V1) and a downstream area LI of head-restrained Long Evans rats. During recordings for each examined multi-unit site we identified two non-overlapping positions within its receptive field and then probed the activity of that site with 3 different stimuli evoking a strong, an intermediate and little response, respectively. We tested 15 stimulus conditions that were presentations of a single stimulus at either position ($N = 6$) and presentations of either two identical ($N = 3$) or two different ($N = 6$) stimuli in all combinations at the two identified positions. Stimulus conditions were delivered to the animals in sequences ($N = 10$), with each sequence including all possible pairwise transitions between the tested conditions ($N = 226$ presentations). Each stimulus condition was presented for 300 ms and separated from each other by a 300 ms long blank inter-stimulus interval. We collected 58 ($N = 4$ rats) and 52 ($N = 3$) multi-unit sites in the areas V1 and LI, respectively. We analyzed the data separately for the early (25-175 ms relative to stimulus onset) and late (175-325 ms) phases of the neural response. Neural adaptation was present in each of the 2 areas. We observed no difference in the degree of adaptation across the 15 conditions in either brain area and response phase. Yet, the area LI showed a significantly ($p < 0.05$) higher degree of adaptation than V1 (67% vs. 33%) for both response phases. The latter held true irrespective of the response strength to the adapter stimulus ($p < 0.05$). We found significant position tolerance (preservation of stimulus selectivity across the two positions, $p < 0.05$) only for the early phase of the neural response in the area LI but not for either response phase in V1. Importantly, we failed to reveal position tolerance in V1 despite increasing the sensitivity of our tests. To conclude, our results (*increase in neural adaptation and position tolerance*) parallel those of primates. As thus, this provides further evidence in support of the use of rats as an animal model to study the visual system.

Disclosures: D. Kaliukhovich: None. **H. Op de Beeck:** None.

Poster

797. Mouse Visual Cortex

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 797.25/Y4

Topic: D.06. Vision

Support: CIHR MOP-14825

FESP-ÉOUM

CONICYT-Becas Chile

Title: Modulation of V1 neurons activity by the lateral-posterior nucleus in mice.

Authors: *U. KEYSAN, N. CORTES, S. THOMAS, C. CASANOVA;
École d'optométrie, Univ. de Montréal, Montreal, QC, Canada

Abstract: In mammals, information about the visual world reaches the primary visual cortex (V1) via the lateral geniculate nucleus. Subsequently, through cortico-cortical connections, specific aspects of the visual scene are processed by higher visual areas. In conjunction with this hierarchical organization, there is a complex network of bilateral connections between visual cortices and the pulvinar, considered as the largest extrageniculate visual thalamic nucleus. Despite an increasing number of studies on pulvinar and associated pathways, the exact function of this thalamic complex remains unknown. In this study, we investigate the functional impact of the lateral posterior (LP) nucleus (homologue of the primate pulvinar) on the activity of V1 neurons in mice using optogenetic stimulation. LP nucleus of transgenic mice expressing Channelrhodopsin-2 under Thy-1 promoter (strain : B6.Cg-Tg (Thy1-COP4 / EYFP) was stimulated by light pulses (470 nm, 20 pulse trains of 5 ms each at 10 Hz) delivered by an optical fiber. Extracellular recording of the activity of V1 neurons was performed using tungsten electrodes. Visual stimuli consisted in moving bars and drifting sinewave gratings of varying parameters (direction, contrast, spatial or temporal frequency and size). Preliminary data show that a subset of V1 neurons could be directly activated by the photostimulation of the LP nucleus. In contrast, when LP stimulation was performed in association with visual stimuli, neural responses were decreased by 30 % in average. Further, the response profiles of V1 neurons to size-increasing stimuli were affected by the photostimulation of LP. In summary, these preliminary data suggest that the LP nucleus can exert a contextual modulation of the activity of neurons in the mouse primary visual cortex.

Disclosures: **U. Keysan:** None. **N. Cortes:** None. **S. Thomas:** None. **C. Casanova:** None.

Poster

798. Visual Cortex Human

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 798.01/Y5

Topic: D.06. Vision

Support: NIH

NSF

IARPA

Title: Understanding neural representations in early visual areas using convolutional neural networks

Authors: *Y. ZHANG[1], C. MASSOT[1], T. ZHI[2], G. PAPANDREOU[3], A. YUILLE[3], T. LEE[1]; [1]Ctr. for the Neural Basis of Cognition and Computer Sci. Dept., Carnegie Mellon Univ., Pittsburgh, PA; [2]Peking Univ., Beijing, China; [3]UCLA, Los Angeles, CA

Abstract: We compared the neural representations of population of macaque V1 and V2 neurons in response to visual stimuli of different degrees of complexity with model representations of AlexNet (a convolutional neural network) and several models of V1 and V2. We found that AlexNet matched the neural data better than others, particularly for complex stimuli. Our analysis showed that it matched better because of (1) normalization and nonlinear pooling mechanism, and (2) more complex and diverse stimulus preference. Among all layers of AlexNet, the first pooling layer matched V1 neurons the best in terms of individual tuning as well as population representation, and the second pooling layer matched V2 neurons the best. We visualized the preferred features of the units corresponding to real neurons using deconvolutional networks and found that some V1 neurons could not be described by simple Gabor filters, and that some V2 neurons appeared to encode more complex surface structures such as textures. These findings suggest that V1 and V2 neurons might have more complex codes than previously thought.

Disclosures: Y. Zhang: None. **C. Massot:** None. **T. Zhi:** None. **G. Papandreou:** None. **A. Yuille:** None. **T. Lee:** None.

Poster

798. Visual Cortex Human

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 798.02/Y6

Topic: D.06. Vision

Support: Medical Research Council

Title: Tracking neurochemical and BOLD-changes in the human visual cortex using simultaneous short echo semi-LASER spectroscopy and BOLD-imaging at 7 Tesla

Authors: *B. IP, A. BERRINGTON, A. T. HESS, A. J. PARKER, U. E. EMIR, H. BRIDGE; Univ. of Oxford, Oxford, United Kingdom

Abstract: Magnetic resonance imaging using the blood-oxygenation-level-dependent response (BOLD-fMRI) is the technique of choice for non-invasive, high spatial resolution measurement

of human brain activity. Proton magnetic resonance spectroscopy (^{1}H-MRS) can be used to quantify neurochemical concentrations, both at rest and during brain activity. Combining BOLD-fMRI with ^{1}H-MRS provides insight into the neurochemical changes during brain activity. However, successful combination of these measurements must address two issues: 1) the BOLD-response affects ^{1}H-MRS spectra, causing artefactual changes in signal that limit the interpretability and strength of metabolite quantifications; 2) BOLD-fMRI and ^{1}H-MRS measurements must be collected simultaneously to support a direct comparison. Previous ^{1}H-MRS studies have corrected for BOLD-induced artefacts using estimates of spectral line narrowing, and collected BOLD-fMRI and ^{1}H-MRS data in separate scans. Here, we acquired short echo semi-LASER ^{1}H-MRS and BOLD echo planar imaging (EPI) data in the same time volume at 7T. Participants viewed 64-sec stimulus blocks of a flickering checkerboard alternating with a blank screen. Correction for the BOLD-response was achieved by measuring subject specific T2* changes using the unsuppressed water signal, and by correcting metabolite data for BOLD-induced spectral line narrowing. After BOLD-correction, LCModel quantification detected differences between stimulation and rest periods in multiple metabolites, most notably significant increases in glutamate (2.27 % ± 0.69 s.e.m., $p < 0.01$) and glutamate + glutamine (3.38 % ± 0.89 s.e.m., $p < 0.01$), consistent with previous studies using prolonged visual stimulation. We also found a significant correlation between glutamate and BOLD-fMRI time courses ($r = 0.56$, $p = 0.001$). Here we demonstrate the feasibility of simultaneous ^{1}H-MRS and BOLD-fMRI at 7 T to track dynamic neurotransmitter and BOLD-changes using stimulation blocks of 64-sec, a time scale well suited to the study of human brain function.

Disclosures: **B. Ip:** None. **A. Berrington:** None. **A.T. Hess:** None. **A.J. Parker:** None. **U.E. Emir:** None. **H. Bridge:** None.

Poster

798. Visual Cortex Human

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 798.03/Y7

Topic: D.06. Vision

Support: NIH

NSF

IARPA

Title: Sparse and distributed codes of neuronal population in primary visual cortex

Authors: *Z. LI[1], Y. ZHANG[1], M. LI[2,3], F. LIU[2,3], H. JIANG[2,3], T. LEE[1], S. TANG[2,3];
[1]Ctr. for the Neural Basis of Cognition and Computer Sci. Dept., Carnegie Mellon Univ., Pittsburgh, PA; [2]Sch. of Life Sci. and Peking-Tsinghua Ctr. for Life Sci., Peking Univ., Beijing, China; [3]IDG/McGovern Inst. for Brain Res. at Peking Univ., Beijing, China

Abstract: Large-scale Ca imaging in neurons in the superficial layer of V1 in awake behaving monkeys (Tang et al. 2015) showed that the rigorous responses of the neural population are extremely sparse, only 0.5% of the 1225 neurons that can be activated by a large set of natural images will respond to a given image at each trial at a magnitude that is greater than half of its peak response. These neurons did exhibit weak and moderate responses to a larger set of stimuli. To understand the amount of the image information is encoded in the strong sparse responses and the amount encoded in the weak responses, we perform decoding analysis of the neural signals. We applied K-Nearest Neighbor classifier to do decoding experiments. Every time we use some of the repeated trails in the Ca imaging dataset to train and do test on the left out trails, and report the accuracy as the average of all experiments. The basic finding is that the responses of 0.5% of the neurons help to achieve almost 50% of the achievable accuracy. Important to emphasize that different sets of 0.5% are activated for different images. But almost 50% of the accuracy is help achieved by the weak responses of the other 99.5% of the neurons as distributed codes. This suggests each V1 neuron serves as a specialist, encoding specific feature with rigorous response, as well as a generalist, participating in population coding of a large set of stimuli using weak or moderate responses.

Disclosures: Z. Li: None. **Y. Zhang:** None. **M. Li:** None. **F. Liu:** None. **H. Jiang:** None. **T. Lee:** None. **S. Tang:** None.

Poster

798. Visual Cortex Human

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 798.04/Y8

Topic: D.06. Vision

Support: NRF-2013R1A2A2A03017022

NRF-2015M3C7A1031969

NRF-2015R1A5A7037676

Title: Tuning similarity predominates over retinal or cortical proximity in accounting for the correlated spontaneous activity in human visual cortex

Authors: *J. RYU, S.-H. LEE;
Dept. of Brain and Cognitive Sci., Seoul Natl. Univ., Seoul, Korea, Republic of

Abstract: The brain perceives and acts on the environment by recruiting a large pool of neurons, which are often far apart but act in concert, affecting animal or human sensory, motor, and cognitive behavior. Intriguingly, these large-scale activities are far from random, exhibiting robust patterns of correlation in the absence of stimulation or task. Thus, for understanding the neural processes substantiating a given cognitive function, it is important to identify what relationships in neural populations contribute, and with what degrees, to the structure of correlated activity. To this end, we used functional magnetic resonance imaging in human visual cortex (V1,V2,V3), and explored systematic patterns that govern the slow correlated activities arising spontaneously. Previous imaging studies reported the resting-state correlation in visual cortex varies as a function of distance between receptive fields ('retinotopic distance') or over cortical surface ('cortical distance'). However, single cell studies have indicated that neuronal activities are correlated among neurons tuned to similar stimulus features ('tuning similarity'). However, it is difficult to tease apart these three factors' contributions to the correlated activities in human visual cortices, because systematic representation of stimulus tuning over the cortical surface imposes interdependency between tuning similarity and spatial proximity. Here, we evaluated the individual contributions of tuning similarity and distance factors to correlated variability in resting-state cortical activity by separating out confounded contributions from other factors. We found that it is the tuning similarity that governs the correlated fMRI activity both within and between early visual areas. The tuning similarity in spatial frequency predominated over the other factors in explaining the correlated activity in V1, and the tuning similarity in orientation did so in V2 and V3. The superiority of tuning similarity factors was most pronounced at short retinotopic and/or cortical distances and held true irrespective of presence or degree of external visual stimulation. Our findings were robust, being replicated in another experiments conducted on a different pool of subjects and surviving an exhaustive set of control analyses, where alternative spatial metrics such as eccentricity or polar angle distances were applied. Our study incorporates and goes beyond previous human imaging studies by demonstrating, for the first time, that slow and large-scale neural co-fluctuations in human visual cortex are intrinsically tuned to visual features.

Disclosures: J. Ryu: None. **S. Lee:** None.

Poster

798. Visual Cortex Human

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 798.05/Y9

Topic: D.06. Vision

Support: EY022116

R01NS078396

BCS1358907

Title: Quantifying the links between electrical stimulation of the human primary visual cortex, size of affected cortical area, neuronal population activity, and subjective experience

Authors: J. WINAWER[1], *J. PARVIZI[2];
[1]New York Univ., New York, NY; [2]Neurol. and Neurolog. Sci., Stanford Univ., Stanford, CA

Abstract: Focal stimulation of the human cerebral cortex has long been known to elicit, or to interfere with, specific and complex behaviors and experiences, and as such has been a powerful tool for investigating the cortical basis for perception, thought and behavior. However, the spatial extent of cortical tissue affected by electrical stimulation remains unknown. Moreover, responses in the cortex have been characterized as arising from multiple types of neural signaling extending over different spatial scales and ranging from evoked stimulus-locked responses to induced asynchronous broadband activity. Bridging the behavioral and subjective changes elicited by electrical brain stimulation (EBS) with different signatures of cortical activity is essential for developing integrated theories of the structure and physiology of the human brain. Here, we measured different neural responses and the effects of EBS in human primary visual cortex in four patients implanted with intracranial electrodes. By combining stimulation, behavior, and retinotopic mapping in the same subjects, we show the relationship between the size of affected cortical area and the magnitude of electrical charge. Furthermore, we show that the spatial location of electrically induced visual sensations is precisely matched to the spatial receptive field of the cortical site when it is measured with broadband field potentials, and significantly less so with event related potentials. Together, these findings quantify the link between electrical brain stimulation, induced sensory experiences, and neural responses.

Disclosures: J. Winawer: None. **J. Parvizi:** None.

Poster

798. Visual Cortex Human

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 798.06/Y10

Topic: D.06. Vision

Support: NRF-2015M3C7A1031969

NRF-2015R1A5A7037676

Title: Coaxial anisotropy shared between perceptual and cortical point spreads in human visual system

Authors: *J. RYU[1], S. LEE[2];
[1]Brain and Cognitive Sci., Seoul-City, Korea, Republic of; [2]Brain and Cognitive Neurosci., Seoul-City, Korea, Republic of

Abstract: A focal visual stimulus can evoke widespread neural activation far beyond the directly stimulated site referred to as "cortical point spread, CPS" and the lateral connections early visual cortex neurons have been proposed as a likely anatomical conduit. Consistently, studies on humans and non-human primates showed that the CPS spreads preferentially along with the axis of stimulus orientation—'coaxial anisotropy', dovetailing with the bias in spatial extension of horizontal connections. However, it remains unknown whether, and how if so, the coaxial anisotropy in CPS (CAI_C) relates to that in "perceptual point spread, PPS".
We acquired fMRI measurements from the early visual areas of subjects who viewed traveling Gabor arrays. The orthogonal combination of the drifting directions and stimulus orientations created the coaxial and orthoaxial conditions. We quantified CAI_C **(Fig 1B)** and it was robustly observed in all conditions for all the individuals (**Fig 1C**), and yet it varied substantially over individuals (+0 ~ +0.113).
To measure the PPS, we showed subjects a pair of Gabors and asked them to judge which one had a more circular envelope. We could compute the CAI of PPS (CAI_P) identical to that for CAI_C. The CAI_P was positive and showed substantial individual differences (+0 ~ +0.12). More importantly, the CAI_C was correlated with CAI_P over individuals (**Fig 2C**; r=0.873~0.878, V1>V2>V3). Our findings suggest that the CPS in V1 substantiates the perceived spatial spread of oriented stimuli.

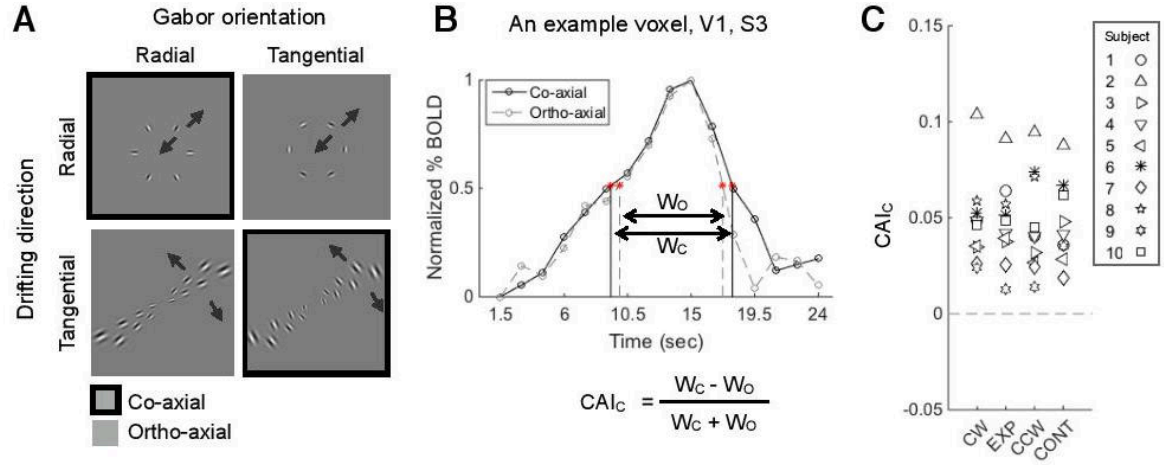


Fig 1. CAI_C. **A,** Snapshots of traveling Gabor arrays. **B,** The half-max widths of fMRI profiles were estimated for the coaxial (Wc) and orthoaxial (Wo) conditions and then normalized in the Michelson contrast term. **C,** Population summary

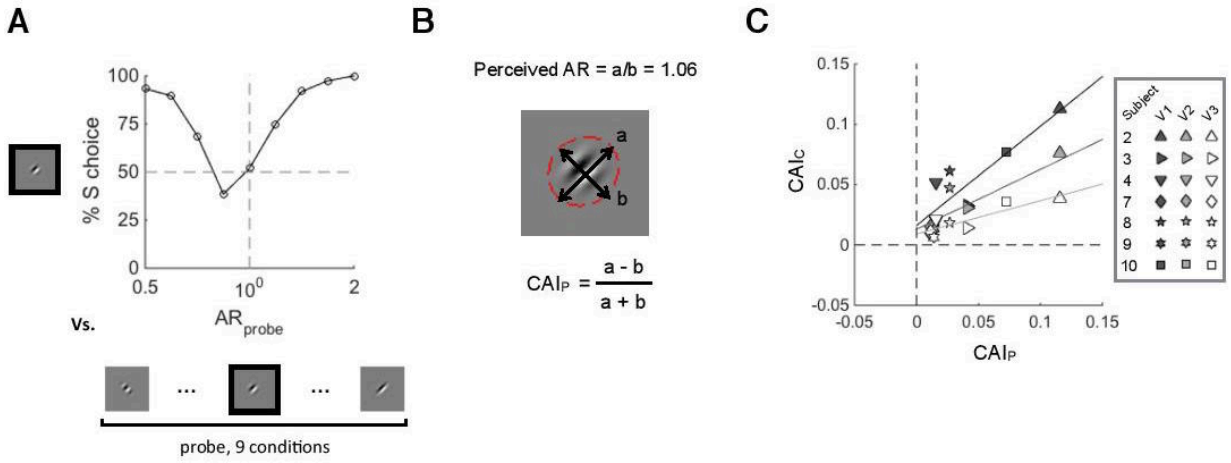


Fig 2. CAI_P. **A,** The aspect ratio (AR) of the Gabor was set to 1 for the 'standard' and varied from 0.5 to 2 for the 'probe' stimuli. **B,** Computation of CAI_P from perceived AR. **C,** Regression of CAI_C on CAI_P for V1,V2,V3.

Disclosures: J. Ryu: None. **S. Lee:** None.

Poster

798. Visual Cortex Human

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 798.07/Y11

Topic: D.06. Vision

Support: ERC Grant 67640

Title: Investigating cortical feedback of objects and background scene to foveal and peripheral V1 using fMRI

Authors: *M. BENNETT, L. S. PETRO, L. MUCKLI;
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Abstract: Introduction When discriminating abstract objects isolated in peripheral visual field, object information can be detected in non-stimulated foveal but not peripheral cortex (Williams et al., 2008). Conversely, complex natural scene information can be detected in non-stimulated peripheral cortex (Smith & Muckli, 2010; Muckli et al. 2015). This demonstrates cortical feedback contributions to object and scene representation in V1. Whether object and scene feedback are automatically directed to foveal versus peripheral V1, or if this is due to varying stimulus complexity/naturalism remains unknown. We addressed this question using computer-generated images of objects embedded in naturalistic scenes. **Methods** Nine subjects underwent

block-design fMRI (3T). Eight naturalistic computer-generated images variously combined objects and background scenes (Figure 1). The central portion and upper-right quadrant were occluded, preventing feed-forward stimulation of the ROIs, allowing isolation of feedback signals. Subjects discriminated either the scene or object. Multivoxel patterns (TR 2s; voxel-size $2mm^3$) from the ROIs were entered into support vector machine (SVM) classifiers. Bootstrapping determined above-chance group-level classification. **Results** In fovea (Figure 2), we classified object presence regardless of task (55.7%, 53.8%, collapsing task: 56.5%). Classifying object identity was only possible when collapsing task (55.9%). Also in fovea, we classified scene information during the scene task (56.7%) and when collapsing task (59.5%) but not during object task (52.2%). Therefore, the non-stimulated fovea contains object and task-dependent scene information. In periphery (Figure 3), no object information was detected. We classified scene information during object task (57.4%) and when collapsing task (55.3%), but not during scene task (54.6%). Therefore the non-stimulated periphery contains only scene information. **Conclusions** Our data suggest specialisation in cortical feedback to V1 cortex: scene information is fed-back diffusely to foveal and peripheral V1, whereas object feedback is directed to foveal cortex - possibly for high resolution scrutiny (Williams et al., 2008; Levy et al., 2001).

Disclosures: **M. Bennett:** None. **L.S. Petro:** None. **L. Muckli:** None.

Poster

798. Visual Cortex Human

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 798.08/Y12

Topic: D.06. Vision

Support: Wellcome Trust Institutional Strategic Support Fund to CM

ERC Starting Grant (310829) to DSS

Deutsche Forschungsgemeinschaft (Ha 7574/1-1) to BdH

Title: Population coding in visual cortex underlies visual size perception

Authors: *C. MOUTSIANA[1], B. DE HAAS[2], A. PAPAGEORGIOU[4], N. FINLAYSON[2], D. SCHWARZKOPF[3];
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Abstract: The subjective appearance of visual stimuli varies not only between participants but also across visual field locations. Here we used a newly developed psychophysics method, Multiple Alternatives Perceptual Search (MAPS), that efficiently measures perceptual biases when stimuli are simultaneously presented in different spatial locations. We found that judgments of the size of small visual stimuli are correlated with population receptive field (pRF) sizes in corresponding locations of V1. Our findings thus support a population coding model of size perception in which size is inferred from the spread of visual cortical activation. Bias estimates are very stable when measured dichoptically further corroborating the interpretation that they are at least in part mediated by visual cortex. In control experiments we further show that bias estimates from MAPS are similar to those obtained with traditional psychophysical methods. Finally, cueing spatial attention to a stimulus location enhances the magnitude of perceptual biases at the cued relative to non-cued locations.

Disclosures: C. Moutsiana: None. **B. de Haas:** None. **A. Papageorgiou:** None. **N. Finlayson:** None. **D. Schwarzkopf:** None.

Poster

798. Visual Cortex Human

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 798.09/Y13

Topic: D.06. Vision

Title: Retinotopically-specific variation in cortical thickness in V1 relates to performance on a central visual discrimination task

Authors: *D. LEE, W. K. BURGE, A. S. ELKHETALI, K. M. VISSCHER;
The Univ. of Alabama At Birminghan, Birmingham, AL

Abstract: The anatomy of primary visual cortex (V1) has been hypothesized to relate to visual behavior. Indeed, recent studies have examined the relationship of surface size of V1 to visual performance. However, these studies have not typically addressed the fact that different portions of V1 correspond to different locations within visual space. Anatomical variations across the visual cortex as a whole could give rise to a generalized visual improvement; conversely it could be the case that anatomical variation in V1 influences behavior in a retinotopically-specific manner. In this study, we examine how cortical thickness in segments of V1 corresponding to more central and more peripheral regions of space relate to visual performance in a central vision task.
Anatomical T1 weighted scans of participants (*n*=22) were collected and reconstructed to create regions of interest (ROI) corresponding to segments of V1 with varying visual eccentricity. For

the visual discrimination task, participants were presented with two sequential 500ms Gabor patches of different spatial frequencies and asked to determine which had the higher spatial frequency. Just noticeable difference (JND) thresholds were calculated as the difference in spatial frequency needed for participants to correctly perform the task 70% of the time. Thresholds were correlated with cortical thickness from ROIs for each participant.
We found that thicker V1 correlated to lower JND thresholds ($p < 0.05$), indicating that thicker cortex related to better visual discrimination ability. However, this relationship was specific to ROIs corresponding to central vision. Moving from centrally-representing to peripherally representing cortex, the correlation to behavior decreased. These results show that the thickness of V1 relates to visual behavior in a retinotopically specific way, and are an important step in better understanding experience-driven shifts in cortical thickness.

Disclosures: D. Lee: None. **W.K. Burge:** None. **A.S. Elkhetali:** None. **K.M. Visscher:** None.

Poster

798. Visual Cortex Human

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 798.10/Y14

Topic: D.06. Vision

Support: ERC-2012-AdG 320708-iCONNECT

Title: Visual mental imagery in high-field fMRI

Authors: *M. A. VAN DEN BOOM, M. J. VANSTEENSEL, M. A. H. RAEMAEKERS, N. F. RAMSEY;
Brain Ctr. Rudolf Magnus / Neurol. and Neurosurg., Univ. Med. Ctr. Utrecht, Utrecht, Netherlands

Abstract: Communication Brain Computer Interfaces (BCIs) are developed to allow severely paralyzed people to communicate with the outside world. Using their brain signals to control a spelling device, people should be able to spell letters, words and sentences. An intuitive approach for a communication BCI could be based on visual mental imagery of symbols or letters. Previous 3T fMRI research has achieved recognition of two imagined symbols from visual cortex with 70 % accuracy. In the current study we examined the feasibility of decoding three visually imagined symbols from the visual cortex with the use of 7T fMRI.
Five healthy subjects participated in a 7T fMRI experiment (TR/TE: 1.5 s/25 ms; voxel size 1.5 mm). The experiment contained perceived and imagined tasks. During the perceived task (one run), at every trial, one of three symbols was shown. During the imagined task (two runs),

participants were required to imagine the symbol. The perceived task served as a reference for evaluating decoding performance. We used three symbols: a cross, a plus and a circle (visual angle ~11 degrees). Per task, 140 voxels with the highest t-values for each symbol were selected. A union of these voxels was then used as features in a Support Vector Machine. Leave-one-out cross validation was applied on all trials per task. We tested the classification score significance using a Monte Carlo simulation for each task. To check for the effect of subject head movement we investigated if there was a correlation (across subjects) between movement parameters and the classification scores.
The average classification score for the perceived task was 91.2 % (sd: 7.8 %) with all subjects significantly above chance level. The classification score for the first imagined run was 61,8 % (sd: 21.2 %) and that of the second imagined run 67.3 % (sd: 30%). In both imaged runs respectively 4 and 2 subjects were significantly above chance level. There was a negative correlation between the classification scores and subject head motion (translations r = -0.65, -0.50, -0.50, rotations r = -0.61, -0.46, -0,36).
Our preliminary results suggest feasibility of decoding visually imagined symbols from the visual cortex. The negative correlation between the classification scores and the head motion provides a possible explanation for the relative large variance in classification scores between the subjects. So far we have limited this study to three symbols, but considering our current results, it could be speculated that it is possible to decode a larger number of symbols as well with fair accuracy. In conclusion, our data suggests that using visual mental imagery for communication BCI purposes could well be feasible.

Disclosures: **M.A. Van Den Boom:** None. **M.J. Vansteensel:** None. **M.A.H. Raemaekers:** None. **N.F. Ramsey:** None.

Poster

798. Visual Cortex Human

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 798.11/Y15

Topic: D.06. Vision

Support: Grant 2013070 from the US-Israel Binational Science Foundation

Title: Evoked and high-frequency markers of sustained visual perception in scalp EEG

Authors: *E. M. GERBER[1], L. Y. DEOUELL[2];
[1]Edmond and Lily Safra Ctr. for Brain Sci., [2]Dept. of Psychology and the Edmond and Lily Safra Ctr. for Brain Sci., Hebrew Univ. of Jerusalem, Jerusalem, Israel

Abstract: Little is known about the cortical activity that supports visual perception beyond the initial stimulus onset driven responses. In a previous study using intracranial electrocorticographic (ECOG) data in humans, we found that the ongoing presence of a sustained visual stimulus is accompanied by sustained high frequency broadband activity (>30 Hz, "gamma", HFBA) appearing predominantly in early visual cortex (EVC), as well as by sustained slow potentials appearing in a smaller subset of EVC sites. ECOG data has high spatial and temporal resolution but only sparsely samples the brain. In the current study, we show that similar duration-tracking sustained responses can be seen in scalp recorded HFBA as well as in the slow evoked potential. In a series of experiments we found sustained HFBA which is strongly lateralized to the hemisphere contralateral to the stimulus and is modulated by the position of the stimulus relative to the horizontal meridian. These features, together with a circumscribed occipital scalp distribution, indicate early visual cortex origin. Concurrently recorded high resolution eye tracking data provide conclusive evidence that this scalp EEG gamma response is indeed neural in origin and not a result of eye movement artifacts. Consistently across experiments, the high frequency response can be detected in only about a third of participants, likely due to individual differences in the projection of cortical dipoles to the scalp. Comparable to the intracranial findings, the scalp EEG high-frequency and slow sustained responses are topographically distinct, suggesting they reflect different cortical processes.

Disclosures: **E.M. Gerber:** None. **L.Y. Deouell:** None.

Poster

798. Visual Cortex Human

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 798.12/Y16

Topic: D.01. Sensory Disorders

Support: NIH NEI F31EY025920

UAB Vision Science Research Center P30 EY003039

Civitan International Research Center

McKnight Brain Research Foundation

Edward R. Roybal Center for Translational Research on Aging and Mobility

NIA 2 P30 AG022838

UAB Comprehensive Center for Healthy Aging

Title: Eccentricity-specific characteristics of V1 are altered following central vision loss

Authors: *W. BURGE[1], J. GRIFFIS[2], R. NENERT[3], M. DEFENDERFER[4], D. DECARLO[5], L. ROSS[6], K. VISSCHER[4];
[2]Psychology, [3]Neurol., [4]Neurobio., [5]Opthalmology, [1]Univ. of Alabama At Birmingham, Birmingham, AL; [6]Human Develop. and Family Studies, The Pennsylvania State Univ., State College, PA

Abstract: Central and peripheral vision have different functions. For example, central vision shows biases for processing detailed visual objects such as faces, while peripheral vision shows bias for processing more integrated visual objects such as buildings. After losing central vision, however, people must use peripheral vision for many tasks they used to rely on central vision for. Here, we address two linked hypotheses: that the structure and functional connectivity of primary visual cortex (V1) depends on eccentricity, and that these characteristics are altered following loss of central vision. For our functional analyses of healthy vision, we collected fMRI on a sample of 20 younger adults. For an anatomical analysis of healthy vision, we collected T1 MRI on a sample of 73 older and younger adults as well as utilizing the ABIDE and ADNI datasets. For our analyses of central vision loss, we collected T1 MRI and fMRI data from a group of 10 patients with Macular Degeneration (MD) who had lost central vision bilaterally, and their 10 matched controls. V1 was identified anatomically and segmented into central and peripheral portions using Freesurfer software. We tested how centrally-representing and peripherally-representing parts of V1 differed in cortical thickness and resting state functional connectivity in all groups. In healthy participants, central and peripheral V1 have striking differences in cortical thickness and functional connectivity between central and peripheral vision. The cortex was thicker in central V1 compared to peripheral V1. Further, central V1 was more strongly functionally connected to several fronto-parietal attentional regions. Conversely, peripheral V1 was more strongly functionally connected to the cingulo-opercular control network. Several differences were observed for participants who had lost central vision due to MD. Most strikingly, parts of peripheral V1 were significantly thicker in MD participants than controls. Consistent with this increase in thickness, MD participants' peripheral V1 had stronger functional connections to several cognitive control and higher order visual processing regions. Together, these findings suggest that the anatomy and connections of V1 differ between central and peripheral representations in a way that is consistent with their putative functions. Further, these anatomical and functional characteristics are altered following central vision loss. Our data are consistent with the idea that peripheral visual cortex structure and functional connections adapt to compensate for central vision loss.

Disclosures: W. Burge: None. **J. Griffis:** None. **R. Nenert:** None. **M. Defenderfer:** None. **D. DeCarlo:** None. **L. Ross:** None. **K. Visscher:** None.

Poster

798. Visual Cortex Human

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 798.13/Y17

Topic: D.06. Vision

Support: European Research Council (ERC StG 2012_311751-BrainReadFBPredCode)

Title: A cortical and cerebellar network for dynamic visual prediction in humans

Authors: *L. S. PETRO[1], F. M. CARVALHO[2], A. T. PATON[1], F. W. SMITH[3], L. MUCKLI[1]; [1]Univ. of Glasgow, Glasgow, United Kingdom; [2]Univ. of Sao Paulo, Sao Paulo, Brazil; [3]Univ. of East Anglia, Norwich, United Kingdom

Abstract: The brain uses memory to form internal representations of the environment. These internal models are hypothesized to engage mental time travel and to generate predictions of the environment. These predictions (of present or future context) are generated in high areas and carried to sensory cortex by feedback pathways. Investigating predictive processing in sensory cortex is essential for understanding the brain's modelling of the world. Feedback to V1 carries spatiotemporal predictions of sparse sensory inputs, such as the apparent motion illusion. This spatiotemporal motion prediction in V1 causes a reduced BOLD signal to the more predictable stimulus. We tested if predictions similarly alter processing in V1 in the context of complex scenes, which are the content of real-world predictions and may be used for cognitive tasks such as mental time travel. In 3T fMRI, 13 subjects saw movie clips consisting of a priming sequence, followed by a blank frame of 800ms, then a test frame. The test frame matched the expectation after the blank interval (800ms) or was from a later (4000ms) or earlier point (300, 600ms). Subjects mentally extrapolated the motion during the blank screen and rated the test frame as delayed or ahead of time. MRI parameters:18 slices; TR1s; isotropic voxel 3mm^3 (3x3x4mm^3 six subjects). We acquired T1 anatomical scans. We used general linear model deconvolution to estimate the BOLD response to the test frame conditions. In V1 and V3, we found a lower BOLD response to the 800ms frame compared to the 4000ms (t=2.24, p=0.02; t=2.07, p=0.04). In V1, V2 and V3 we found a lower BOLD response to the 600ms frame compared to the 4000ms, suggesting early visual cortex extrapolates motion from scenes with a precision spanning time delays of 600 and 800ms (t=2.18, p=0.03; t=1.99, p=0.05; t=2.2, p=0.03). In six subjects, a contrast of activation to the 600ms compared to the 4000ms frame revealed activity in the medial parietal cortex and medial temporal lobe. We find evidence that there is lower BOLD response to the 800ms test frame compared with the 4000ms condition in the cerebellum. Early visual cortex extrapolates motion from complex scenes with a precision spanning 200ms. We find that medial parietal cortex and medial temporal lobe engage in the prediction of dynamic scene inputs. The MPC and MTL are part of the default mode (Raichle at al., 2001) and

contextual association network (Bar, 2007), which have a role in translating internal models into predictions. We have evidence the cerebellum contributes to the cortical network for motion prediction. Internal models in the cerebellum may act alongside the cortex to predict the temporally-specific dynamics of our visual world.

Disclosures: **L.S. Petro:** None. **F.M. Carvalho:** None. **A.T. Paton:** None. **F.W. Smith:** None. **L. Muckli:** None.

Poster

799. Striate Cortex Plasticity II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 799.01/Y18

Topic: D.06. Vision

Support: R01EY016431

Title: Matrix metalloproteinase-9 induced by light reintroduction reactivates plasticity in adult mouse visual cortex

Authors: ***S. MURASE**, E. M. QUINLAN;
Biol., Univ. of Maryland at Col. Park Dept. of Biol., College Park, MD

Abstract: Chronic monocular deprivation (cMD) induces severe amblyopia that is highly resistant to reversal in adulthood. However, binocular visual deprivation through dark exposure (DE) reactivates synaptic plasticity in the adult primary visual cortex (V1), promoting the structural and functional recovery of deprived eye visual responses. One attractive idea is that the extracellular matrix (ECM) contributes to the constraint of plasticity in adults by limiting morphological remodeling. We therefore hypothesized that degradation of the ECM may contribute to the reactivation of plasticity by DE in the adult V1. We focused on the activity of matrix-metalloproteinase-9 (MMP-9), an extracellular zinc-dependent endopeptidase degrades ECM proteins and participates in activity-dependent remodeling of dendritic spine morphology. Indeed, light reintroduction induces degradation of perineuronal net (PNN) in bionocular V1 (V1b), including PNN-rich layers 3 and 4. PNN-degradation by light reintroduction, measured by intensities of either WFA or anti-aggrecan IHC is completely blocked by infusion of MMP-9 inhibitor 1 (Millipore) to V1 (WFA: 92.8±14.8% and anti-aggrecan: 97.6±6.5%), compared to saline control (WFA: 54.0±6.9% and anti-aggrecan: 52.2±3.6%). In vivo delivery of an MMP-9 biomarker demonstrates that MMP-9 activity induced by light reintroduction co-localizes with markers of excitatory synapses. In particular, there is a two-fold increase by light reintroduction in the co-localization of MMP-9 activity with vesicle glutamate transporter 2 (light reared

control: 33.4±4.7% reintroduced to light after DE: 65.3±9.7%), suggesting that MMP-9 activity may mediate remodeling of thalamic input to V1b. To examine a known structural correlate of ocular dominance plasticity, dendritic spine densities of pyramidal neurons in layer 2/3 are analyzed. Spine densities of neurons in cMD hemisphere do not recover spontaneously, but do recover when reverse occlusion follows DE (0.77±0.065/micron to 0.95±0.080/micron). However, MMP-9$^{-/-}$ mice do not demonstrate structural plasticity with cMD or DE. Degradation of the PNN with the enzyme hyaluronidase rescues structural plasticity, resulting in an increase in spine density of neurons in non-deprived hemisphere (0.64±0.038/micron to 0.92±0.048/micron). Together, this suggests that the activity of MMP-9 plays a critical role in plasticity in response to DE.

Disclosures: S. Murase: None. **E.M. Quinlan:** None.

Poster

799. Striate Cortex Plasticity II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 799.02/Z1

Topic: D.06. Vision

Support: NSERC Discovery Grants 7660, 298167

CIHR Operating Grant 102653

Title: A crucial role for the fellow eye in the darkness-induced recovery of visual acuity in the amblyopic eye of felines

Authors: *D. E. MITCHELL, P. BOBBIE-ANSAH, K. R. DUFFY;
Dept of Psychology and Neurosci., Dalhousie Univ., Halifax, NS, Canada

Abstract: Following a short period of monocular deprivation (MD) imposed in the early postnatal life of kittens, there is a profound reduction of the vision of the deprived eye. The size of the reduction of vision as assessed by the loss of spatial acuity is dependent upon the animal's age at the time of deprivation and its duration. While some recovery of the acuity of this eye can occur, a substantial deficit in visual acuity usually remains with characteristics similar to those observed in human amblyopia. Recently we showed (Duffy & Mitchell, 2013) that a ten day period of total darkness introduced at between 3 and 4 months of age can induce recovery of the visual acuity of the amblyopic eye to normal levels in just 5-7 days without any decrement of the acuity of the fellow (stronger) eye. The speed and magnitude of this recovery suggest that neural connections with the fellow eye, that support normal vision retained by this eye following the

period of darkness, may play a crucial role in the recovery of visual acuity of the amblyopic eye. We investigated the possibility that activity in cortical cells mediated by neural connections from the fellow eye may serve to guide the darkness-induced recovery of the amblyopic eye. The possible role of the nondeprived eye as a mediator of visual recovery of the amblyopic eye was assessed by elimination of its potential role by occluding it immediately after the period of darkness.
The study was conducted on animals reared as before with a period of MD from P30-37 followed by a 10 day period of total darkness at P92. Immediately upon emergence from the darkroom at P102 days of age, the nondeprived eye was occluded for 11 days. Control kittens were reared identically with the exception that they were not exposed to darkness before the nondeprived eye was occluded at P102 for a similarperiod (16- 21days). In remarkable contrast to the rapid and complete recovery of the visual acuity of the deprived eye observed when both eyes are open after the period of darkness, occlusion of the nondeprived eye during this period appeared to block improvement of the acuity of the amblyopic eye beyond the very small changes observed in control animals that received a similar period of occlusion of the nondeprived eye without a prior period of darkness. It appears that the rapid recovery of vision of the amblyopic eye induced by darkness is dependent upon visually - driven neural activity mediated by the nondeprived eye. Additional observations from the animals that had the nondeprived eye occluded after the period of darkness suggest that darkness may be beneficial for only a limited time afterward.
Duffy, KR, Mitchell, DE *Current Biology* **23**, 382-386, 2013.

Disclosures: D.E. Mitchell: None. **P. Bobbie-Ansah:** None. **K.R. Duffy:** None.

Poster

799. Striate Cortex Plasticity II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 799.03/Z2

Topic: D.06. Vision

Support: NSERC 298167

NSERC 7660

CIHR 102653

NIH 5R01EYO2303-03

Title: Recovery from the effects of long-term monocular deprivation following dark exposure or retinal inactivation

Authors: *K. DUFFY[1], M.-F. FONG[2], M. F. BEAR[2], D. E. MITCHELL[1];
[1]Dalhousie, Halifax, NS, Canada; [2]MIT, Boston, MA

Abstract: A brief duration of monocular deprivation (MD) beginning at the peak of the critical period in kittens can cause a visual impairment in the deprived eye (amblyopia), and can lead to pronounced shrinkage of deprived-eye neurons in the lateral geniculate nucleus (dLGN) that originates from synaptic changes within striate cortex. We recently demonstrated that either immersion in complete darkness (Duffy & Mitchell, 2013) or binocular retinal inactivation for 10 days following one week of MD promotes a rapid and full recovery of visual acuity, and stimulates a recovery of neuron soma size within the dLGN. In the current study we assessed the effectiveness of 10 days of darkness or retinal inactivation (with intravitreal TTX injections) to promote anatomical recovery from longer durations of MD that precipitate much larger anatomical deprivation effects. The cross-sectional soma size of neurons in the dLGN was measured using the nucleator stereology probe, and all measurements were made blind to rearing condition.

Comparison of the soma size of deprived and non-deprived neurons revealed that, as expected, the extent of deprived neuron atrophy increased as MD duration was extended to 6 weeks. Although substantial recovery of neuron soma size was observed when 6 weeks of MD was followed by darkness or binocular retinal inactivation, complete recovery was not achieved with either treatment. In an attempt to promote better recovery from the effects of 6 weeks of MD, we opened the deprived eye and inactivated only the fellow (stronger) eye for 10 days. Inactivation of the fellow eye led to a complete recovery of neuron soma size so that originally deprived and non-deprived neurons were equal in size and comparable to the size of neurons from normal controls. Importantly, 10 days of fellow eye lid closure (reverse occlusion) following the same duration of MD drove a smaller degree of recovery than 10 days of fellow eye inactivation. Furthermore, fellow eye inactivation was effective at promoting recovery in animals subjected to MD for even longer durations that extended to 18 weeks.

We conclude that while 10 days of darkness or binocular inactivation can promote substantial recovery from the anatomical effects of long-term MD, it nevertheless remained incomplete. However, full recovery following the same MD was achieved when the deprived eye was opened while the fellow eye was inactivated for 10 days.

Duffy KR and Mitchell DE (2013) *Current Biology*

Disclosures: **K. Duffy:** None. **M. Fong:** None. **M.F. Bear:** None. **D.E. Mitchell:** None.

Poster

799. Striate Cortex Plasticity II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 799.04/Z3

Topic: D.06. Vision

Support: RGPIN-2015-0621

Title: Waves of inter-individual variability during development of human visual cortex

Authors: *K. M. MURPHY[1], S. BESHARA[2], C. R. SIU[2], J. G. A. PINTO[2], D. G. JONES[3]; [1]Dept Psychol Neurosci & Behaviour, [2]McMaster Univ., Hamilton, ON, Canada; [3]Pairwise Affinity, Hamilton, ON, Canada

Abstract: The human visual cortex has tremendous capacity for plasticity, especially during development when visual experience drives maturation of cortical circuits. Studies of visual perception and neurobiological changes in V1 have identified infancy and childhood as stages of development when there are large steps towards a mature visual system. We have been studying development of excitatory and inhibitory receptor systems in human V1 have uncovered a new aspect of its development -- waves of inter-individual variability that occur during through infancy and childhood.

We used Western blotting of postmortem tissue samples from human V1 (n=30) ranging in age from 20 days to 80 years to quantify expression of a group of glutamatergic and GABAergic synaptic proteins. We measured expression of the proteins, plotted how they changed across the lifespan and then calculated the variability in a sliding window that included 3 adjacent cases. That inter-individual variability was analyzed using the Fano Factor where we calculated the Variance-to-Mean-Ratio (VMR) in the sliding window and plotted the VMR to visualize how variability of each protein changed across the lifespan. We found waves of high inter-individual variability during infancy and childhood that were not present in adults. Each protein had a different wave of variability. For example, Gephyrin the GABA receptor anchoring protein had high variability under 1 year of age while PSD95 was low at that time and then rose to have a wave of higher variability through childhood. Other glutamate receptor proteins had a progression of waves peaking during childhood starting with GluN1 and GluN2B at about 1 year, GluN2A at 1.5 years, GluA2 at 2 years and PSD-95 at 2.5 years.

These waves of variability are a new feature of human V1 development that may reflect stages of vulnerability or dynamics that drive maturation of an adaptive network of cortical circuitry. We think these waves both reflect and contribute to big steps in maturation of visual perception during infancy and childhood.

Disclosures: K.M. Murphy: None. **S. Beshara:** None. **C.R. Siu:** None. **J.G.A. Pinto:** None. **D.G. Jones:** None.

Poster

799. Striate Cortex Plasticity II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 799.05/Z4

Topic: D.06. Vision

Support: NEI R01EY024918

Title: Nicotinic activation of somatostatin inhibitory neurons by Lypd6-nAChRa2 system restores plasticity in adult visual cortex.

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Abstract: Experience-dependent cortical plasticity declines into adulthood, posing a challenge for recovery of function. A network of inhibition is critical for plasticity, yet contributions of interneurons other than Parvalbumin interneurons have largely been unexplored. Here we show Lypd6, an endogenous positive modulator of nicotinic acetylcholine receptors, as a specific molecular target in Somatostatin interneurons to reactivate cortical plasticity in adulthood. Lypd6 decreases its expression in adult primary visual cortex in concert with declining ocular dominance plasticity. Overexpression of Lypd6 specifically in adult Somatostatin interneurons reactivates plasticity through α2 subtype of nicotinic receptor by activating Somatostatin interneurons which in turn inhibit Parvalbumin interneurons, a key early trigger of plasticity in juvenile cortex. Identification of the first Somatostatin interneuron-specific plasticity regulators provides novel therapeutic targets for disorders with limited recovery due to diminished plasticity such as amblyopia as well as for psychiatric disorders with deficits in Somatostatin interneurons.

Disclosures: **M. Sadahiro:** None. **M.P. Demars:** None. **P.N. Burman:** None. **A. Zimmer:** None. **H. Morishita:** None.

Poster

799. Striate Cortex Plasticity II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 799.06/Z5

Topic: D.06. Vision

Title: Neuronal responses correlated with shifts in interocular balance induced by short-term deprivation in adult macaque visual cortex.

Authors: *R. A. MILLER, III[1], M. BEGUM[2], D. TS'O[2];
[2]Neurosurg., [1]SUNY Upstate Med. Univ., Syracuse, NY

Abstract: Short-term monocular deprivation (STMD, depriving one eye for 1-3 hours, either total occlusion or pattern deprivation) disrupts interocular balance in adult humans, as measured psychophysically, and also in our present studies using anesthetized adult macaques, assessed with intrinsic signal optical imaging of the V1 ocular dominance columns. Surprisingly, in all these studies, the relative contribution of the deprived eye was elevated for more than an hour after deprivation ends. In addition, our V1 imaging studies show a rapid reduction in the contribution of the nondeprived eye during the deprivation of the other eye. Once the deprivation period ended, the nondeprived eye dramatically increased in strength, despite the stimulation to this eye remaining the same during the entire experiment.
We have now conducted multi-electrode recordings in V1 with the STMD paradigm. Single cell responses to monocular and binocular stimuli were measured before, during and after STMD. The single-unit recordings revealed several different types of cell responses. One class of neurons did not exhibit any striking changes in responses during STMD. These cells were often highly monocular. Another class of cells displayed a marked enhancement of responses in the deprived eye once the deprivation period ended, attaining activity levels beyond that of the pre-deprivation period and persisting for at least an hour. A third class of cells exhibited a surprising decline in responses during the deprivation period to stimulation in the non-deprived eye: in some cells, beginning gradually upon deprivation, while in others, curiously beginning sometime in the middle of the deprivation period. Responses to non-deprived eye stimulation began to return towards pre-deprivation levels once the deprivation of the other eye ended. This weakened response for the non-deprived eye during the deprivation period was striking. It cannot be explained by adaptation or fatigue in the eye or cortex. Another small population of cells showed deprivation responses more consistent with the classical notion of the non-deprived eye gaining in strength. Overall, the electrophysiological results show, in certain classes of V1 cells, response behaviors that may constitute components of the shifts in interocular balance induced by STMD observed in the imaging studies and psychophysically. The findings suggests a dynamic binocular mechanism for regulating interocular balance and gain that involves the neurons in V1.

Disclosures: **R.A. Miller:** None. **M. Begum:** None. **D. Ts'o:** None.

Poster

799. Striate Cortex Plasticity II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 799.07/Z6

Topic: D.06. Vision

Support: CIHR Grant MOP-111003

NSERC Grant 238835-2011

Title: Time-course of the involvement of cholinergic receptors subtypes in a repetitive visual / cholinergic stimulation

Authors: ***M. GROLEAU**, M. CHAMOUN, M. BHAT, E. VAUCHER;
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Abstract: Cholinergic stimulation coupled to visual exposure to a specific stimulus enhances the long-term cortical response to visual stimuli. However, there are a variety of cholinergic receptors subtypes in the visual cortex that play distinct and sometime opposite roles in the modulation of the visual cortex (V1) neurons. The weight of these different receptors in the different steps of cholinergic modulation of repetitive visual stimulation is still unclear. To determine which cholinergic receptors were involved in the increased cortical reactivity induced by cholinergic enhancement, RT-PCR was used. Cholinergic enhancement was performed either by an electrical stimulation of the basal forebrain or a pharmacological stimulation of the cholinergic system (donepezil, 1mg/kg, daily i.p. administration). A daily visual exposure of the rats to sine-wave gratings (training) was paired or not with this cholinergic enhancement. RT-PCR was performed without any visual exposure/cholinergic stimulation, or at 10 minutes, one week or two weeks of this visual/cholinergic training. V1, the frontoparietal cortex and the basal forebrain were analysed for the muscarinic receptors expression (M1, M2, M3, M4, M5), the nicotinic receptors subunits (α3, α4, α7, β2, β4) and NMDA receptors, GAD65 and ChAT. Statistical analysis was performed using Two-way ANOVA to evaluate the interaction between the treatment and the time-course for each cholinergic receptor tested and in each region evaluated. The results showed interactions in V1 between the treatment and the time-course. This suggests that when using the cholinergic enhancement treatments over time, the effect of the treatment is dependent of the number of visual exposure sessions and alters the mRNA expression of M1, M3, M4, β4, NMDA and GAD65. In the basal forebrain an interaction between the treatment and the time-course was observed for M3 and β4. In the frontoparietal

cortex, an interaction between the treatment and the time-course was detected only for the α3 nicotinic receptor. This suggests that the combination of cholinergic enhancement and visual exposure is specific to V1 and does not alter a control cortex. This study clearly shows that the involvement of the cholinergic receptors is involved in long-term changes related to plasticity processes sustaining perceptual learning.

Disclosures: **M. Groleau:** None. **M. Chamoun:** None. **M. Bhat:** None. **E. Vaucher:** None.

Poster

799. Striate Cortex Plasticity II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 799.08/Z7

Topic: D.06. Vision

Support: RGPIN-2015-06215

Title: Protracted development of human V1: Glutamate receptors linked with plasticity and orientation selectivity

Authors: ***C. SIU**[1], S. BESHARA[1], D. G. JONES[3], K. M. MURPHY[2];
[1]MiNDS, [2]Psychology, Neurosci. and Behaviour, McMaster Univ., Hamilton, ON, Canada;
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Abstract: Maturation of glutamate synapses in visual cortex regulates experience-dependent plasticity and drives development of receptive field properties to support visual perception. Human vision matures in stages that continue into adulthood, and that extended development has lead to the idea that V1 regulates an early stage while extrastriate areas mediate later stages of visual development. Very little is known, however, about the rate of development of glutamate receptors in human V1. This leaves unanswered if this neurobiological mechanism necessary for neuroplasticity matures early, or has lifelong changes in V1 that could support the dynamics of human visual perception across the lifespan.
Both plasticity and orientation tuning change across the lifespan so we quantified expression of 2 NMDA receptor subunits (GluN2A & GluN2B) involved in these functions. The developmental switch from GluN2B to GluN2A regulates the effect of visual experience on ocular dominance plasticity by controlling the synaptic modification threshold, while the increase in GluN2A controls maturation of orientation selectivity. We did Western blotting using 30 postmortem tissue samples from human V1 that ranged in age from 20 days to 80 years.
We found that GluN2B expression is relatively constant across the lifespan. In contrast, GluN2A expression is low in infancy, increases gradually to peak at ~30 years, then drops in aging. An

index of relative GluN2A:GluN2B expression shows a protracted shift that begins with more GluN2B early in infancy, switches to more GluN2A at 12 years, peaks at 40 years, then shifts in favour of GluN2B in aging. This age-related shift is driven by the loss of GluN2A.
The protracted GluN2A:GluN2B shift points to V1 involvement in the capacity for plasticity across the lifespan. The loss of GluN2A in aging provides a 'new' neurobiological mechanism for the loss of orientation tuning in aging V1 neurons. Perhaps this loss of GluN2A is preferentially on GABAergic neurons, identifying excitatory synapses as the site of age-related changes in inhibition in human V1. Together these results indicate it is time to formulate new hypotheses about the potential for plasticity in human V1 and the mechanisms that underlie age-related loss of visual perception.

Disclosures: **C. Siu:** None. **S. Beshara:** None. **D.G. Jones:** None. **K.M. Murphy:** None.

Poster

799. Striate Cortex Plasticity II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 799.09/Z8

Topic: D.06. Vision

Support: NIDCR-Interdisciplinary Training Fellowship T32HD075735 (M.R.S)

P30 NIEHS Grant P30ES023515 (J.T.D and H.M.)

Mindich Child Health and Development Institute Pilot Fund (J.T.D. and H.M.)

R01EY024918 (H.M.)

R01EY026053 (H.M.),

Knights Templar Eye Foundation (H.M.)

March of Dimes (H.M.)

Title: Postnatal systemic inflammation suppresses developmental cortical plasticity

Authors: ***M. R. SMITH**[1], P. BURMAN[2], M. SADAHIRO[2], B. A. KIDD[2], J. T. DUDLEY[2], H. MORISHITA[2];
[1]Icahn Sch. of Med. At Mount Sinai, New York, NY; [2]Icahn Sch. of Med. at Mount Sinai, New York, NY

Abstract: Childhood and adolescent critical periods of heightened neuroplasticity are essential for development of normal brain function and behavior. Disruption of these periods of developmental plasticity may alter the neurodevelopmental trajectory and contribute to brain-related disorders. Given the high prevalence of psychiatric and neurodevelopmental disorders, identifying disruptors of plasticity represents an essential step for developing strategies for prevention and therapeutic interventions. Applying a novel computational approach that systematically assessed connections among 436 transcriptional signatures of disease and multiple signatures of neuroplasticity, we identified inflammation as a common pathological process central to a diverse set of diseases predicted to dysregulate molecular processes associated with plasticity. To experimentally test the hypothesis that inflammation disrupts developmental plasticity *in vivo*, we used the ocular dominance model of experience-dependent cortical plasticity. We found that systemic lipopolysaccharide suppresses postnatal cortical plasticity with accompanying transcriptional changes in a specific set of molecular regulators of plasticity. These findings suggest inflammation in children may have unexpected negative consequences on the postnatal developmental trajectory by disrupting neuroplasticity during critical windows of development. Suppressed developmental neuroplasticity may in part underlie the pathophysiology of psychiatric and neurodevelopmental disorders associated with inflammation.

Disclosures: **M.R. Smith:** None. **P. Burman:** None. **M. Sadahiro:** None. **B.A. Kidd:** None. **J.T. Dudley:** None. **H. Morishita:** None.

Poster

799. Striate Cortex Plasticity II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 799.10/Z9

Topic: D.06. Vision

Support: NIH R01-EY12124

Title: Neuromodulator induced bidirectional changes in ocular dominance in the mouse primary visual cortex

Authors: *S. HONG, S. HUANG, A. KIRKWOOD;
Mind Brain Inst., Johns Hopkins Univ., Baltimore, MD

Abstract: Neuromodulatory signals mediated by G protein-coupled receptors are essential for the induction of experience-dependent cortical plasticity. *In vitro*, neuromodulators can exert a pull-push control of Hebbian plasticity, with receptors coupled to Gs and Gq11 respectively promoting the induction of LTP and LTD. Importantly, β-adrenergic receptors (coupled to Gs)

and 5-HT2c serotonergic receptors (coupled to Gq11) can provide a cellular substrate for reinforced learning as these receptors can transform the so-called “eligibility traces” into lasting LTP and LTD. We tested, therefore, whether the activation of these receptors *in vivo* can promote lasting bidirectional changes in visual responses. Using optical imaging of intrinsic signal we found that the pharmacological activation of 5-HT2c receptor, in conjunction with brief visual conditioning of one eye, induces LTD-like changes of the responses evoked by the conditioned eye only, thus shifting the natural ocular dominance balance. The same visual stimulation, but paired with activation of β-adrenergic receptors results in LTP-like changes, and the opposite ocular dominance changes. These results suggest that the pull-push regulation of Hebbian plasticity underlies the neuromodulation of experience dependent ocular dominance plasticity. Currently we are using optogenetics to evaluate the role of endogenous released noradrenaline and serotonin in this type of plasticity.

Disclosures: **S. Hong:** None. **S. Huang:** None. **A. Kirkwood:** None.

Poster

799. Striate Cortex Plasticity II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 799.11/Z10

Topic: D.06. Vision

Support: CRCNS/NIH Grant EY026273

NIH Grant EY011488

CRCNS/BMBF Grant 01GQ1507

Title: The role of spontaneous correlations in structuring co-tuned networks in cortical development

Authors: *B. HEIN[1,2,3], G. B. SMITH[4], D. E. WHITNEY[4], P. HUELSDUNK[1,2,3], D. FITZPATRICK[4], M. KASCHUBE[1,2,3];
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Abstract: In visual cortex, local networks of co-tuned neurons manifest in a columnar organization, but also form distributed circuits with distant, but similarly co-tuned neurons several millimeters away. It has been hypothesized that co-tuning between neurons in visual cortex might be dynamically established using patterns of spontaneous activity, however,

experimental evidence supporting this scenario is scarce. Here we combined chronic epifluorescence and two-photon imaging with quantitative analysis and modeling to dissect the organization of spontaneous activity in the early ferret visual cortex in relation to the developing networks of orientation selective domains which become apparent upon eye opening.
We find that by ten days prior to eye opening, cortical activity is already spatially coherent on a columnar scale. The local activity correlation structure resembles a Mexican-hat profile, an organization consistent with models for the activity dependent development of orientation domains. Remarkably, strong correlations were also present between cortical domains several millimeters apart, even at a stage in development when horizontal connections of layer 2/3 pyramidal cells remain primarily local. To understand how long-range correlations could arise in the early cortex from purely local connectivity, we generated a circuit model of rate units receiving weakly modulated random input drive with connectivity reflecting the experimentally observed Mexican-hat structure. This model produced modular activity patterns with long-range spatial correlations, arising through multi-synaptic heterogeneous recurrent feedback loops. Interestingly, although activity correlations in this model vary smoothly across the cortex, they are systematically punctuated by abrupt discontinuities, reminiscent of the fracture and pinwheel discontinuities found in the mature orientation map. Notably, we also observed such 'correlation fractures' in the structure of spontaneous activity *in vivo*, where they tend to co-align with pinwheel locations in the orientation preference map after eye-opening. Further, we find that several days prior to eye opening, long-range correlations in spontaneous activity were predictive of future tuning similarity in the mature orientation map, providing additional evidence for a developmental relationship between spontaneous activity and co-tuned networks. We conclude that the primitive circuits of the early cortex robustly generate both local and long-ranging structured correlations in spontaneous activity, which might form the basis for the development of co-tuned spatially distributed cortical networks.

Disclosures: **B. Hein:** None. **G.B. Smith:** None. **D.E. Whitney:** None. **P. Huelsdunk:** None. **D. Fitzpatrick:** None. **M. Kaschube:** None.

Poster

799. Striate Cortex Plasticity II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 799.12/Z11

Topic: D.06. Vision

Support: NIH 5R01EYO23037-03

CIHR 102653

NSERC 298167

NSERC 7660

Picower Institute Innovation Fund

Howard Hughes Medical Institute

Title: Temporary retinal inactivation promotes rapid recovery from monocular deprivation in mice and kittens

Authors: *M.-F. FONG[1], D. E. MITCHELL[3], K. R. DUFFY[3], P. NORTHRUP[3], Y. ATIYAS[1,2], F. M. VAN DESSEL[1,4], J. U. DEERE[1,4], M. F. BEAR[1];
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Abstract: A brief period of monocular deprivation (MD) during early postnatal life drives structural and functional changes in the mammalian central visual pathway that lead to impaired visual acuity in the previously deprived eye. While MD is a classic paradigm for studying experience-dependent plasticity, it has also become an established model for study of the pathophysiology of amblyopia, a widespread form of human visual disability that arises due to imbalanced visual input between the two eyes during infancy or early childhood. Therefore, identifying strategies for reversing the consequences of early life MD are particularly relevant to developing targeted interventions for effective treatment of amblyopia. In this study, we tested the hypothesis that temporary inactivation of the retinas using tetrodotoxin (TTX) could promote recovery from MD in mice and cats. While long-lasting impairments in deprived eye vision following MD have been demonstrated in kittens, the stability of these deficits is not well characterized in mice. For this reason, we first conducted a longitudinal electrophysiological study to track visual ability in awake mice for several weeks following early life MD. Seven days of MD drove a profound reduction in visual cortical responsiveness to vision through the deprived eye that persisted for > 1 month after restoring binocular vision. However, the persistent reduction in deprived eye responses could be stably reversed when binocular visual experience followed temporary bilateral retinal inactivation. Further, in kittens, we found that bilateral retinal inactivation followed by a short period of binocular visual experience promoted fast recovery of the visual acuity of the deprived eye to normal levels. Finally, we show that even in the absence of subsequent visual experience, prolonged TTX treatment leads to recovery from the anatomical consequences of MD on the visual thalamus of kittens. We conclude that temporary retinal inactivation represents a highly efficacious strategy for promoting recovery from MD-driven visual impairments.

Disclosures: **M. Fong:** None. **D.E. Mitchell:** None. **K.R. Duffy:** None. **P. Northrup:** None. **Y. Atiyas:** None. **F.M. Van Dessel:** None. **J.U. Deere:** None. **M.F. Bear:** None.

Poster

799. Striate Cortex Plasticity II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 799.13/Z12

Topic: D.06. Vision

Support: NIH Grant EY024678

Curci Foundation

Title: Impact of PV neuron development on visual responses

Authors: *S. J. KUHLMAN, B. FEESE, N. MCGUIER, J. KAUTTONEN;
Carnegie Mellon Univ., Pittsburgh, PA

Abstract: During postnatal development, maturation of sensory circuits depends on the statistics encountered in the local environment. This is largely achieved by stimulus-instructed tuning of neuronal receptive fields. Such changes in tuning improve the information that is ultimately used to guide appropriate behavior and learning. The impact of visual experience on the maturation of cortical response properties varies among cell types contained within a microcircuit (Kuhlman et al. Nat Neurosci 2011). The differential impact of experience may support the division of labor among cell types that is essential for proper signal transformation and sensory encoding. The extent to which visual experience is required to maintain recently developed PV neuron response properties is unknown. Using two-photon guided cell attached recording of PV neurons in vivo we find that 1 day of binocular deprivation is sufficient to alter recently developed response properties. We are also exploring the impact that disrupted PV development has on population activity among excitatory neurons using calcium imaging in awake mice.

Disclosures: S.J. Kuhlman: None. **B. Feese:** None. **N. McGuier:** None. **J. Kauttonen:** None.

Poster

799. Striate Cortex Plasticity II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 799.14/Z13

Topic: D.06. Vision

Support: NIH Grant EY016431

Title: Prominent role of MMP9 in the bidirectional regulation of visual cortex synaptic plasticity by visual experience.

Authors: *C. L. LANTZ, E. M. QUINLAN;
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Abstract: Ocular dominance plasticity is robust in juveniles, but is significantly constrained in adults. We have previously demonstrated that dark exposure reactivates plasticity in the adult visual cortex, which can be harnessed by visual experience to drive recovery from amblyopia. One attractive candidate for the developmental constraint on ocular dominance plasticity is the maturation of the extracellular matrix, and its influence on excitability. Interestingly, the levels and activity of matrix-metalloproteinase-9 (MMP9), an activity-dependent protease known to degrade extracellular matrix components, is increased by light reintroduction following dark exposure (Murase et al., 2016).
Here we show that MMP9 is necessary for the reactivation of plasticity by adult dark exposure. Electrophysiological recordings in head-fixed awake mice revealed that pyramidal neurons in $MMP9^{-/-}$ adult cortex had increased visually-evoked spike rates (WT: 2.36 ± 0.8 Hz; $MMP9^{-/-}$: 3.75 ± 0.8 Hz). Despite this hyperexcitability, visual acuity (WT: 0.85 ± 0.04 cpd; $MMP9^{-/-}$: 0.78 ± 0.13 cpd) and contralateral bias (WT: 0.37±0.05; $MMP9^{-/-}$: 0.23 ± 0.04), as estimated by VEP amplitudes, were normal in $MMP9^{-/-}$ mice. However, dark exposure in adulthood, which reactivated robust ocular dominance plasticity in wild-types (post 3 day MD, Contra: 87.35 ± 20.4μV; Ipsi: 111.01± 0.24 μV; Bias: -0.133 ± 0.11), failed to activate plasticity in $MMP9^{-/-}$ adults (post 3 day MD, Contra: 86.40 ± 5.0 μV; Ipsi: 72.62 ± 11.8 μV; Bias: 0.11±0.03). Similarly, reducing excitability in $MMP9^{-/-}$ mice with diazepam, which rescued ocular dominance plasticity in other hyperexcitable transgenic lines such as $NARP^{-/-}$ mice, failed to activate plasticity (Pre- MD: 0.23±0.04, post 3 day MD:0.21±0.07), despite a diazepam mediated reduction in spike rates (Pre-MD: 2.75±0.15 Hz, post 3 day MD: 1.94±0.16 Hz). To ask if plasticity in $MMP9^{-/-}$ mice could be reactivated by degradation of the extracellular matrix, we delivered the enzyme hyaluronidase to adult primary visual cortex. Hyaluronidase rescued ocular dominance plasticity in $MMP9^{-/-}$ mice, revealed by a significant increase in the amplitude of non-deprived eye VEP following prolonged MD (Pre-MD: 152.3 ± 18.1 μV; post MD: 202.7± 21.6 μV). Together these data suggest that MMP9 plays a prominent role in the bidirectional regulation of synaptic plasticity in primary visual cortex by visual experience.

Disclosures: C.L. Lantz: None. **E.M. Quinlan:** None.

Poster

799. Striate Cortex Plasticity II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 799.15/Z14

Topic: D.06. Vision

Support: NIH Grant R01-EY022720

Title: Cross-modal plasticity at thalamocortical synapses

Authors: G. RODRIGUEZ[1], *H.-K. LEE[2];
[1]Biol., [2]Dept. of Neurosci., Johns Hopkins Univ., Baltimore, MD

Abstract: Loss of a sensory modality leads to widespread compensatory adaptation in the brain, which allows the remaining senses to guide behavior. We previously reported that such cross-modal plasticity is manifested as synaptic changes across different primary sensory cortices. In particular, in the spared sensory cortices we found strengthening of thalamocortical (TC) synapses as a result of sensory deprivation in adult mice. This was quite surprising in light of previous studies demonstrating that TC plasticity is lost after the second postnatal week of development in mice. Therefore, our observations indicate that cross-modal sensory deprivation may be able to recover synaptic plasticity mechanisms at TC synapses in adults. By combining primary visual cortical slice electrophysiology with optogenetic techniques, we are investigating the molecular and cellular mechanisms leading to TC synaptic potentiation in the primary visual cortex (V1) of deafened adult mice. In addition, we are determining *in vivo* functional changes caused by deafening in V1 of adult mice by measuring optical intrinsic signals during presentation of visual stimuli.

Disclosures: G. Rodriguez: None. **H. Lee:** None.

Poster

799. Striate Cortex Plasticity II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 799.16/AA1

Topic: D.06. Vision

Support: NIH/NEI RO1-EY9314

The Fred Plum Fellowship in Systems Neurology and Neuroscience

Title: Tuned inhibition model accounts for adaptation-induced tuning shifts in macaque V1 and V2

Authors: *D. J. THENGONE, Y. YU, J. VICTOR;
Brain and Mind Res. Inst., Weill Cornell Grad. Sch. of Med. Sci., New York, NY

Abstract: The visual system utilizes inputs from the recent past to adjust its representations of the sensory world. This ubiquitous property of sensory systems - adaptation - influences neural response characteristics including gain, stimulus preference, and degree of selectivity. To identify the specifics of adaptation-induced alterations in tuning properties, we measured and modeled the effects of adaptation on excitatory and inhibitory neurons in V1 and V2 of the primate visual cortex. We used a multitetrode array to record neuronal responses from neurons in V1 and V2 of 6 macaques under anesthesia and paralysis. We compared baseline orientation tuning curves to tuning curves measured after brief (400 ms) and prolonged (40 s) adaptation. Both durations of adaptation induced changes in bandwidth and tuning preferences in excitatory and inhibitory neurons. We found increases and decreases in bandwidth in both cell types, and shifts of the tuning preference either away from (repulsive) or towards (attractive) the adapting stimulus. Differences between V1 and V2 were relatively subtle. In V1, prolonged adaptation could either broaden or narrow the bandwidth of both cell types, while in V2, bandwidth changes were selective, with broadening in inhibitory cells and narrowing in excitatory cells. To account for the effects of adaptation on the orientation tuning of visual neurons, we considered several firing-rate models (80% excitatory neurons and 20% inhibitory neurons) of V1. The models are distinguished by the site of adaptation (post-synaptic vs pre-synaptic), and whether inhibitory neurons contribute to orientation selectivity. This results in four model classes: (1) untuned inhibition with postsynaptic adaptation; (2) tuned inhibition with postsynaptic adaptation; (3) untuned inhibition with presynaptic adaptation; (4) tuned inhibition with presynaptic adaptation. Neither model with post-synaptic adaptation (models 1 and 2) could account for changes in half-bandwidth or shifts in tuning curve peak. Pre-synaptic adaptation could induce such effects, but models differed in the kinds of tuning shifts they yielded. Specifically, if adaptation is pre-synaptic and inhibition is untuned (model 3), then adaptation to a non-preferred stimulus only produced repulsive shifts. In contrast, pre-synaptic adaptation with tuned inhibition (model 4) can lead to both repulsive and attractive shifts along with bandwidth decreases, similar to the experimental data. More broadly, our findings demonstrate that adaptation in inhibitory neurons is critical for shaping sensory representations as stimulus characteristics change over time.

Disclosures: D.J. Thengone: None. **Y. Yu:** None. **J. Victor:** None.

Poster

799. Striate Cortex Plasticity II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 799.17/AA2

Topic: D.06. Vision

Support: NIH R01 EY017707

Title: Changes in peripheral vision induced by simulated central field loss

Authors: *N. CHEN[1], K. SHIN[2], R. MILLIN[3], M. KWON[4], B. S. TJAN[5];
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Abstract: The human fovea serves both as the locus for fixations and the oculomotor reference for saccades. Training normally sighted adults with occluded central vision can reliably induce a preferred retinal locus (PRL) in peripheral vision for fixation with re-referenced saccades (Kwon, Nandy & Tjan, 2013, Curr. Biol.). Does the development of a PRL in peripheral vision alter the neural processing of the visual inputs? Crowding, the impediment of object recognition by clutter, is a hallmark of form-vision deficits in peripheral vision. Here we asked if the spatial extent of crowding can be altered as a consequence of the training-induced PRL. We trained nine human subjects using the object-following-and-visual-search task with a simulated central-field scotoma and a prescribed PRL. After 20 hours of training in 2-3 weeks, subjects' saccades were re-referenced to the prescribed PRL location in the presence of the simulated central scotoma. Before and after training, we measured the spatial extent of crowding behaviorally at two locations: the prescribed PRL location in the upper-left visual field and a symmetric "sideways" location in the upper-right field where one third of the saccade targets were presented during training. We found that training led to a shrinkage of the crowding zone along the radial axis at the PRL location, causing the crowding zone to become roundish, consistent with findings from patients with central field loss (Chung, 2013, J. Neurosci.). The crowding zone along the radial axis at the sideways location was also reduced. With fMRI measurements before and after training, we found a radial-specific reduction of crowding-related suppression (Millin et al., 2013, Cereb. Cortex; Kwon et al., 2014, J. Neurophysiol.) across visual areas V1-V4. However, this reduction, which parallels the behavioral finding, was observed only at the PRL location. These findings suggest that human crowding zones dynamically reorganize relative to the reference point of saccade, consistent with a theory that attributes crowding to image representation using saccade-biased image statistics (Nandy & Tjan, 2012, Nat. Neurosci.). By demonstrating that training with a simulated central-field scotoma facilitates peripheral vision

via reshaping the crowding zones, this study reveals the residual plasticity in adult peripheral vision and sheds light on new mechanisms of rehabilitations for patients with central field loss.

Disclosures: **N. Chen:** None. **K. Shin:** None. **R. Millin:** None. **M. Kwon:** None. **B.S. Tjan:** None.

Poster

800. Extrastriate Cortex II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 800.01/AA3

Topic: D.06. Vision

Support: JSPS KAKENHI Grant Number 26430031

Title: *In vivo* visualization of multiple areas around the superior temporal sulcus of the common marmoset

Authors: *W. SUZUKI[1,2], T. TANI[2,1], T. BANNO[3,1], N. MIYAKAWA[1], H. ABE[2,1], T. HAYAMI[1], N. ICHINOHE[1,2];
[1]Natl. Ctr. of Neurol. and Psychiatry, Natl. Inst. of Neurosci., Kodaira, Japan; [2]Ichinohe group, Lab. for Mol. Analysis of Higher Brain Function, RIKEN BSI, Wako, Japan; [3]Dept. of Otorhinolaryngology:Head and Neck Surgery, Univ. of Pennsylvania Sch. of Med., Philadelphia, PA

Abstract: Superior temporal sulcus (STS) of humans and old world monkeys contains multiple cortical areas that have been recognized as regions for integration of dorsal/ventral visual pathways. Although the individual areas can be anatomically and physiologically distinct, they are folded in the sulcus, which makes it difficult to experimentally access especially *in vivo* in those species. A small New World monkey, the common marmoset (*Callithrix jacchus*) has a lissencephalic brain with those cortical areas exposed on the surface, and thus is an adequate primate model to examine the functional roles of each area for the information processing in the STS. In the present study, to identify the multiple areas around the STS *in vivo*, we applied optical intrinsic signal imaging (OISI) technique to the marmoset STS and visualized the spatial organization in activities of the multiple visual cortical areas when several kinds of visual stimuli were presented. A large region of the caudal STS was exposed and illuminated with a band-passed light of 535 nm center wavelength. The stimulus evoked signals were defined by the changes in backscattered light following a visual stimulus presentation. First, we visualized retinotopic organization in the signals evoked by flashing random dots appeared within annuluses for eccentricity (~14 degree) or those within wedges for polar-angle (45-degree step).

A visual field sign map was computed from the evoked signals and showed two retinotopically organized areas in the STS; MT cluster and FSTd. Second, to identify motion sensitive areas we presented moving random dots with a uniform motion or expansion/contraction. The moving dots evoked signals in a larger region in the STS, including the MT cluster and FSTd. Especially, moving dots that expanded from a center to the periphery evoked the maximum responses in the MT cluster and a distinct area dorsal to the MT cluster that would correspond to MST. Third, movies showing marmoset grasping action evoked signals in a further large region that extended ventrally and rostrally from the one evoked by the moving random dots. We observed an additional distinct area rostral and ventral to the FSTd that would correspond to FSTv. Finally, we confirmed that the evoked optical signals reflected cell responses using multi-unit recording. Thus, we conclude that OISI is an optimal tool to visualize multiple areas in the STS on the lissencephalic cortical surface of marmosets. By identifying multiple STS areas *in vivo* with OISI, we will be able to advance the study in the STS to understand hierarchical information processing for integration between dorsal and ventral pathways.

Disclosures: W. Suzuki: None. **T. Tani:** None. **T. Banno:** None. **N. Miyakawa:** None. **H. Abe:** None. **T. Hayami:** None. **N. Ichinohe:** None.

Poster

800. Extrastriate Cortex II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 800.02/AA4

Topic: D.06. Vision

Support: NIH R01 EY-008128 (YC)

NIH R01 EY-003611 (ES)

NIH CORE EY-00

Title: Spiking irregularity in V2 neurons of amblyopic monkeys

Authors: *Y. WANG[1], B. ZHANG[2], X. TAO[3], G. SHEN[3], E. L. SMITH, III[1], Y. M. CHINO[1]; [1]Col. of Optometry, Univ. of Houston, Houston, TX; [2]Col. of Optometry, Nova Southeastern Univ., Fort Lauderdale, FL; [3]Baylor Col. of Med., Houston, TX

Abstract: Experiencing interocular decorrelation of cortical inputs early in life can cause compromised binocular vision and often amblyopia, a developmental disorder of spatial vision. According to recent perceptual studies, abnormally enhanced ‘noise’ in the visual system is thought to prevent amblyopic humans from reliably discriminating visual stimuli. However, the

neural basis for such high-level of noise in amblyopes is not known. By using established optical means we created macaque models of anisometropic amblyopia exhibiting a range of visual deficits (e.g., amblyopia index of 0.3-0.8). We recorded from a population of neurons in visual area V2 of anesthetized monkeys. We quantified the spiking noise (variability) in response to brief (640 ms) sine wave gratings that were optimized for orientation and spatial frequency for each unit and varied for contrast between 5% and 80%. To assess spiking noise, we quantified the *spiking irregularity* by calculating the square of the coefficient of variation (CV^2) and the *trial-to-trial variability* of the spike count by calculating the mean-matched Fano factor (FF) for individual neurons. We found: 1) Average spike count was significant higher in amblyopes only at high contrast (50-80%). 2) Spike count dynamics was abnormal in that the onset latency was shorter and the response decay following the transient discharge was delayed or absent in amblyopic neurons. 3) Average operational CV^2 was significantly higher in amblyopes only at high contrast. 4) Average mean-matched FF was 'normal' in amblyopic V2 neurons at high contrasts while significantly elevated at lower contrasts (10-25%). 5) Average CV^2 of individual monkeys were well correlated with their depth of amblyopia (amblyopia index). 6) However, the average mean-matched FF of individual monkeys were not well correlated with their amblyopia index values. 7) Importantly, the average CV^2 of individual monkeys, but not mean-matched FF, was highly correlated with the prevalence of binocularly suppressive neurons. These results suggest that the increased spiking irregularity (CV^2) and spike count dynamics, linked to a high level of binocular suppression in V1 and V2, adversely affect the information processing in V2 and presumably, visual areas downstream from V2. We conclude that the observed spiking irregularities in V2 may be involved, at least in part, with reducing the visual performance of amblyopic monkeys in simple or complex visual tasks.

Disclosures: **Y. Wang:** None. **B. Zhang:** None. **X. Tao:** None. **G. Shen:** None. **E.L. Smith:** None. **Y.M. Chino:** None.

Poster

800. Extrastriate Cortex II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 800.03/AA5

Topic: D.06. Vision

Support: FWO

IUAP

PF

HBP

Title: In-vivo visualization of myelin, color- and disparity-biased stripes in monkey area v2 using sub-mm resolution (f)mri at 3 tesla

Authors: *X. LI[1], J. ARSENAULT[1,2], T. JANSSENS[1], Q. ZHU[1], W. VANDUFFEL[1,2,3]; [1]Res. Group Neurophysiology, KU Leuven, Leuven, Belgium; [2]A. A. Martinos Ctr. for Biomed. Imaging, MGH, Charlestown, MA; [3]Dept. of Radiology, Harvard Med. Sch., Boston, MA

Abstract: Cytochrome oxidase stainings revealed three types of stripes in macaque and human area V2. The widths of these stripes are roughly 1 - 1.5 mm in macaque and 2.5 - 3.5 mm in human. Stripes of the same kind are seperated from each other by ~4 mm in macaque (Roe and Ts'o 1997) and ~7 mm in human (Nasr et al. 2016). Different functional properties are attributed to thin and thick dark stripes, for example based on separated color, direction, and disparity-selective cells (Chen et al. 2008, Tootell et al. 2004). Nevertheless, the stripes remain difficult to segregate using conventional fMRI due to their size. Recently, an fMRI study (Nasr et al. 2016) using high field (7T) and 1 mm isotropic voxels exquisitely revealed this stripe-like functional organization in human area V2. Here, we visualized the stripes in awake macaques using sub-mm resolution and conventional field fMRI (3T). We used the same isoluminant color and achromatic radial grating stimuli as in our previous double-label deoxyglucose study (Tootell et al. 2004) to detect the color-biased thin stripes. A size-matched binocular disparity defined radial sine-wave grating and its monocular counterpart was used to activate the disparity-biased stripes. Furthermore, myelination density mapping using T1- and T2-weighted MRI with 0.4 mm isotropic voxel size was acquired in an attempt to visualize the pale stripes which are more myelinated compared to thin and thick stripes (Horton and Hocking 1997). During the functional scans, monkeys fixated at the center of the stimulus. Contrast-enhanced fMRI data with 0.6 mm isotropic voxels (EPI, TR 3 s) was acquired using implanted phased-array receive coils developed in our lab (Janssens et al. 2012). To minimize image artifacts caused by monkey motion, several image processing algorithms were implemented, including an optimized GRAPPA algorithm for image reconstruction (Hoge et al. 2009), a B-spline grid based nonlinear registration algorithm for EPI to EPI distortion correction and a fieldmap-based distortion correction algorithm for EPI to structue registration. Finally, a GLM denoising algorithm (Kay et al. 2013) was used to reduce physiological and other nuisance noise in the temporal domain. We found stripe-like color activations interdigitated with disparity activations in retinotopically-defined area V2, which are reproducible across monkeys and across scan sessions of the same monkeys. Furthermore, we observed higher myelinated stripes largely separated from color- and disparity-selective stripes. These results show that high-resolution 3T fMRI can be reliably used to study in-vivo submillimeter-scale functional organizations of the primate brain.

Disclosures: X. Li: None. **J. Arsenault:** None. **T. Janssens:** None. **Q. Zhu:** None. **W. Vanduffel:** None.

Poster

800. Extrastriate Cortex II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 800.04/AA6

Topic: D.06. Vision

Support: NIH Grant EY23952

Mahoney Postdoctoral Fellow

Title: A retinotopic proto-organization in IT present at birth

Authors: *M. J. ARCARO, J. L. VINCENT, P. SCHADE, K. SRIHASAM, M. S. LIVINGSTONE;
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Abstract: In adult primates, inferior temporal cortex (IT) is subdivided into domains selectively responsive to particular categories, such as bodies, places, and faces. Notably, the locations of these domains are consistent across individuals, suggesting a common constraint on their development. Recent experiments from our lab demonstrated that novel domains could be formed in IT of juvenile monkeys in response to intensive experience (Srihasam et al. 2014). The locations of these training-induced domains were also consistent across individuals and depended on the stimulus set, not on the degree of expertise or the symbols' functionality. Taken together, these data suggest that a pre-existing, "proto-" organization in IT guides and constrains the spatial organization of developing domains.

To look for any such proto-organization, we imaged monkeys longitudinally starting as early as 1-week through two years of age. Previously, our lab found that visual responsiveness and category-selectivity in IT are not detectable with fMRI until several months of age (Vincent et al. 2015, SfN). While evoked responses were not detectable in newborns, it is possible that early functional organization of IT could be reflected in patterns of synchronous signal fluctuations. To identify the organization of IT in newborns, we used correlation analyses on data collected during resting states and while monkeys viewed static and dynamic images.

We observed significant correlations between IT cortex and primary visual cortex as early as 1-week of age. The correlations in IT were retinotopically organized, with the fovea of V1 most strongly correlated with the lower bank of the STS, and peripheral portions of V1 most strongly correlated with ventral portions of IT (as well as parietal cortex). The portions of IT that correlated at birth with the fovea of V1 later in development showed selectivity to foveal stimulation (vs. peripheral) and faces (vs. objects) in the same monkeys. Taken together, these results suggest that a retinotopic organization of IT is present at birth (if not beforehand), and may provide the scaffolding for functional domain development in IT.

Disclosures: **M.J. Arcaro:** None. **J.L. Vincent:** None. **P. Schade:** None. **K. Srihasam:** None. **M.S. Livingstone:** None.

Poster

800. Extrastriate Cortex II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 800.05/AA7

Topic: D.06. Vision

Support: NSERC Discovery Grant

Title: Convolutional network modeling of the primate dorsal and ventral visual streams

Authors: *B. P. TRIPP;
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Abstract: Convolutional neural networks (LeCun et al., 1990, NIPS) are a kind of artificial neural network that has a number of parallels with the primate visual cortex. These include deep structures with retinotopic connections, in which abstract representations emerge in later stages. Notably, in addition to structural similarities, convolutional networks perform as well as humans in object recognition in natural scenes. Furthermore, convolutional networks trained for object recognition have been found to predict activity in the inferotemporal cortex and V4 (Yamins et al., 2014, PNAS). Similar networks also perform well in depth and optic flow estimation, and other visual tasks. Convolutional networks also differ from the visual cortex in important ways, for example they have traditionally lacked recurrent connections and attention mechanisms. However, such details have been incorporated in more recent networks. The “dropout” regularization method, which is very effective in these networks, is on a continuum with Poisson spike variability. Also, importantly, there is growing hardware and software support for fast simulation of very large convolutional networks. For these reasons, convolutional networks may serve as a good starting point for large, integrated models of the whole visual cortex. A preliminary attempt to develop such a model will be presented. The model approximates the structure of a large network that includes multiple early, dorsal, and ventral visual areas. It exhibits features of neural activity in each of these areas, and performs a variety of visual processing, including estimation of self-motion and grasp affordances.

Disclosures: **B.P. Tripp:** None.

Poster

800. Extrastriate Cortex II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 800.06/AA8

Topic: D.06. Vision

Support: National Natural Science Foundation of China (31571078)

Title: Revealing Details: spatial-frequency selective domains for a coarse-to-fine processing in macaque V4

Authors: *Y. LU[1], J. YIN[1], Z. CHEN[1,2], Y. LIU[1,2], H. GONG[1,2], L. QIAN[1], X. LI[1], I. M. ANDOLINA[1], W. WANG[1];
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Abstract: Spatial vision is critical for primates to see effortlessly. One seemingly paradox in the primate ventral stream concerns the increasing complexity of encoded features while spatial frequency (SF) selectivity decreases drastically along the hierarchy. However this inconsistency does not appear to affect our sight, because at the highest levels of the ventral stream neurons are capable of invariantly encoding complex patterns or figures with high spatial resolution. Straddling a unique position along the ventral stream, how does V4 serve as a connecting link between the preceding and the following processing stages for spatial vision? Combing simultaneously intrinsic-signal optical imaging of V1, V2, and V4, anatomical CTb injections and electrophysiological neuronal recordings in awake macaques, here we discovered that neurons with low and high SF preferences clustered into columns in V4 but not in V1 and V2. These isolated high SF preference domains (SFPD) were surrounded by numerous low SFPD. CTb injections in V4 showed that neural projections to high SFPD come not only from V2 but also from V1, suggesting an extra spatial integration directly from primary visual cortex. Neuronal responses within the high SFPD favored local features, whereas those within low SFPD signaled the orientation of global patterns. By analyzing response latency, we found neurons located in high SFPD (SF≥4c/d) responded substantially later than those in low SFPDs (SF≤1.5c/d) to their preferred SF (60.3±5.8ms versus 50.7±7.2ms, N=186 versus N=198, $P<0.001$, t-Test). This suggests a non-parallel spatial analysis by neurons in low and high SF channels, supporting a role in coarse-to-fine (global ⇨ local) processing occurring at this intermediate processing stage of the ventral stream. Our findings demonstrate an unexpected columnar organization of neurons with low and high SF preferences in macaque V4. The differential processing of local and global patterns at different spatial scales with different processing time windows across these domains shed light on spatial analysis along the visual hierarchy, and helps us to better understand the integration of local spatial features into global representations.

Disclosures: **Y. Lu:** None. **J. Yin:** None. **Z. Chen:** None. **Y. Liu:** None. **H. Gong:** None. **L. Qian:** None. **X. Li:** None. **I.M. Andolina:** None. **W. Wang:** None.

Poster

800. Extrastriate Cortex II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 800.07/AA9

Topic: D.06. Vision

Support: NHMRC AUSTRALIA

Title: Feedback signals from higher-order visual cortex affect spike-responses of neurons in the 'intermediate' area in the pattern-processing stream

Authors: ***J. Y. HUANG**[1], C. WANG[2], B. DREHER[2];
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Abstract: In domestic cat, a subset of neurons in the postero-temporal visual (PTV) cortex - a higher-order pattern/form-processing area sends direct 'feedback' projection to the ipsilateral cytoarchitectonic area 19 (area V3). Reversible inactivation of PTV achieved by cooling it to 10°C, silences spike-activity of neurons in the area - no feedback signals to area 19. In anesthetized and immobilized cats, the background spike-activities and spike-responses to visual stimuli of single area 19 neurons were recorded extracellularly before, during cooling and after rewarming of ipsilateral PTV to physiological temperature. Transient inactivation by cooling of PTV very rarely resulted in significant reductions in background spike-activity of area 19 cells. By contrast, in a substantial proportion of area 19 neurons, transient inactivation of PTV resulted in: i) significant reversible changes in peak magnitude of spike-responses to visual stimuli (35.5%; 10/28); ii) substantial reversible changes in their direction selectivity indices (43%; 12/28) and iii) reversible, upward shifts in their preferred stimulus velocities (37%; 7/19). However, substantial ($\geq 15^{\circ}$) shifts in preferred orientation and/or substantial ($\geq 20^{\circ}$) changes in width of orientation tuning curves were less common (26.5%; 4/15). Thus, higher-order pattern/form-processing visual cortical signals tend to play an important role in determining the spike-responses and some 'motion-related' receptive field properties of a proportion of neurons in area 19 - an 'intermediate' form-processing visual area.

Disclosures: **J.Y. Huang:** None. **C. Wang:** None. **B. Dreher:** None.

Poster

800. Extrastriate Cortex II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 800.08/AA10

Topic: D.06. Vision

Support: HHMI

Title: Interactions between macaque retinotopic areas and IT for segmenting and recognizing objects in a visual scene

Authors: *J. K. HESSE, D. Y. TSAO;
Biol., Caltech, Pasadena, CA

Abstract: Segmentation of the visual scene and recognition of the objects therein are two interdependent problems that are hard to solve separately from each other. When trying to segment a scene, it is helpful to already know the present objects and their shapes. However, for recognizing an object in clutter, one would like to consider its isolated segment alone to not get confounded by features of other objects.
Using fMRI in macaque IT we found that segmenting the scene is indeed crucial for successful recognition: By changing the texture of an occluder we controlled the segmentability of a face stimulus while keeping the features of the face identical and found that responses in face patches drop significantly when the face is rendered unsegmentable.
To study the interaction between recognition and segmentation, we next looked for areas involved in segmentation. Presenting stimuli containing distinct figures defined by luminance, texture, motion or disparity revealed a set of distinct patches in retinotopic areas that were activated significantly more by the figure stimuli than by their respective background control stimuli. We targeted these different patches with multi-site electrophysiological recordings to compare their information about figure-ground segmentation by presenting figure stimuli across multiple positions and trying to decode from neuronal responses whether different regions of the scene belong to a figure, background or a border belonging to either side of a figure.
The different levels of figure-ground information encoded in each patch indicate to which extent different retinotopic areas are involved in segmentation and may thereby aid recognition in IT.

Disclosures: **J.K. Hesse:** A. Employment/Salary (full or part-time): HHMI. **D.Y. Tsao:** A. Employment/Salary (full or part-time): HHMI Fellow.

Poster

800. Extrastriate Cortex II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 800.09/AA11

Topic: D.06. Vision

Support: DFG Emmy Noether Grant 2806

Title: Theta-rhythmic spiking of visual cortical area V4 neurons arises from receptive field center-surround interactions

Authors: *R. KIENITZ[1], J. T. SCHMIEDT[1], K. A. SHAPCOTT[1], K. KOUROUPAKI[1], M. C. SCHMID[2];
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Abstract: Rhythmic modulation of neural activity is an important aspect of brain function. However the generative mechanisms underlying many brain rhythms in the awake state are not fully understood. A study by Rollenhagen et al. (2005) had shown that theta (~4 Hz) rhythmic spiking in inferotemporal cortex (IT) may result from a finely tuned balance of excitation and inhibition between two neural populations representing separate visual objects. In cortical area V4, we recently found that theta (~4 Hz) rhythmic spiking is elicited by the presentation of a Kanizsa illusion, when illusion inducing stimuli were positioned around the neuron's receptive field (RF) center (Cox et al., 2013). The aim of our present study was to test whether rhythmic theta spiking in V4 can be explained by interactions between the excitatory RF center and its inhibitory surround.
To this end we recorded multi-unit activity (MUA) and local field potential (LFP) using chronically implanted "Utah" arrays in area V4 of two awake macaque monkeys performing passive viewing tasks.
As a first step we assessed the extent of the RF center and surround subregions by increasing simple visual stimuli in size up to ~7° diameter. As expected, enlargement of a black disc (gray background) up to an optimal size (~2-3°) resulted in elevated firing rates while further increase reduced the neuronal firing again (normalization), likely due to an increasing inhibitory drive from the neuron's suppressive surround (e.g. Desimone, Schein, 1987). Under these conditions with a single homogeneous stimulus no rhythm emerged. However, when we stimulated the neuron's center and surround independently using two spatially separated and simultaneously presented stimuli (e.g. a 2° disc and a 6° annulus separated by a gap at 4°), neurons started to engage in ~4 Hz rhythmic spiking. Similarly, theta spiking was also observed for single large stimuli, when a black center was accompanied by a white surround, or vice versa (gray background).

Finally, taking advantage of the array's spatial coverage, we positioned two smaller stimuli such that each of them stimulated the center of one and the surround of the other neuronal population, respectively. We found that temporary excitation of one group was accompanied by inhibition of the other group, yielding two populations of neurons oscillating in an anti-phase theta rhythm. Taken together, we found that spiking activity in extrastriate area V4 switches from a tonic to a 4-5 Hz rhythmic firing mode during the presentation of multiple or heterogeneous visual stimuli. This can be explained by inhibitory center-surround interactions.
Support: DFG Emmy Noether Grant 2806

Disclosures: **R. Kienitz:** None. **J.T. Schmiedt:** None. **K.A. Shapcott:** None. **K. Kouroupaki:** None. **M.C. Schmid:** None.

Poster

800. Extrastriate Cortex II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 800.10/AA12

Topic: D.06. Vision

Support: FWO

IUAP

PF

European Community FP7/2007-2013 PITN-GA-2008-290011 (ABC)

Title: Effect of adapter duration on repetition suppression in macaque inferior temporal cortex.

Authors: ***P. KURAVI**, R. VOGELS;
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Abstract: Repetition suppression, the attenuation of neural activity for a repeated visual stimulus, is a well-known phenomenon in the inferior temporal (IT) cortex of the rhesus monkey. A previous adaptation study of primary visual cortex, V1, suggests that prolonged exposure to the adapter stimuli strengthens the adaptation effect in comparison to a brief exposure of the same stimuli. Here we investigate whether this property of V1 neurons prevails in macaque IT, an area hierarchically at a higher stage. To determine this we presented an adapter stimulus for durations ranging between 300 and 3000ms followed by a test stimulus of 300ms, with an interstimulus interval of 300ms. Single units were recorded from the rostral lower bank of the superior temporal sulcus during passive fixation. Two stimuli (A, B) were selected from a set of

52 images of various object categories, based on their response strength. These stimuli were either presented in repetition trials, i.e. repetition of the same stimulus (AA, BB), or in alternation trials, i.e. alternation of the stimuli (AB, BA). Our data show repetition suppression for both the short (300ms; $p < 0.0001$, 60 units) and long adapter durations (3000ms; $p< 0.0001$, 60 units). However, in contrast to V1, the degree of repetition suppression did not differ significantly between adapter durations (300 vs. 3000ms, n.s., 60 units). To examine whether the repetition suppression effect in IT was inherited from early visual areas, we performed an independent set of recordings where the adapter (300 or 3000ms duration) and test stimuli were presented either at the same or different locations, above or below the fixation dot, at an eccentricity of 5 visual degrees. We observed a significant repetition suppression effect for both adapter durations when test and adapter stimuli were presented either at the same or a different location ($p's < 0.001$, 38 units). The suppression effect didn't differ between 300 and 3000ms adapter durations when presented at the same or at a different location (n.s, 38 units). As a control, we performed additional single and multi-unit recordings where an adapter of 300ms was repeated 7 times with an interstimulus interval of 150ms (multiple adapter condition), followed by a 300 ms test stimulis, in addition to single 300 and 3000ms adapters (as above). We found that the multiple adapter showed the strongest suppression effect ($p < 0.0001$, 41 single units and $p < 0.0001$, 37 multiunits) although the stimulus exposure duration (adapter, 7 * 300 = 2100ms) was less than that of the 3000ms adapter condition. These surprising data constrain computational models of stimulus selective adaptation in IT (see Giese et al., SFN abstracts, 2016).

Disclosures: P. Kuravi: None. **R. Vogels:** None.

Poster

800. Extrastriate Cortex II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 800.11/AA13

Topic: D.06. Vision

Support: nIH 1R01EY02391501A1

Title: A cross-validated cytoarchitectonic atlas of the human ventral stream

Authors: *M. ROSENKE[1], K. S. WEINER[1], M. BARNETT[1], M. FROST[2], K. ZILLES[3,4], K. AMUNTS[4,5], R. GOEBEL[2,6], K. GRILL-SPECTOR[1,7];
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Abstract: Eight cytoarchitectonic regions (cROIs) have been identified in the human ventral stream extending from primary visual cortex to higher visual areas (Amunts et al., 2000; Rottschy et al., 2007, Caspers et al., 2013; Lorenz et al., 2015). Four areas are located in occipital cortex (hOc1, hOc2, hOc3v, hOc4v) and four areas are located on the fusiform gyrus (FG; FG1-FG4). Based on these cytoarchitectonic delineations, the goal of the present study is to create a cross-validated cytoarchitectonic atlas of the human ventral stream. To do so, each of the eight cROIs was projected to the cortical surface of each subject's brain, from which we generated a group map of each cROI by transforming individual subjects' cROIs into a common anatomical space. We tested three types of alignments: (1) volume-based alignment to the MNI template, (2) cortex-based alignment (CBA) to the Freesurfer average brain (CBAfs), and (3) CBA to the group average of the nine postmortem brains (CBApm). Across alignment techniques, we compared (1) the consistency of a cROI averaged across subjects and (2) the ability to predict the location and spatial extent of a cROI in a new subject. Results show that group cROIs generated using CBAfs or CBApm have higher across-subject consistency and higher predictability compared to volume alignment ($F(2,13) = 80.4$, $p < .001$; average predictabilities: MNI: .21.11, CBApm: .54, CBAfs: .55). However, there were no significant differences across CBAfs and CBApm. Additionally, while the group hOc1 showed the highest between-subjects consistency and predictability, FG cROIs did not show lower consistency or predictability compared to occipital cROIs hOc2-hOc4v. Addition of other anatomical landmarks to the CBA further improved the group cROIs: (1) Adding the collateral sulcus increased the between-subject consistency of FG1 and FG3 ($p<.001$) and (2) adding the anterior tip of the mid-fusiform sulcus reduced inter-subject variability of the FG3/4 boundary ($p<.001$). Overall, these results suggest that CBA generates more accurate atlases of the cytoarchitectonic structure of the ventral stream by preserving the location of cROIs relative to the cortical folding. This atlas will be freely available and can be used to compare functional activations in typical and atypical populations to cytoarchitectonic partitions.

Disclosures: **M. Rosenke:** None. **K.S. Weiner:** None. **M. Barnett:** None. **M. Frost:** None. **K. Zilles:** None. **K. Amunts:** None. **R. Goebel:** None. **K. Grill-Spector:** None.

Poster

800. Extrastriate Cortex II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 800.12/AA14

Topic: D.06. Vision

Support: ECOR 2015A051305

NIH 5P41-EB-015896-17

Title: Impact of visual cortico-striatal loop disruption on neural processing within the parahippocampal place area

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Abstract: Visual perception is often considered as the product of a multi-stage feedforward neural processing in which visual information is relayed from thalamus to the early visual areas and then to a sequence of higher, more selective visual regions within the temporal visual cortex. However, this neural processing is not purely feedforward. Rather, neuroanatomical studies in non-human primates (NHPs) have shown that almost all visual regions project back to striatum (mainly to caudate nucleus), which is connected to thalamus and together generate the Visual Cortico-Striatal Loop (VCSL). Despite perceptual and navigation impairments in patients with striatum atrophy (e.g. in Huntington's disease (HD)), the relevance of VCSL on cortical visual processing is not fully understood. In this study, we examined the contribution of VCSL on visual processing using fMRI and behavioral tests in healthy controls and HD patients. Experiment 1 (n=31), tested the level of functionally connectivity between caudate and temporal visual areas. Results showed a significantly stronger functional connection between caudate and the Parahippocampal Place Area (PPA) compared to other visual areas including V1, FFA and RSC ($p<0.05$). Experiment 2 (n=43) tested visual stimulus selectivity of caudate. Consistent with its functional connection to PPA, caudate showed a scene-selective response. Experiment 3 tested the impact of VCSL disruption on neural processes within PPA. We found that in HD patients (n=16), compared to healthy matched controls (n=18), scene-selective activity in PPA was reduced significantly ($p<0.0001$). This impairment was more prominent in the portion of PPA that showed a stronger functional connection to caudate. In contrast to PPA, the level of face-selective activity in Fusiform Face Area (FFA) and Amygdala remained intact between HD patients and controls. In behavioral level, consistent with decrease in PPA selective response, HD patients (n=12) compared to controls (n=12) showed a lower shape comparison performance for houses and simple objects. In contrast, we did not find a significant difference between spatial comparison performance of HD patients and controls ($p=0.11$). These results suggest a direct impact of VCSL on perceptual categorization and generation of 'selective' activity within PPA. These findings also broaden our understanding of neurodegenerative disorders (e.g. Huntington's, Alzheimer's and Parkinson's diseases) in which caudate degeneration has been shown.

Disclosures: **S. Nasr:** None. **H.D. Rosas:** None.

Poster

800. Extrastriate Cortex II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 800.13/AA15

Topic: D.06. Vision

Support: NIH Grant EY001778

NIH Grant EY008126

NIH Grant EY025422

NIH Grant EY007135

NIH Grant HD015052

Title: Does the dorsal medial visual area represent a unique target of the koniocellular pathway?

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Abstract: The primate visual system exhibits a well-studied division of labor whereby projections from the lateral geniculate nucleus (LGN) terminate in separate compartments of primary visual cortex (V1) with the parvocellular (P) pathway synapsing in the ventral tier of layer 4, the magnocellular (M) pathway terminating in the dorsal tier of layer 4, and the koniocellular (K) pathway synapsing in the cytochrome oxidase (CO) blobs of layer 3B. Even after V1, the M and P pathways appear to differentially extend to extrastriate visual areas with the P pathway targeting the second visual area (V2) and the M pathway predominately acting on the Middle Temporal (MT) visual area (Casagrande & Kaas, 1994). These differences offer clues concerning the role of different extrastriate areas. With this in mind and given that various hypotheses have been put forward about the role of the dorsal medial (DM) visual areas (Rosa et al., 2009), we asked whether the projections to DM, the likely homologue of area V3a or V6 in macaques, are from a specific layer of V1. To reach this goal, we conducted a retrograde tracer study and examined the labeled cells in V1.
Area DM was anatomically identified in a population of bush babies and pressure injections of cholera toxin subunit B conjugated to 7nm colloidal gold (CTB-Au) were made at a depth of 100μm. Each subject received multiple 1μL injections placed 500-700μm apart covering the entirety of DM in one hemisphere. After a 3 day survival period, the animals were perfused and posterior cortex was flattened into a block that was sectioned tangentially into 50μm sections. Tissue slides were imaged, posterized, and divided into blob and interblob regions (Shipp &

Zeki, 1989). A computerized image quantification system was used to calculate the area of blob and interblob regions as well as to count the number of labeled cells occurring within these regions.
Results show that the labeled cells tightly correlate with CO blobs throughout the entirety of V1. This finding suggests that DM may be driven by input from the K pathway - at least in bush babies. It is noteworthy that although CO blobs are often considered uniquely composed of color selective cells, bush babies only have a single cone type resulting in color blindness. The presence of blobs in these animals can be explained by the hypothesis put forward by Allman & Zucker (1990) who proposed that CO blobs take a more generalized role in processing surface features which include color, texture, and contrast. This suggests that the K pathway could serve as the first step in surface context information that eventually drives area DM. More analysis is needed to further elucidate the functional role of this extrastriate area.

Disclosures: B. Moore: None. **J.D. Boyd:** None. **O.P. Roy:** None. **J.A. Mavity-Hudson:** None. **V.A. Casagrande:** None.

Poster

800. Extrastriate Cortex II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 800.14/AA16

Topic: D.06. Vision

Support: NEI 16941

DARPA 029182

Title: A deep convolutional energy model of V4 accurately predicts responses to natural movies

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Abstract: Area V4 is an important intermediate stage of visual processing. However, it has been very difficult to characterize and model the tuning properties of V4 neurons. For example, no current models of V4 neurons can accurately predict responses to natural images. This is in stark contrast to models of V1 and MT, where responses can be predicted well. V4 neurons have large, nonlinear receptive fields, and this makes it difficult to estimate their tuning properties using conventional methods; modeling V4 amounts to solving a high-dimensional non-linear regression problem with limited data.
To effectively attack this problem, we first sought to collect as much data as possible by

chronically implanting electrode arrays in area V4 of two macaque monkeys. Neurons were recorded while the awake animals viewed clips of large, full color natural movies. The chronic recordings were stable enough that neurons could often be held for several days. This allowed us to collect responses to hundreds of thousands (up to over 1 million) of distinct movie frames, for hundreds of different V4 neurons.
We then used several different neural network architectures to fit the data obtained from each V4 neuron. The training signals for each fit neural network were the stimulus movie and the response from one neuron. The most successful neural network architecture that we tested was one that combined insights from the cortical magnification factor, the Adelson-Bergen energy model, the scattering transform and deep convolutional neural networks. We call this the deep convolutional energy model. This model is simple and interpretable, and it predicts V4 responses significantly better than previous models. The predictions of deep convolutional energy models fit to V4 neurons stimulated with natural movies approach the prediction performance of the best current models of V1 and MT neurons. The models trained on natural movies also accurately predict V4 responses to various types of synthetic stimuli similar to those used in previous studies of V4. Finally, the trained V4 models can also be used to generate optimal stimuli for each neuron, which provides important insights about the representation of visual information in area V4.

Disclosures: **M.D. Oliver:** None. **J. Gallant:** None.

Poster

800. Extrastriate Cortex II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 800.15/AA17

Topic: D.06. Vision

Support: NSF GDE-114747

NIH Grant 1RO1EY02231801A1

NIH Grant 1R01EY02391501A1

Title: Proliferation of macromolecular tissue in human cortex underlies development of face processing

Authors: *J. GOMEZ[1], M. BARNETT[1], V. NATU[1], A. MEZER[2], K. S. WEINER[1], K. AMUNTS[3], K. ZILLES[4], K. GRILL-SPECTOR[1];
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Abstract: Computations performed by a given cortical region are a product of its underlying cytoarchitecture and likely sculpted through development. Yet, how does cortical tissue change as brain function and behavior improve from childhood to adulthood? Human high-level visual cortex, with its prolonged development and causal role in perception, provides an ideal test bed to answer this question. We employ novel quantitative magnetic resonance imaging (qMRI) to quantify the volume and composition of brain tissue, such as the lipids and cholesterol in cell walls, dendrites, and myelin (measured through proton relaxation time: T1, and macromolecular tissue volume: MTV). Combining qMRI, functional MRI, and visual recognition behavior in a large sample of children (n=26, 5-12 years old) and adults (n=26, 22-28 years old), we make unprecedented measurements of the tripartite relationship between structure, function, and behavior in the developing brain. We find differential development of ventral high-level visual areas involved in face and place recognition, where development of face-selective regions (red in Fig. 1), but not place-selective regions (yellow in Fig. 1), is predominated by lowered T1, which is indicative of macromolecular tissue proliferation. These anatomical developments are correlated with specific increases in functional selectivity to faces in face-selective regions (Fig. 1B) as well as improvements in face recognition ability (Fig. 1C). Ultimately, this development leads to differentiated tissue properties between face- and place-selective regions in adulthood, which we validate with postmortem cytoarchitectonic measurements in independent brains. These results suggest a rethinking of fine-grained anatomical development of cortex, as macromolecular tissue proliferation implicates a different neural mechanism of development during childhood than infancy pruning. We offer a new model by which behavior emerges from an interplay between structural and functional changes in the cortex.

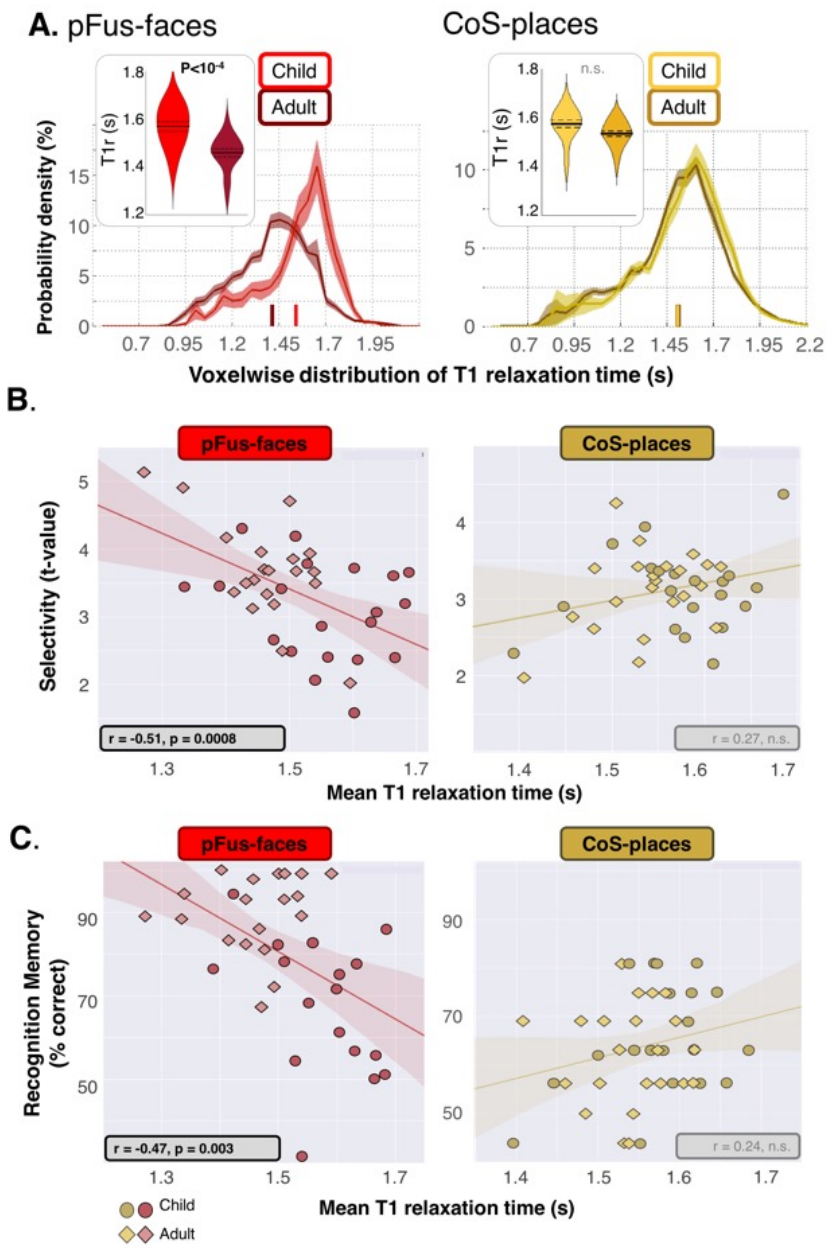

Figure 1: Proliferation of cortical tissue in face-selective regions impacts function and behavior. **(A)** T1 relaxation times averaged within a region of interest (inset violin plots) or shown as voxelwide distributions across subjects (lower curves, shaded region is standard error), for either a face-selective region on the posterior fusiform gyrus (pFus-faces, red) or a place-selective region in the collateral sulcus (CoS-places, yellow). Data are averaged across 20 children and 20 adults for pFus-faces and 20 children and 22 adults for CoS-places. **(B)** *Left:* pFus-faces mean t-values for the contrast faces versus all other stimuli plotted against pFus-faces mean T1 relaxation time. Each point is a subject (circles: children; diamonds: adults. Line of best fit plotted with 95% confidence obtained from bootstrapping. *Right:* same as left, but for places vs. other stimuli in CoS-places. **(C)** *Left:* face recognition memory vs. pFus-faces mean T1 relaxation. *Right:* place recognition memory vs. CoS-places mean T1 relaxation time.

Disclosures: **J. Gomez:** None. **M. Barnett:** None. **V. Natu:** None. **A. Mezer:** None. **K.S. Weiner:** None. **K. Amunts:** None. **K. Zilles:** None. **K. Grill-Spector:** None.

Poster

800. Extrastriate Cortex II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 800.16/AA18

Topic: D.06. Vision

Support: NIH Grant EY008128

NIH Grant EY003611

NEI Grant EY007551

MEXT Grant KAKENHI 22135006

MEXT Grant 15H05921

Title: Sensitivity of v2 neurons to curvatures in infant monkeys

Authors: ***B. ZHANG**[1], Y. WANG[2], X. TAO[2], G. SHEN[2], E. L. SMITH, III[2], I. OHZAWA[3], Y. CHINO[2];
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Abstract: Non-human primates can discriminate texture-defined form as early as 6-8 weeks of age despite their relatively low visual acuity. The sensitivity to texture-defined form is influenced by the ability to extract the appropriate image properties, to integrate these properties, and to segment the shape that is represented. The neuronal mechanisms underlying this remarkable visual capacity of infant primates have not been extensively studied. In adult monkeys, neurons in 'extrastriate visual areas are thought to act as "integrators" of local stimulus information that is processed by V1. As a result, V2 and in particular, V4 neurons become sensitive to angled contours that make up critical aspects of global shape by efficiently linking local feature information. Our previous developmental study on the receptive-field subunits of V2 neurons (Zhang et al, 2013) implied that V2 neurons in infant monkeys can encode angles or curvatures. In this study we tested this idea more directly by using two-dimensional dynamic noise stimuli and a new analytical method called "Transform Domain Reverse Correlation (TDRC)", which computes spike-triggered average of stimuli after transforming them into curvature domain. The resulting map reveals the stimulus selectivity of individual neurons for angled or curved contours. Unit recordings were made in V2 of anesthetized infant macaque monkeys (4, 8, and 16 weeks) and adult monkeys. We found: 1) Signal strength and reliability (Zmax) for infant neurons were not significantly different from that for adults. 2) The optimal curvature tuning widths were similar in infants and adults. 3) The variance of curvatures of subunits for infant monkeys was lower in infants than in adults. 4) There was no bias in optimal

curvature direction in any age group, and 5) Most importantly, the percentage of neurons that were sensitive to curvatures was similar in infants and adults. The results suggest that as early as 4 weeks of age, about 40% of V2 neurons in non-human primates are sensitive to angled or curved contours in image sub-regions. Our results provide a physiological substrate for the aforementioned perceptual finding that infant monkeys are capable of discriminating texture-defined visual borders as early as 6 weeks of age (El-Shamayleh et al, 2011) and that human infants can detect texture-defined patterns as early as 3-5 months of age (roughly equivalent to 3-5 weeks in non-human primates)(Norcia et al, 2005; Sireteanau et al, 2005).

Disclosures: **B. Zhang:** None. **Y. Wang:** None. **X. Tao:** None. **G. Shen:** None. **E.L. Smith:** None. **I. Ohzawa:** None. **Y. Chino:** None.

Poster

801. Representation of Objects and Scenes

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 801.01/BB1

Topic: D.06. Vision

Support: Hyde Fellowship

Title: Neural mechanisms for visual object detection in *Drosophila*

Authors: *M. KELES, M. A. FRYE;
UCLA, Los Angeles, CA

Abstract: A visual object is perceptually distinguished from the moving visual surround by optical disparities such as relative motion, size, texture, and brightness. Visual circuits must implement the parametric detection of these cues. Although the neural circuitry for motion vision is well studied in the mammalian retina and the fruit fly optic lobe, the neural mechanisms for object detection are not well resolved in either system. Behavioral analysis in *Drosophila* reveals robust visual perception of salient objects such as conspecifics and landscape features. Neurogenetic and physiological experiments have recently demonstrated that the neural circuits for motion vision that supply the lobula plate of the optic lobe are dispensable for intact object vision, indicating a separate neural pathway. Using 2-photon GCaMP imaging, we hypothesized that neurons in the lobula compartment of the optic lobe are selective object detectors. To test this hypothesis we have investigated a specific class of lobula columnar neuron, LC-11. We show that LC11 dendrites and axons respond only to the motion of small, solid, high-contrast objects, with little or no responses to elongated bars or panoramic gratings. We show that the receptive field of each cell in the columnar palisade is tuned to an object subtending 8-degrees

with suboptimal yet robust activation of an object subtending less than one inter-receptor angle, and is activated by non-directional motion of a dark object within its 20-degree functional receptive field (1/3rd the size of the anatomical receptive field). Blocking inhibitory ionic currents with PTX abolishes object selectivity and releases responses to large moving features and gratings. All LC11 axon terminals ramify within a compact glomerulus in the central brain, where retinotopy is lost. We suggest that strong activation of the LC11 glomerulus conveys the perception of a small object moving across the ipsilateral frontal eye. Future research will focus on the use of this information by downstream circuits.

Disclosures: M. Keles: None. **M.A. Frye:** None.

Poster

801. Representation of Objects and Scenes

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 801.02/BB2

Topic: D.06. Vision

Title: A fusion mechanism for depth cues in monkey MT?

Authors: *M. ARMENDARIZ[1], H. BAN[2,3], A. WELCHMAN[4], W. VANDUFFEL[1,5,6];
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Abstract: To reconstruct the third dimension from flat retinal images, the brain exploits a range of monocular and binocular depth cues. However, the neural mechanisms underlying cue integration is still poorly understood. Traditionally, this process has been broadly conceived in modular terms, with the independent processing of individual cues followed by a combination stage in which the influence of each cue reflects the reliability with which it is encoded. Computational and recent imaging studies in humans suggested the existence of a fusion mechanism that combines the information of different depth cues (Ban et al. 2012; Murphy et al. 2013). In particular, the latter studies showed, rather unexpectedly based on previous monkey research, that area V3B/KO may house neurons coding for a fusion mechanism of different depth cues. To investigate cue integration in monkeys using exactly the same paradigm as in Ban et al. (2012), we performed an equivalent fMRI study. Specifically, we showed monkeys a set of stimuli representing near or far depth planes defined by motion parallax, binocular disparity and the combination of both in either a congruent (i.e. the two cues signal the same depth planes) or incongruent fashion (i.e. the two cues signal different depth planes). We used a linear support

vector machine to classify between near and far patterns in retinotopically defined regions of interest (ROI) of visual cortex. To quantify differences in prediction accuracies across conditions and to assess fusion, we conducted three test for cue integration: integration index, congruent vs incongruent cues and transfer index (similar to Ban et al. 2012). We found that fMRI responses are more discriminable when the two cues signal depth concurrently, and that depth information provided by one cue might be diagnostic of depth indicated by the other. We revealed that monkey area MT shows fMRI signals consistent with a fusion mechanism of independent depth cues. In fact, these results may reconcile the human imaging data with previous monkey electrophysiological studies implicating area MT in depth perception based on motion and binocular disparity signals (Nadler et al. 2008; Nadler et al. 2013; DeAngelis et al. 1998). In general, our findings together with those obtained in humans provide evidence for a fusion mechanism for depth perception in the dorsal stream of primates. The fusion of depth cues, however, appears to be computed in different areas in humans (V3B/KO) and monkeys (MT). Therefore it is tempting to speculate that human V3B/KO may have been part of the MT cluster in an ancestor of monkeys and humans which has drifted in a caudo-dorsal direction during human evolution.

Disclosures: **M. Armendariz:** None. **H. Ban:** None. **A. Welchman:** None. **W. Vanduffel:** None.

Poster

801. Representation of Objects and Scenes

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 801.03/BB3

Topic: D.06. Vision

Support: R01-EY002966

R01-EY016281

ONRBAA08-019

Title: Neural representation of occluded objects in macaque V4

Authors: ***S. D. ZHU**[1], L. ZHANG[1], R. VON DER HEYDT[1,2];
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Abstract: In everyday vision objects often occlude one another from sight. Despite this erratic inflow of visual information, we perceive objects as permanent. Evidence from human and animal behavioral studies indicates that occluded objects are still represented in the brain, and

imaging studies found correlating activity in several cortical areas. Finding persistence of border ownership signals O'Herron & von der Heydt (Neuron 61;801-9, 2009) speculated that activity might persist in hypothetical "grouping cells" that link distributed features to objects. However, grouping cells have not been demonstrated and the neural mechanism of object permanence remains poorly understood. Here we searched for object-related activity in macaque V4, a candidate area for grouping cells. Monkeys performed a visual foraging task in which they sequentially fixated individual figures of an array of 10 figures in search for reward. The array was constructed so that, in most cases, fixating one figure would bring another figure into the receptive field (RF) of the neuron under study, in other cases, a region of uniform background. During the presentation of the array, a grating of parallel opaque stripes drifted over the array, variably occluding some figures, each for about 0.25s. To a human observer, the 10 objects appeared permanent despite the transitory occlusions. We measured the firing rates following the saccades that brought a figure into the RF during phases of visibility (VIS) and during phases of occlusion (OCC), and compared both with the activity following the saccades that brought no figure to the RF during the corresponding phases (NOF). The difference VIS-NOF is the representation of a visible object and the difference OCC-NOF is the representation of an occluded object ("permanence activity"). Note that this cannot be persistence of responses, because before these saccades the RF 'saw' the same random mix of stimuli in both OCC and NOF. We calculated a permanence index PERMI = (OCC-NOF)/(VIS-NOF). Preliminary results indicate that V4 cells show robust permanence activity (PERMI=0.53, SEM=0.08, N=40) whereas such activity is weak in cells of V1/V2 (PERMI=0.22, SEM=0.09, N=13). We conclude that V4 may contribute to the perceptual capacity for object permanence.

Disclosures: S.D. Zhu: None. **L. Zhang:** None. **R. von der Heydt:** None.

Poster

801. Representation of Objects and Scenes

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 801.04/BB4

Topic: D.06. Vision

Support: IRP

NIMH

NIH

DHHS

Title: Dual mechanisms of pattern completion in macaque identified by removal of visual area TE

Authors: *J. M. FREDERICKS, M. A. G. ELDRIDGE, K. A. LOWE, B. J. RICHMOND; NIMH, NIH, Germantown, MD

Abstract: Introduction: Bilateral removal of temporal lobe area TE causes impairments in discriminating categories and pairs of patterns. Here we explore whether monkeys with bilateral area TE removals are impaired in tests of pattern completion and figure-ground discrimination.
Methods: Three control monkeys and three monkeys with bilateral TE ablations were tested on a cat vs. dog categorization task comprising 440 unique stimuli per session. Monkeys were trained to touch a bar to initiate a trial, and release the bar during one of two intervals; early (signaled by a red central dot) if they identified the stimulus as cat, or late (signaled by a green central dot) if the stimulus was identified as dog. A correct response resulted in the delivery of a liquid reward, an incorrect response led to a time-out. Once the animals performed this simple categorization task we introduced visual noise.
Results: Monkeys were presented with interleaved trials of foreground and background noise (11 levels, from 0 - 100 %) that was generated by replacing randomly chosen stimulus pixels with a randomly chosen greyscale pixel. In the absence of noise, the performance of monkeys with TE removals was moderately degraded relative to that of controls. The presence of background noise did not further degrade the ability of the TE-lesioned monkeys to categorize stimuli, indicating that TE is not necessary for figure-ground discrimination as configured in this experiment. Increasing levels of foreground noise caused decreased accuracy of categorization in both experimental and control groups. As foreground noise increased from 0 - 40% noise, the performance of control and TE-lesioned monkeys degraded in parallel. Beyond 60% foreground noise, control monkey performance dropped abruptly becoming indistinguishable from that of monkeys with ablations; at 90% foreground noise both groups were performing at chance levels.
Discussion: Pattern completion appears to depend on two mechanisms. A TE-independent mechanism supports a basic ability to perform categorization at modest levels. A TE-dependent mechanism confers a substantial advantage at lower noise levels.

Disclosures: J.M. Fredericks: None. **M.A.G. Eldridge:** None. **K.A. Lowe:** None. **B.J. Richmond:** None.

Poster

801. Representation of Objects and Scenes

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 801.05/BB5

Topic: D.06. Vision

Title: Spiking neuronal network for optimal context integration in vision

Authors: ***J. LEE**[1], R. IYER[2], S. MIHALAS[2];
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Abstract: Neurons in the primary visual cortex (V1) predominantly respond to a patch of the visual input, their classical receptive field. These responses are modulated by the visual input in the surround. This reflects the fact that features in natural scenes do not occur in isolation: lines, surfaces are generally continuous. There is information about a visual patch in its surround. This information is assumed to be passed to a neuron in V1 by neighboring neurons via lateral connections. The relation between visual evoked responses and lateral connectivity has been recently measured in mouse V1. By combining natural scene statistics, mouse V1 neuron responses and their connectivity, we are interested in addressing the question: Given a set of natural scene statistics, what lateral connections would optimally integrate the cues from the classical receptive field with those from the surround?
First, we assumed a neural code: the firing rate of the neuron maps bijectively to the probability of the feature the neuron is representing to be in the presented image. We generated a database of features these neurons represent by constructing a parameterized set of models from V1 electrophysiological responses. We used the Berkeley Segmentation Dataset to compute the probabilities of co-occurrences of these features. We computed the relation between probabilities of feature co-occurrences and the synaptic weight which optimally integrates these features. The relation between evoked responses and connectivity which leads to optimal context integration is qualitatively similar to the measured one, but several additional predictions are made.
We implemented the predicted optimal connectivity in a spiking model of the visual processing in mouse. The network has the capacity to infer from context when presented with images with gaps. We hypothesize that this computation: optimal context integration is a general property of cortical circuits, and the rules constructed for mouse V1 generalize to other areas and species.

Disclosures: **J. Lee:** None. **R. Iyer:** None. **S. Mihalas:** None.

Poster

801. Representation of Objects and Scenes

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 801.06/BB6

Topic: D.06. Vision

Support: Wellcome Trust DBT India Alliance

Startup grant from IISc

Council for Scientific and Industrial Research

Ministry of Human Resource Development

International Brain Research Organisation

Title: Familiarity sculpts figure ground selectivity through inhibitory interactions in monkey inferotemporal cortex

Authors: *N. RATAN MURTY[1], S. P. ARUN[2];
[2]Ctr. for Neurosci., [1]Indian Inst. of Sci., Bangalore, India

Abstract: Contours in the visual world are inherently ambiguous, and are assigned to either side through a process known as figure-ground segmentation. In the high level visual areas responsible for recognition such as the inferior temporal cortex, neurons are sensitive to the outcome of figure-ground organization, implying that segmentation precedes recognition. But can recognition processes influence segmentation? To address this issue, we recorded extracellular neuronal responses from 116 visual neurons in the anterior inferior temporal cortex from 2 monkeys (60 from M1 and 56 from M2) that were familiarised in a counter-balanced fashion 1) to only one side 2) to both sides and 3) to neither side of arbitrary contours. We observed many more neurons that preferred the unfamiliar side over the familiar side of each contour. However, neurons that preferred the familiar side of the contour showed enhanced selectivity for the familiarised side during the early part of the visual response (50-150ms post stimulus onset). Both effects were present only when one side was familiar but not when both sides were familiar or unfamiliar. These effects were also specific to putative inhibitory but not putative excitatory neurons. Taken together, our results show that familiarity sculpts figure-ground selectivity through inhibitory interactions.

Disclosures: N. Ratan Murty: None. **S.P. Arun:** None.

Poster

801. Representation of Objects and Scenes

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 801.07/BB7

Topic: D.06. Vision

Support: EC Fp7-PEOPLE-2011-ITN PITN-GA-011-290011 (ABC), FP7-ICT-2013-FET-F/604102 (HBP), FP7-ICT-2013-10/611909 (Koroibot)

DFG GI 305/4-1 + KA 1258/15-1

Title: Neural model for stimulus-specific adaptation of neurons in area IT

Authors: *M. A. GIESE[1], P. KURAVI[2], R. VOGELS[2];
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Abstract: Many neurons in visual cortex show adaptation effects for repeated stimulation, providing a potential neural basis for repetition suppression effects in fMRI studies and high-level after-effects observed in behavioral studies. A variety of theoretical explanations has been discussed, which so far have been difficult to distinguish without detailed electrophysiological data. Recent electrophysiological data on the adaptation of shape-selective neurons in inferotemporal cortex (area IT) provides substantial constraints that narrow down the spectrum of possible computational mechanims. We propose a biophysically plausible neurodynamical model that reproduces these results. METHODS: Our model consists of a neural field (neural mass model), which models the population activity dynamics of shape-selective neurons in area IT, and integrates several adaptive mechanisms: (i) spike-rate adaptation; (ii) input fatigue adaptation, modeling adaptation in synaptic inputs and earlier levels of the visual hierarchy; (iii) a firing-rate fatigue mechanism that depends on the output firing rates of the neurons. RESULTS: The model reproduces the following experimental results: (i) Shape of typical PSTHs of IT neurons (Kaliukhovich & Vogels, Cereb. Cortex, 2011); (ii) temporal decay of adaptation with number of stimulus repetitions (Sawamura et al., Neuron, 2006); (iii) dependence of adaptation on effective and ineffective adaptor stimuli, which stimulate the neuron strongly or only moderately (deBaene & Vogels, Cereb. Cortex, 2011); (iv) dependence of the strength of the adaptation effect on the duration of the adaptor (see Kuravi & Vogels, SFN abstracts, 2016). All proposed mechanisms are necessary to account for the data. CONCLUSIONS: A mean field model that includes several physiologically plausible adaptive processes provides a unifying account for critical experimental observations on the adaptation of IT neurons.

Disclosures: **M.A. Giese:** None. **P. Kuravi:** None. **R. Vogels:** None.

Poster

801. Representation of Objects and Scenes

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 801.08/BB8

Topic: D.06. Vision

Support: Simons foundation grant ID# 325023

Conte (P50 MH942581A)

Title: Building object view invariance in a newly-discovered network in inferior temporal cortex

Authors: *P. BAO, D. Y. TSAO;
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Abstract: Object recognition in primates is mediated by hierarchical, multi-stage processing of visual information within occipital and inferior temporal (IT) cortex. Insight into the functional organization of IT has rapidly accumulated in recent years. It is known that IT contains several networks that process specific categories (e.g., faces, bodies, scenes) or stimulus dimensions (e.g., color, curvature). Furthermore, at least in the case of the network for face processing, the nodes appear to be organized hierarchically, e.g., neurons in the middle faces patches are tuned for specific facial views, while those in the most anterior patch are tuned for the identity of faces in a view-invariant way. However, there remains a fair amount of IT cortex that doesn't belong to any known network, raising the question: are there any new, undiscovered networks not yet accounted for by existing functional parcellation studies? If so, what are these networks processing and how are they organized? To address this question, we exploited the technique of electrical microstimulation combined with simultaneous functional magnetic resonance imaging. Electrical microstimulation of a region of macaque IT cortex not belonging to any known network produced strong activation in three patches that also didn't overlap with any known networks. We targeted single-unit recordings to these three patches, while monkeys viewed an image set consisting of 51 objects with 24 views for each object; the objects included faces, animals, houses, vegifruit, vehicle, and man-made objects. The monkey was rewarded with juice for fixating the center of the images. Average responses across neurons from the three patches revealed high similarity in object preferences between the patches, further confirming these patches belong to a common network; for example, all three patches showed the smallest response to faces. We determined high- and low-preference objects based on mean singe-unit responses from cells in the three patches, and then performed an fMRI experiment contrasting responses to these high- and low-preference objects; this revealed the same network as the original microstimulation+fMRI experiment. Representational similarity analysis on population single-unit responses in each of the three patches revealed the most view-invariant representation in the most anterior patch, and the least view-invariant representation in the posterior patch, suggesting that, analogous to the face patch network, view-invariant object representation is built up hierarchically within this new network.

Disclosures: P. Bao: None. **D.Y. Tsao:** None.

Poster

801. Representation of Objects and Scenes

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 801.09/BB9

Topic: D.06. Vision

Support: KAKENHI(15H05919)

CREST, JST

Title: Modeling electrocorticography signals on the macaque inferior temporal cortex in space, time and frequency domains using hierarchical visual features of convolutional neural networks

Authors: *H. DATE[1,2], K. KAWASAKI[2], M. OZAY[1], T. HONGO[2], I. HASEGAWA[2], T. OKATANI[1];
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Abstract: Primates can easily recognize objects in their complex environment. The ability is thought to be achieved by hierarchical information processing along the ventral stream, which starts from the primary visual cortex and ends at the anterior inferior temporal cortex (ITC). In computer vision, convolutional neural networks (CNNs) have achieved nearly human-level performance for object category recognition tasks. CNNs are hierarchical learning models originally developed by inspirations from the primate ventral stream. Previous studies indicate a hierarchical similarity between CNNs and the primate ventral stream, where features extracted at lower and higher layers of CNNs can be employed to better predict neural responses measured at lower and higher areas in the ventral stream, respectively. However, a more detailed analysis of the relationships between CNN features and neural responses expressed in other domains than space is required to establish more biologically plausible models, because neural information processing in the brain may occur simultaneously in space, time and frequency domains. In this study, we simultaneously recorded the cortical potentials of 128 channel electrocorticogaphy (ECoG) covering from macaque's posterior to anterior ITC while presenting natural images consisting of 12 categories, each of which contains 1000 examples. We then extracted features at each layer of a pre-trained CNN model (VGGNet-16) from the same images. Using the CNN features, we estimated encoding models to predict ECoG features at each electrode location, time window and frequency. Finally, we tested prediction accuracy of each model while conducting permutation tests. Comparing the prediction accuracy among CNN layers, we found that, in space domain, ECoG features measured in posterior and anterior electrodes were better predicted from CNN features extracted at lower and higher layers, respectively. Moreover, in time domain, ECoG features extracted in earlier and later time windows were better predicted from lower and higher layers, respectively. Finally, in frequency domain, ECoG features extracted in gamma and

theta bands were better predicted from lower and higher layers, respectively. Our results indicate that feature representations extracted at different CNN layers are related to particular subspaces of space, time and frequency domains of neural responses measured along the primate ITC.

Disclosures: H. Date: None. **K. Kawasaki:** None. **M. Ozay:** None. **T. Hongo:** None. **I. Hasegawa:** None. **T. Okatani:** None.

Poster

801. Representation of Objects and Scenes

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 801.10/BB10

Topic: D.06. Vision

Support: NIH Grant R01-EY014970

ONR MURI-114407

Title: A simple, wireless system for remote, high-throughput behavioral testing of nonhuman primates

Authors: *E. B. ISSA, K. M. SCHMIDT, 02139, S. OHAYON, J. J. DICARLO;
Brain and Cognitive Sci., Massachusetts Inst. of Technol. Dept. of Brain and Cognitive Sci., Cambridge, MA

Abstract: Behavioral training and testing of animals in their home environment allows simultaneous measurements across many animals with little time required of lab personnel. This approach has been widely adopted in rodent work; however, in-colony behavioral testing is less widespread in nonhuman primate work. Here, we have developed an in-cage, touchscreen system that because of its low cost, scalability, and overall simplicity can be widely adopted by the primate community. The web-based system uses a single client-side web application that can run on any device (tablet, laptop, smartphone) and on any operating system. Recent advances in Javascript made it possible to deliver auditory and visual stimuli at high temporal precision and to leverage smart Bluetooth closed-loop communication with peripheral devices from within the web browser. Behavioral performance is monitored in near-realtime through the cloud from a web page which can be viewed on any device including a smartphone. To date, we have used this system to collect ~1 million behavioral trials on a visual object recognition task across multiple subjects and across different nonhuman primate species (macaques and marmosets). We have found that animals will often perform more trials and work for more fluid reward in the colony setting compared to a lab setting. When animals were brought to lab for physiological

testing, we found a rapid switch of effector from reaching movements (touchscreen) to eye movements (camera-based eye tracking) while retaining task knowledge suggesting that home cage, touchscreen testing is an efficient method for training naïve animals when precise eye tracking is not required. Future extensions of this system will include RFID-based subject identification so that each animal can activate the touchscreen ("log-in") loading their specific task in a group housed setting.

Disclosures: E.B. Issa: None. **K.M. Schmidt:** None. **S. Ohayon:** None. **J.J. DiCarlo:** None.

Poster

801. Representation of Objects and Scenes

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 801.11/BB11

Topic: D.06. Vision

Support: Simons Foundation 325500

ONR MURI SPO 114407

Title: Image-grain comparison of core object recognition behavior in humans, monkeys and machines

Authors: *R. RAJALINGHAM[1], E. B. ISSA[2], K. KAR[2], K. SCHMIDT[2], J. J. DICARLO[1]; [1]Brain and Cognitive Sci., [2]MIT, Cambridge, MA

Abstract: Humans can rapidly and accurately recognize objects in spite of high variation in viewing parameters (e.g. position, pose, and size) and background conditions. To uncover the algorithms underlying this ability, quantitative benchmarks of human behavior can be used to test animal, neural, and computational vision systems. Recently, we compared the core object recognition behavior of humans against that of monkeys and machines and found that monkeys not only matched human-level performance but also exhibited a pattern of object confusions that was indistinguishable from humans, a pattern that was also shared with high performing object recognition models (convolutional neural networks, CNNs). Object-level confusions, however, fail to capture image-level variation as each object can produce myriad images under variations in viewing parameters, with some images being more challenging than others. Here, we obtained the much larger datasets that are required to measure object recognition behavior at a higher resolution, the image-grain. This allowed us to systematically ask whether human, monkey and machine vision systems differ in their pattern of image-by-image performance.We tested object recognition performance on a binary choice match-to-sample paradigm using brief presentations

of images of 3D objects rendered with high viewing parameter variation on natural backgrounds. To collect large behavioral datasets, we used high-throughput psychophysical techniques: Amazon Mechanical Turk for humans, and a novel home-cage behavioral system ("MonkeyTurk") for monkeys. Over a million behavioral trials across hundreds of humans and five monkeys were aggregated to characterize each species on each image. To test multiple layers of high-performing CNN models on the same tasks, we trained linear classifiers on the model features. Our results show that monkeys are highly consistent with the pooled human in their pattern of image difficulties and are indistinguishable from individual human subjects. In contrast, all tested CNN models were significantly less consistent with the pooled human. This gap in consistency at the image level, though small, could not be easily attributed to our choice of linear classifiers, training images, viewing parameters or retinal sampling. Thus, current CNN models may not perfectly capture the representations that underlie core object recognition behavior in humans and monkeys. Moreover, these results show that high-resolution, image-grain behavioral measures serve as stronger constraints than object-level measures for uncovering mechanistic models of human visual object recognition.

Disclosures: R. Rajalingham: None. **E.B. Issa:** None. **K. Kar:** None. **K. Schmidt:** None. **J.J. DiCarlo:** None.

Poster

801. Representation of Objects and Scenes

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 801.12/DP04 (Dynamic Poster)

Topic: D.06. Vision

Title: A stimulus-driven analysis of convolutional neural network models of visual cortex

Authors: *M. MCGILL[1,2], D. TSAO[3], P. PERONA[4];
[2]Computation and Neural Systems, [3]Biol., [4]Electrical Engin., [1]Caltech, Pasadena, CA

Abstract: Convolutional neural networks (CNNs) trained for object recognition are useful tools for reasoning about the primate ventral visual stream. For a given stimulus, the activity of a CNN layer is predictive of neural activity in the corresponding brain region(s). This suggests that CNNs may perform object recognition using similar mechanisms to those used by the primate visual system, and that studying CNNs may yield hypotheses to test in biological systems. As artificial neural networks are universal function approximators, the space of algorithms that may use for recognition is large and the transformations that images undergo while moving through network layers are poorly understood. Existing analyses characterize single-unit receptive fields but fail to describe the computations being performed by CNN layers as populations, operating

on natural images. To better understand how the representations of natural images are transformed by CNNs, we study (1) the image information that can be decoded from each layer's activity, (2) how sensitive each layer is to object transformations (e.g. shifts and rotations), and (3) how clusters of image representations warp, split, and merge moving from earlier through later layers.

Disclosures: **M. McGill:** None. **D. Tsao:** None. **P. Perona:** None.

Poster

801. Representation of Objects and Scenes

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 801.13/BB12

Topic: D.06. Vision

Title: Object classification and separation of object manifolds in the human brain

Authors: ***C. JEW**[1], X. WANG[2], R. D. S. RAIZADA[1];
[1]Brain and Cognitive Sci., [2]Biomed. Engin., Univ. of Rochester, Rochester, NY

Abstract: No two instances of an object projected onto a person's retina are ever the same. An object's position, size, pose, or illumination are features that change from one image to the next depending on the viewer's perspective or the environment's conditions. The set of these different views is known as a viewpoint manifold. Manifolds have been applied in the field of computer vision to perform object recognition and pose estimation, but can the same or similar methods also be applied to brain patterns as a way to uncover how objects might be neurally represented? In computer vision, Murase and Nayar (1995) proposed a way to compress a set of images of the same object in order to represent the varying images within a lower-dimensional subspace than the retinal or pixel-level representations. All the images of the same object within this lower-dimensional space make up that object's manifold. For example, within the manifold for a mug, a snapshot of the mug at 10 degrees will occupy a point along the manifold that is closer to the point that represents the same mug rotated at 15 degrees than the point at which the same mug is rotated at 45 degrees. A point's position along the manifold represents a specific view or image of the object. If two objects' manifolds are separable within the same subspace, then the objects can be easily recognized. If the manifolds are tangled, however, transformations must be carried out on the manifolds to separate them (DiCarlo & Cox, 2007).
Participants' brain patterns were collected during a functional magnetic resonance imaging (fMRI) paradigm in which they observed four tools rotating individually on the screen. Multi-class classification of the objects with cross-validation is performed using the brain patterns for all objects within regions of interest extracted based on the Harvard-Oxford atlas. For each

classifier, a subset of the brain patterns corresponding to a portion of the rotation is withheld as the test set. We find the greatest classification accuracy in the temporo-occipital portion of the inferior temporal gyrus and the lowest accuracy in occipital pole. After performing classification, we then examine the manifolds for each of the objects based on the brain patterns elicited within the most and least accurate regions. We hypothesize that regions that are more successful at classifying the objects will also demonstrate greater separation between the manifolds within the low-dimension subspace. We find no evidence to support this hypothesis after performing principal components analysis on the brain patterns; instead, the manifolds appear tangled in all regions we examine. Other dimensionality reduction methods are now being tested.

Disclosures: **C. Jew:** None. **X. Wang:** None. **R.D.S. Raizada:** None.

Poster

801. Representation of Objects and Scenes

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 801.14/BB13

Topic: D.06. Vision

Title: Manifolds of tool-graspability and viewpoint in the human brain

Authors: ***X. WANG**, C. JEW, R. RAIZADA;
Univ. of Rochester, Rochester, NY

Abstract: Consider an object, such as a spoon, which at a coarse-grained level can be viewed simply as an oriented bar, but at a finer-grained level is a tool with a graspable handle at only one of its two ends. When an object of this sort rotates though 360 degrees, a brain region which represents it merely as an oriented bar, ignoring which end has the handle, will perceive this as two full rotations, as 0, 180 and 360 degrees would all look the same. In contrast, a brain region which is sensitive to the object as a 3D shape with a handle at one end will treat this as only one single rotation (DiCarlo and Cox 2007, Murase et al 1995, Elgammal & Lee 2004, Rahami 2005). We investigated this question by extracting object viewpoint manifolds from multivoxel patterns of fMRI activation in people viewing movies of slowly rotating tools: a spoon, fork, knife and scissors.
We tested this new representation structure by analyzing fMRI data of people observing those four continuous rotating tools. We addressed the following key questions: what do the manifold representation structures look like for different brain regions under those stimuli? What methods can we apply to select voxels that are sensitive to either rotations or shapes? Can we estimate rotation angles using manifolds from certain brain areas? Can we classify different objects based on manifold structures in certain areas?

fMRI images were first preprocessed and normalized to standard MNI templates. We then divided the registered fMRI volumes into 48 regions based on Harvard-Oxford atlas (from FSL package). Since the fMRI task paradigm has constant-periodic (T = 60 s), in order to select voxels whose signal changes are temporally correlated with rotation task frequency, we proposed a voxel selection method based on ranked Fourier Power spectrum. We then constructed manifold structures for both full ROIs and voxels selected within in each ROI using principal component analysis (PCA). We found lower level visual regions can be represented by manifolds that are merely sensitive to symmetrical elongated shapes. We also find regions that are sensitive to objects' graspability based on their corresponding manifold structures.

Disclosures: **X. Wang:** None. **C. Jew:** None. **R. Raizada:** None.

Poster

801. Representation of Objects and Scenes

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 801.15/BB14

Topic: D.06. Vision

Support: NIH grant 1R01EY022355

Title: Neural representation of action-related object pairs in human visual cortex

Authors: ***R. WANG**, Y. XU;
Harvard Univ., Cambridge, MA

Abstract: Objects are not shown in isolation; instead, they appear in pairs with contextual association (e.g., a cake and a platter) or interact with each other in a predictable action-related manner (eg., a pitcher and a cup). Using fMRI MVPA, we previously reported that contextual association significantly affected object pair representation in posterior fusiform gyrus (pFS), an object-related processing region. Here we examined how and where action-related information within an object pair is represented and whether or not it is represented similarly as the contextual association between objects. We measured responses in human retinotopically defined early visual areas, object-related processing regions in lateral and ventral occipital regions, and action-related processing regions in visual cortex (defined by contrasting action-related object pairs with their constituent objects shown in isolation). We manipulated contextual association and action-related interaction between the objects in the pair. For the contextual association manipulation, a pair of objects could be either contextually congruent (e.g., a pitcher and a cup) or incongruent (e.g., a pitcher and a nail). For the action manipulation, a pair of objects could appear either in a familiar action colocation (e.g. a pitcher pointed towards a cup), an unfamiliar

action colocation (e.g., a pitcher pointed away from a cup), or a non-action colocation (e.g., a pitcher and a cup appeared side by side). To investigate the effect of contextual association and action-related interaction, in a given brain region, we measured the Euclidean distance between the voxel response patterns of an actual pair and the averaged voxel response patterns of the constituent objects shown in isolation. Replicating our previous results, in both pFs and action-related processing regions, we found that contextually associated non-action pairs were more dissimilar to the average of their constituent objects than pairs containing two unrelated objects. Interestingly, this contextual effect disappeared in contextually associated action pairs in action-related processing regions, resulting in a significant interaction between contextual congruency and action-related colocation. These results suggest that whereas contextual association integrates objects to form an integrated whole, action-related interaction breaks such integration, likely providing our visual system more independent access to the individual objects for the purpose of action perception and planning.

Disclosures: **R. Wang:** None. **Y. Xu:** None.

Poster

801. Representation of Objects and Scenes

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 801.16/BB15

Topic: D.06. Vision

Support: DFG Grant HI 1371/2-1.

Title: The cortical network of usability evaluations for unknown tools

Authors: ***M. A. GANN**, M. HIMMELBACH;
Hertie-Institute For Clin. Brain Res., Tuebingen, Germany

Abstract: In daily life we are surrounded by different tools. Most often, we encounter familiar tools, and we can retrieve information about them from our semantic knowledge. Sometimes, however, we are confronted with new and unfamiliar tools. We must analyze and interpret their properties and infer a possible use. We assumed that such sensory and cognitive processing of unfamiliar tools will place a higher demand on a previously reported left-hemispheric network comprising the IFG/vPMC, anterior and dorsal IPL, and posterior ITG/IOG. In contrast, retrieving the well-known functionality of highly familiar tools should result in higher demands on the posterior MTG which has been associated with the retrieval of information from semantic networks before.
We asked 25 healthy participants to decide whether visually presented tools were useful in

various mechanical tasks. Brain activity was measured with 3T BOLD fMRI. We used a multiband EPI sequence with TR = 670 ms. Tools were either highly familiar or unfamiliar according to a preceding behavioral study.
The analysis indeed showed higher activation for unfamiliar than for familiar effective tools in the left IFG, left SMG, left MOG and left IOG/ITG. Exploiting our relatively high temporal resolution, we examined the time courses of significant clusters that had been identified in the whole brain analysis. Temporal parameters indicated a temporal order of signal increases in the abovementioned areas, which might represent different processing steps from visual processing to decision making.

Disclosures: **M.A. Gann:** None. **M. Himmelbach:** None.

Poster

801. Representation of Objects and Scenes

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 801.17/BB16

Topic: D.06. Vision

Support: DFG HI1371/2-1

Title: Impairment of tool evaluation in patients with apraxia

Authors: ***M. HIMMELBACH**, M. BARABAS, A. KIRSCHNER;
Hertie-Institute For Clin. Brain Res., Tuebingen, Germany

Abstract: Using objects as tools in everyday situations is usually based on previously acquired knowledge about the typical tools we use. However, when we do not have specific tools at hand or are confronted with new problems that we did not experience before, we have to understand the tool and the respective problem and think about mechanical solutions. Clinical tests in apraxia patients focus on practical demonstrations of typical tool knowledge through tool use pantomimes and real tool use but neglect mechanical thinking and reasoning. Our study focused on deficits of mechanical reasoning in patients who showed tool-related disorders in standard tests of limb apraxia. We devised a large set of typically well known and usually unknown tools. We created combinations of tools and problems that were orthogonalized with respect to the factors familiarity and effectivity. Healthy adults and patients with apraxia were instructed to rate the familiarity and effectivity of tools relative to a given problem. As expected, patients with limb apraxia reliably identified well known typical tools and typical tool/problem combinations. Despite of this rather good performance based on tool knowledge, the patients showed an impairment in mechanical reasoning in comparison to healthy adult controls. Deficits in tool

understanding and mechanical reasoning represent an underdiagnosed component of apraxia. They might play a more important role than hitherto assumed. Investigations in patients with respective disorders can provide important insights into the neuronal implementation of this cognitive process.

Disclosures: **M. Himmelbach:** None. **M. Barabas:** None. **A. Kirschner:** None.

Poster

801. Representation of Objects and Scenes

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 801.18/BB17

Topic: D.06. Vision

Support: NIH Grant R21MH107052-01A1

Title: White matter connectivity of the dynamic object perception network

Authors: *J. A. PYLES, M. J. TARR;
Dept. of Psychology, Carnegie Mellon Univ., Pittsburgh, PA

Abstract: Dynamic objects are ubiquitous in our visual environment. We previously identified a network of brain regions across occipitotemporal cortex recruited during the perception of dynamic objects and provided evidence that most of these regions encode information about dynamic objects invariant across changes in viewpoint, articulation and size (Pyles & Tarr 2013, 2014). Here we investigate how the functional regions of this network are structurally connected. We combined fMRI with diffusion-weighted imaging and deterministic fiber-tracking to identify the white matter connectivity between these regions. Dynamic object-selective regions were identified using a unique fMRI localizer that incorporated short animations of moving, articulating novel objects, contrasted with phase scrambled versions of the same animations. We also ran a MT/MST motion localizer, retinotopy, and a biological motion localizer. Structural connectivity was assessed with multiband diffusion spectrum imaging using a 253 direction sequence reconstructed using a generalized q-imaging method (Yeh, Wedeen, & Tseng, 2010). Consistent with our previous results, during the viewing of dynamic objects we observed the recruitment of large regions of occipitotemporal cortex, substantially overlapping with LOC and hMT+. Dynamic objects also recruited regions of parietal cortex not active when using static objects. These functionally-identified areas as well as results from retinotopy, the MT/MST localizer, and the bio-motion localizer were then used as regions of interest for deterministic fiber-tracking to map the white matter connections between these areas. Results reveal short range connections between nearby regions selective for dynamic objects as well as connectivity

to retinotopic cortex. Fiber streamlines originating in the region overlapping with LOC and hMT+ complex showed longer range connections to anterior temporal lobe and frontal lobe. Critically, differences were seen in the connectivity of the static object selective LOC versus the more superior dynamic object selective regions. A contrast between the connectivity of the dynamic object perception and the bio-motion networks further refines the nature of both networks. Finally, we illustrate the relationship of these tracts to the inferior longitudinal fasciculus and the vertical occipital fasciculus, tracts connecting dorsal and ventral cortex (Yeatman et al. 2014). In sum, our findings provide new insights into the structural connectivity of the dynamic object perception network, and its relationship to other visual regions.

Disclosures: **J.A. Pyles:** None. **M.J. Tarr:** None.

Poster

801. Representation of Objects and Scenes

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 801.19/BB18

Topic: D.06. Vision

Support: NIH: The Temporal Dynamics of Learning

NDSEG

Title: How does movement affect object recognition?

Authors: ***D. BURK**, D. SHEINBERG;
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Abstract: As we move throughout the world, our brains continuously acquire sensory information to make predictions based on what we see. For example, an animal hopping in a foggy park could be perceived as a rabbit, even when the rabbit's form is too far away to be visible. More generally, objects often have stereotypical movements, but it remains unknown how a particular movement becomes associated with an object, and how movement is used in recognition. Previous research has shown that the brain associates features (e.g. color, shape, size) to create a unified percept of an object. This percept can be retrieved when the appropriate group (or possibly a subset) of features is encountered again. We ask whether movement can be used as diagnostic information similar to other features. Specifically, we aim to address (1) under what circumstances a stereotyped, translational movement pattern (e.g. zig-zag, arc, line) associated with an object could aid its identification and (2) the neural mechanisms underlying this behavior. We developed a match-to-sample task for human and non-human primates that

requires the use of movement information to perform object recognition under variable perceptual noise. We manipulate movement-object associations and spatiotemporal characteristics of the movement patterns to demonstrate how these parameters affect recognition. Initial behavioral data suggests that objects can be recognized by their movement patterns and that movement can improve object recognition in the presence of noise, whether the mapping is one object per one movement pattern or many objects sharing a common movement pattern. Computational analysis of the movement trajectories shows a relationship between features of the movement patterns and recognition difficulty. The analysis also provides useful predictions for behavior (reaction times, accuracy) and neural activity in areas sensitive to object features (IT) and movement (MT, MST). Here we aim to demonstrate the learning of associations between movements and objects and real-time acquisition of these associations for object recognition.

Disclosures: D. Burk: None. **D. Sheinberg:** None.

Poster

801. Representation of Objects and Scenes

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 801.20/CC1

Topic: D.06. Vision

Title: Localizing functional regions of interest based on responses to dynamic naturalistic stimuli

Authors: *S. A. NASTASE[1], J. S. GUNTUPALLI[1], J. V. HAXBY[1,2], Y. O. HALCHENKO[1]; [1]Dept. of Psychological and Brain Sci., Dartmouth Col., Hanover, NH; [2]Ctr. for Mind/Brain Sci. (CIMeC), Univ. of Trento, Rovereto, Italy

Abstract: In human neuroimaging, functional regions of interest (ROIs) are typically localized by contrasting responses to several classes of controlled stimuli (e.g., faces, houses). However, the stimulus information driving this localization is also embedded in rich, naturalistic stimuli, albeit in a more complex way. Prior work has demonstrated that dynamic movie stimuli drive neural responses that are consistent across participants and encode extensive perceptual and semantic information. Here we introduce a framework for localizing functional ROIs using naturalistic stimuli: we use machine learning algorithms to assign each voxel in the brain to canonical functional ROIs (e.g., the fusiform face area, FFA, and parahippocampal place area, PPA) based on voxelwise response profiles to a dynamic movie stimulus. In contrast to typical multivariate pattern analyses, in this scenario each voxel is a sample in a feature space where each dimension represents the voxelwise response amplitude for a given time point in the movie stimulus. Framing the problem in this way results in highly correlated features (i.e., time points),

a large pool of samples (i.e., voxels), and very unbalanced class frequencies—of the total number of voxels in the brain, very few are members of any given functional ROI. To cope with these challenges, we used stochastic gradient descent to fit a linear SVM with samples weighted proportionally to class frequency. We are able to classify voxels from the whole brain as belonging to FFA or PPA with high accuracy (FFA: 98.9%, PPA: 98.6%) in left-out participants, correctly identifying 86.6% of voxels belonging to FFA, and 86.9% belonging to PPA. Interestingly, although some proportion of misclassifications are due to noise, some false positives can be interpreted as voxels with similar response profiles to ROI voxels that are not typically assigned to the manually-defined ROI based on conventional univariate contrasts. This approach circumvents the need for anatomical alignment across participants, as voxels can be assigned based purely on their response profiles. We compare these predicted ROI assignments to predictions based on anatomy alone. Anatomical information can be incorporated into the algorithm to improve localization, but at the expense of not discovering voxels with similar tuning at unexpected locations. Overall, our findings suggest that functional ROIs can be accurately identified in novel participants based on voxelwise responses to naturalistic stimuli.

Disclosures: **S.A. Nastase:** None. **J.S. Guntupalli:** None. **J.V. Haxby:** None. **Y.O. Halchenko:** None.

Poster

801. Representation of Objects and Scenes

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 801.21/CC2

Topic: D.06. Vision

Support: MH096482-01

Title: Intrinsic activity of the human brain and stimulus semantics are reflected in patterns of brain activity evoked by natural vision.

Authors: ***D. KIM**[1], K. KAY[2], G. SHULMAN[3], M. CORBETTA[3];
[1]Biomed. Engin., Washington Univ. In St. Louis, Saint Louis, MO; [2]Radiology, Univ. of Minnesota, Twin Cities, MN; [3]Neurol., Washington Univ. Sch. of Med., St. Louis, MO

Abstract: Resting state activity in the human brain is organized in a finite number of brain networks (so called resting state networks, RSNs). The topography of RSNs is highly similar to the patterns of co-activation and functional connectivity (FC) observed during sensory, motor and cognitive tasks (Fox et al., 2006; Smith et al., 2009; Cole et al., 2014; Wilf et al., 2015). The strong spatial correlation (ρ =~0.90) between the spatial topography of resting (intrinsic) and

task-evoked (extrinsic) FC has supported the hypothesis that patterns of synchronized intrinsic activity function as spatiotemporal priors for behaviorally relevant task evoked activities (Raichle, 2011; Petersen & Sporns, 2015; Lewis, 2009).
We compared the FC of intrinsic activity and task-evoked (extrinsic) activity during observation of movie clips (natural vision task) in a Human Connectome Project (HCP) 7 Tesla MRI dataset (11 Subjects, aged 20 ~ 35). Importantly, extrinsic FC was measured after statistically removing the contribution of intrinsic activity based on the temporal correlation of inter-regional signal time series averaged in different group of subjects (inter-subject functional connectivity, ISFC). Under these conditions, the correlation between extrinsic and intrinsic FC was reduced but remained significant ($\rho = 0.59$). Correspondingly, we found a large-scale difference in the spatial topography of extrinsic and intrinsic FC. Intrinsic FC showed the previously reported groupings of externally-oriented (e.g. vision, auditory, somatosensory, motor, dorsal attention) vs internally-oriented (e.g. default mode, fronto-parietal control, cingulo-opercular) networks (Fox et al 2005). Extrinsic FC, however, grouped visual and dorsal attention networks separately from the other networks. This result indicates a systematic difference between the topography of resting and movie-evoked FC, following the removal of the intrinsic component from the movie-evoked activity.
In preliminary work we have also analyzed the contribution of the semantic content of each movie to the topography of FC evoked by the movie. Each frame of each movie was categorized using binary semantic codes (see methods in Huth et al., 2012), yielding a frequency vector for each movie that indicated the number of frames in which each semantic feature was present. Movies that showed a similar semantic content, as indexed by a high correlation between their frequency vectors, showed a similar topography of movie-evoked FC, as indexed by a high spatial correlation between their FC matrices.

Disclosures: **D. Kim:** None. **K. Kay:** None. **G. Shulman:** None. **M. Corbetta:** None.

Poster

801. Representation of Objects and Scenes

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 801.22/CC3

Topic: D.06. Vision

Support: ONR MURI

James S. McDonnell

Title: The neural semantic representations of fine-grained object categories

Authors: *M. KUMAR[1], K. D. FEDERMEIER[2], L. FEI-FEI[3], D. M. BECK[2];
[1]Neurosci., [2]Psychology, Univ. of Illinois at Urbana-Champaign, Urbana, IL; [3]Computer Sci., Stanford Univ., Stanford, CA

Abstract: When we view a picture or read a word, we evoke its meaning (semantics) based on prior knowledge of the concept. We previously showed that pictures and words describing scene categories evoke similar representations in the inferior frontal gyrus, precuneus, angular gyrus and ventral visual cortex. Similar results have been seen for objects such as tools and animals. Here we ask whether these similarities extend to fine grained distinctions ? To examine the nature of differences and similarities between fine grained concepts, we examine the neural activity for pictures and words using a classifier to decode the BOLD signal within modalities and across modalities via multivariate pattern analysis (MVPA). We used picture stimuli of animate and inanimate exemplars from twenty-four categories derived from six classes (big cats, insects, birds, vehicles, tools and fruits. Each class comprised of a diverse set of stimuli (e.g. big cats: tiger, leopard, panther, lion). Word stimuli were approximate "captions" of the types of pictures used for the same category (e.g. 'a panther hunting at night'). In the fMRI experiment, subjects passively viewed first all the word stimuli for all twenty-four categories and then the picture stimuli for the same categories. A whole brain MVPA searchlight with six-way classification was performed. The six-way results from cross-decoding (training on the word stimuli and testing on the picture stimuli) showed similarities across words and pictures in the left precuneus. The results for picture decoding revealed a distributed set of brain regions including the ventral occipito-temporal cortex, parahippocampal gyrus, precuneus, and angular gyrus. These results suggest that like scenes, objects representations evoked by words and picture evoke similar representations even at a fine-grained level.

Disclosures: M. Kumar: None. **K.D. Federmeier:** None. **L. Fei-Fei:** None. **D.M. Beck:** None.

Poster

801. Representation of Objects and Scenes

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 801.23/CC4

Topic: D.06. Vision

Support: TUBA-GEBIP 2015

TUBITAK 3501 Grant 114E546

EMBO Installation Grant IG 3028

Marie Curie Actions PCIG13-GA-2013-618101

NEI Grant EY019684

NSF CSOI Grant CCF-0939370

Title: Human scene-selective cortex represents the statistical distribution of object and action categories in natural movies

Authors: U. KELES[1], D. STANSBURY[2], J. L. GALLANT[2], *T. CUKUR[1];
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Abstract: Three scene-selective regions in the human brain, PPA, RSC and OPA (also known as TOS), are assumed to represent both low-level spatial and high-level semantic information about visual scenes (Kveraga, Bar; 2014). Previous studies on low-level representations argued that these regions represent features related to global spatial layout rather than constituent local features (Epstein, Kanwisher; 1998). It is thus possible that semantic representations in these areas also reflect holistic information that cannot be described as a simple sum of the information provided by the constituent objects and actions. To test this hypothesis, we assessed the semantic representations of natural scenes in PPA, RSC and OPA using two distinct encoding models: a scene-category model reflecting holistic co-occurrence statistics of objects-actions, and a parts-of-scenes model expressing scenes as additive combinations of constituent objects-actions. Human subjects viewed natural movies containing 1705 object-action categories for 210 min. Functional MRI was used to record whole-brain BOLD responses. Voxel-wise encoding models were fit to measure tuning for semantic features. The latent semantic features of the two models were extracted via separate learning algorithms applied on a large database of movie scripts. Latent Dirichlet allocation (Blei, 2003) was used to learn topical scene-category features (e.g. city street) that encapsulated co-occurence statistics of objects-actions. Nonnegative matrix factorization (Lee, Seung; 1999) was used to learn parts-of-scenes features (e.g. car or driving) that reflect additive object-action components of scenes. Voxel-wise models were fit by projecting the stimulus onto semantic features and applying regularized regression. Prediction accuracy was taken as the correlation coefficient between recorded and predicted responses on held-out data. To reveal whether scene-selective cortex represents holistic semantic information beyond what can be ascribed to a sum of information from constituent objects-actions, we compared the prediction accuracy of the two encoding models. In PPA, RSC and OPA, we find that the scene-category model outperforms the parts-of-scenes model, and that it explains significant variance in BOLD responses after accounting for the parts-based model ($P<0.05$, signed-rank test). Yet, we find no significant difference between model performance in other ventral-temporal ROIs. These results suggest that semantic representations in scene-selective cortex reflect holistic scene-category information that cannot be explained by a sum of constituent parts.

Disclosures: **U. Keles:** None. **D. Stansbury:** None. **J.L. Gallant:** None. **T. Cukur:** None.

Poster

801. Representation of Objects and Scenes

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 801.24/CC5

Topic: H.02. Human Cognition and Behavior

Support: NIH NEI R01 EY019684 to J.L.G.

NIH NEI F32EY021710 to M.D.L.

Title: Human scene-selective areas represent the distance to and orientation of large surfaces

Authors: *M. D. LESCROART[1], J. L. GALLANT[2];
[1]Helen Wills Neurosci. Inst., [2]UC Berkeley, Berkeley, CA

Abstract: A network of areas in the human brain—including the Parahippocampal Place Area (PPA), the Occipital Place Area (OPA), and the Retrosplenial Complex (RSC)—respond to images of visual scenes. However, it is still unclear whether these areas represent 3D features related to scene structure or low-level 2D features related to spatial frequency. To better characterize the representation of visual features in PPA, OPA, and RSC, we define feature spaces that quantify scene structure and spatial frequency, and use them to predict brain activity in scene-selective areas. We fit these models to BOLD fMRI data recorded while human subjects viewed movies of a virtual world rendered with 3D graphics software. We used meta-data from the graphics software to define a scene structure feature space that quantifies the distance to and orientation of large surfaces in each movie frame. This feature space uses continuous parameters based on 3D data (surface normals and depth maps) rather than human-assigned categorical labels such as “open” or “closed”. We also used a Gabor wavelet feature space to quantify variation in spatial frequency in each movie frame. We fit models for both feature spaces for every voxel in the brain using L2-regularized regression, and evaluated each model based on how much response variance it predicts in a withheld data set.
We found that the scene structure model explains more response variance in scene-selective areas than the Gabor wavelet model. Furthermore, a variance partitioning analysis revealed that the scene structure model explains a significant amount of *unique* variance that cannot be explained by the Gabor wavelet model. Having validated the scene structure model, we investigated the information it captured by performing principal component analysis (PCA) on the weights of the scene structure model for voxels in scene-selective areas. We found that the first PC distinguishes scenes with enclosing structure (walls and ceilings) from completely open or close-up scenes with no structure. The second PC distinguishes near scenes from far scenes. These results suggest that PPA, OPA, and RSC represent conjunctions of the distance to and orientation of walls, ceilings, and other large objects in scenes, independent of low-level features captured by the Gabor wavelet model. Finally, we used the model weights and a structural prior

to generate reconstructions of the backgrounds in each segment (TR) of the stimulus movies. The reconstructions demonstrate that our scene structure model captures an unprecedented level of information about the geometry of the local visual environment from scene-selective areas.

Disclosures: M.D. Lescroart: None. **J.L. Gallant:** None.

Poster

801. Representation of Objects and Scenes

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 801.25/CC6

Topic: H.02. Human Cognition and Behavior

Support: National Eye Institute (NEI R01EY026042, to SP)

Title: Neural representation of spatial boundary cues in visual cortex

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Abstract: Boundaries are crucial for defining the spatial constraints of an environment, but what are the essential features of a boundary? Developmental studies have demonstrated that not all environmental structures can define an effective boundary (Lee & Spelke, 2011). Four-year-old children were shown the location of a hidden toy in a rectangular arena. After disorientation, they were able to search the correct location and its geometric equivalent location when the arena was marked by continuous, 2cm-tall “curb” structure, but not by isolated columns connected together by a suspended string. This contrast suggests that horizontal continuity could be an important element of what defines a spatial boundary cue. Recent neuroimaging work has shown that the parahippocampal place area (PPA) is sensitive to the presence of vertical boundary structure in visually-presented scenes (Ferrara & Park, 2014). In the present study, we ask whether there exists a neural representation that distinguishes between boundaries with varying degrees of horizontal solidity. The horizontal solidity of boundaries was manipulated by varying the amount of vertical elements (i.e., poles) that extended in horizontal space in artificial scene images. The number of poles increased in a logarithmic scale across conditions: an open field (0 poles), 3 poles, 9 poles, 17 poles, 33 poles and 65 poles (Wall). Participants (N=11) viewed these conditions in blocks of 12 s while performing a one-back repetition task. We measured univariate and multivariate response in two scene-selective regions: PPA and Occipital Place Area (OPA). To evaluate the nature of boundary representation in these two regions, we created

three hypothetical models to test whether a region is sensitive to 1) the presence of vertical structure in a scene 2) the continuity of horizontally extended structures, and 3) the amount of poles along the horizontal extent of the boundary. With these models, we ran within-subject multiple linear regressions on the similarity matrices generated from multi-voxel pattern activity in PPA and OPA. We found that PPA is sensitive to the presence of poles in a scene boundary (beta=0.38, p=0.003) but doesn't distinguish between boundary conditions made up of different numbers of poles (beta=0.043, p=0.26). On the other hand, OPA tracks the amount of poles that make up the boundary (beta=0.17, p=0.004) and it is also sensitive to the continuity of these structures (beta=0.26, p=0.014). Taken together, these results provide insight to the defining geometric features of scene boundaries and how these features are represented differently across scene-selective regions in the brain.

Disclosures: **R. Cheng:** None. **K. Ferrara:** None. **S. Lee:** None. **S. Park:** None.

Poster

801. Representation of Objects and Scenes

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 801.26/CC7

Topic: H.02. Human Cognition and Behavior

Title: The effect of consecutive TMS-fMRI on the contralateral preference for scenes within scene-selective occipital place area

Authors: *E. H. SILSON, I. I. A. GROEN, C. I. BAKER;
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Abstract: Despite demonstrating selective responses to single stimulus categories, several regions of human occipitotemporal cortex have been shown recently to exhibit significant biases for the contralateral visual field (Silson et al., 2015; 2016). Notwithstanding different representations of eccentricity (foveal or peripheral) across category-selective regions, contralateral biases have been identified within object-, body, face- and scene-selective cortices. Such biases mirror those present in antecedent visual cortex and suggest that underlying retinotopic organization may constrain the function of category-selective regions. Here, we used consecutive TMS-fMRI to examine how causal interference of scene-selective occipital place area (OPA) alters the responses elicited therein by contralaterally presented scenes and faces. Given previous reports that TMS to category-selective regions results in a local attenuation of the fMRI response, we hypothesized that TMS of left and right OPA would result in reduced fMRI responses to scenes, but not faces, in the contralateral visual field. Healthy volunteers (n=18) were scanned on a 3T scanner (3x3x4 voxels, whole brain coverage) in three separate

counterbalanced sessions in which they performed four runs of a fixation task both before and after 60 seconds of theta-burst stimulation (30% max output, 50Hz, 900 pulses). In each run, scene and face stimuli (5x5 degrees), centered at 5 degrees eccentricity along the horizontal meridian, were presented into either the left or right visual fields in blocks. Importantly, the specific scene and face stimuli were different between pre and post runs to limit any stimulus specific habituation. In each session participants were removed from the scanner midway in the experiment and received either stimulation of left OPA, right OPA or no stimulation but with a decoy coil placed over right OPA. Target sites (peak voxel for scene > face) and ROIs were based on functional localizers in an independent scanning session. When considering our stimulation sites and their preferred category only, consistent with previous work, we observe decreased fMRI responses to contralaterally presented scenes following TMS, but this effect was limited to right OPA. Beyond this restrictive analysis however, these effects were also present for ipsialterally presented scenes and faces and moreover, were distributed across large swaths of cortex. These data suggest the effects of theta-burst stimulation on fMRI responses shows limited spatial specificity.

Disclosures: E.H. Silson: None. **I.I.A. Groen:** None. **C.I. Baker:** None.

Poster

801. Representation of Objects and Scenes

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 801.27/CC8

Topic: H.02. Human Cognition and Behavior

Support: Intramural Research Program of NIMH

Title: The effect of consecutive TMS-fMRI on scene representations in high-level visual cortex

Authors: *C. I. BAKER, E. H. SILSON, I. I. A. GROEN;
Lab. Brain and Cognition, NIH, Bethesda, MD

Abstract: An extensive neuroimaging literature supports the presence of multiple scene- and face selective regions in high-level visual cortex, which are thought to constitute distinct visual processing networks. Whilst combined transcranial magnetic stimulation (TMS) and fMRI experiments on the face network have demonstrated causal interactions between face regions (Pitcher et al., 2007, 2014), much less is known about the scene network. Here, we used consecutive TMS-fMRI to examine to what extent causal interference with neural activity in a posterior node in the scene network, the Occipital Place Area (OPA), affected representations of visual stimuli in scene-selective regions. We tested whether TMS to OPA affected fMRI

responses in OPA itself, as well as the more downstream Parahippocampal Place Area (PPA) and retrosplenial complex (RSC). In addition, we included two control conditions: an active TMS condition, in which we stimulated the Occipital Face Area (OFA) instead, as well as a no stimulation condition. Healthy volunteers (n=16) were scanned on a 3T scanner (3x3x4 mm voxels, whole brain coverage) in three separate counterbalanced sessions in which they performed eight runs of a 2-back repetition task on 20 s blocks of visual stimuli separated by 8 s fixation gaps. Midway in each session, participants were removed from the scanner to receive 60 seconds of theta-burst stimulation (30% max output, 50Hz, 900 pulses) to either right OPA or right OFA, or no stimulation with a decoy coil placed over right OPA. Target sites (peak voxel for scene > face or vice versa) and ROIs were based on functional localizers from an independent scanning session. In each run, participants were presented with blocks of stimuli from eight different scene categories (man-made open, man-made closed, natural open, natural closed) used in a previous study (Kravitz et al., 2011), as well as images of isolated faces, buildings, and man-made and natural objects. Univariate analysis of fMRI response magnitude revealed distributed effects of TMS across multiple stimulus categories in both scene- and face-selective regions. Whole brain analyses indicated that in general, TMS to OFA induced stronger reductions than TMS to OPA, possibly due to its position near the foveal confluence. Together, these data suggest that the effects of theta-burst TMS on fMRI responses can be widespread and not necessarily restricted to a single visual processing network or stimulus category.

Disclosures: **C.I. Baker:** None. **E.H. Silson:** None. **I.I.A. Groen:** None.

Poster

801. Representation of Objects and Scenes

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 801.28/CC9

Topic: H.02. Human Cognition and Behavior

Support: Intramural research program NIH

Title: The role of the occipital place area in guiding eye movements through scenes

Authors: G. L. MALCOLM[1], E. H. SILSON[2], J. R. HENRY[2], *J. E. INGEHOLM[2], C. I. BAKER[2];
[1]Dept. of Psychology, Univ. of East Anglia, Norwich, United Kingdom; [2]Lab. of Brain and Cognition, NIH / NIMH, Bethesda, MD

Abstract: Despite huge variability in the visual properties of every environment, we are very efficient at processing scenes and finding semantically meaningful consistencies. Scene

processing is supported by cortical regions, which exhibit preferential responses to scenes compared to objects or faces: parahippocampal place area (PPA), retrosplenial complex (RSC) and occipital place area (OPA). Typically, these regions have been studied in terms of what visual information they are responsive to, within the context of scene recognition or navigation. In the present study we move beyond these tasks to investigate eye movement guidance within scenes. Eye movements rely on a scene's visual representation to direct saccades, and thus foveal vision. Here we focus on the contribution of OPA, which is i) located in occipito-parietal cortex, likely feeding information into parts of the dorsal pathway critical for eye movements, and ii) contains strong retinotopic representations, predominantly of the contralateral visual field (Silson et al., 2015). Specifically, we examined how disrupting OPA, via transcranial magnetic stimulation (TMS), affects eye movements while participants (n = 24) searched scenes. Scenes consisted of indoor and outdoor settings, with object position controlled across all four visual quadrants. Scenes were displayed for 1s, followed by two objects presented either side of fixation. Participants indicated which object had been in the previous scene. On half of the trials, participants received repetitive TMS: a five pulse train over 500ms, starting at scene onset. Half of the participants received TMS to rOPA and half to rOFA (occipital face area), which also exhibits a bias for the contralateral visual field. If OPA plays a causal role in the guidance of eye movements within scenes, then TMS to rOPA, but not rOFA, should disrupt the distribution of fixations throughout the scene. In particular, given the contralateral representation within OPA, we predicted that participants should be biased to make eye movements toward the ipsilateral visual field (here, right visual field) following rOPA, but not rOFA stimulation. There was an overall left-to-right pattern in eye movements across all conditions as participants explored the scenes, despite every trial starting with a central fixation cross. Critically, the average fixation position for participants in the rOPA condition was biased toward the ipsilateral visual field. Further, this bias was stronger than either control trials or following rOFA stimulation. These results indicate that OPA might represent local scene information facilitating eye movement guidance

Disclosures: **G.L. Malcolm:** None. **E.H. Silson:** None. **J.R. Henry:** None. **J.E. Ingeholm:** None. **C.I. Baker:** None.

Poster

801. Representation of Objects and Scenes

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 801.29/CC10

Topic: H.02. Human Cognition and Behavior

Support: the National Natural Science Foundation of China 31230031

the National Basic Research Program of China 2014CB846101

the National Natural Science Foundation of China 31221003, 31471067 and 31470055

the National Social Science Foundation of China 14ZDB160 and 15ZDB139

Changjiang Scholars Programme of China

Title: The encapsulated structure of the scene network facilitates scene recognition

Authors: *X. HAO[1], X. WANG[1], X. Z. KONG[1], J. LIU[2];
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Abstract: Humans have an impressive ability to recognize real-world scenes. Previous neuroimaging studies have found that the visual system contains a dedicated scene network (SN) for scene recognition, commonly consisting of the parahippocampal place area (PPA), the retrosplenial complex (RSC), and the transverse occipital sulcus (TOS). These studies mainly focus on the functional characteristics of a specific region within the SN, but the knowledge about how these regions work collaboratively to facilitate scene recognition is limited. The present study characterized the within-network connectivity (WNC, integration) and between-network connectivity (BNC, segregation) of the SN, and then examined their association with behavioral performance in scene recognition in a large sample of participants (N = 228). First, we identified the SN as a set of voxels that responded selectively to scenes over objects with a functional localizer, and the non-scene network (NSN) as the rest of the voxels in the brain. For a voxel in the SN, the WNC was calculated as the averaged functional connectivity (FC) of the voxel to the rest of the SN voxels, whereas BNC was the averaged FC of the voxel to all of the NSN voxels. We found that 85.7% of the voxels in the SN had a significant larger WNC value than BNC value, suggesting that the SN is a relatively encapsulated network. *Then,* we examined the behavioral relevance of the SN by associating the WNC and BNC of the SN with behavioral performance in recognizing scenes based on either local information (location) or global information (configuration). We found that (1) individuals with stronger WNC in the right TOS or weaker BNC in the bilateral TOS and mPFC were more sensitive to configural changes of scenes, and (2) individuals with weaker BNC in the mPFC had a larger location effect. *In short,* our study demonstrated the integration and segregation of the SN could benefit behavioral performance in scene recognition, suggesting the critical role of interaction of local regions in scene recognition.

Disclosures: **X. Hao:** None. **X. Wang:** None. **X.Z. Kong:** None. **J. Liu:** None.

Poster

801. Representation of Objects and Scenes

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 801.30/CC11

Topic: H.02. Human Cognition and Behavior

Support: National Natural Science Foundation of China 31230031

National Natural Science Foundation of China 31221003, 31471067 and 31470055

National Social Science Foundation of China 15ZDB139, 14ZDB160

Changjiang Scholars Programme of China

National Basic Research Program of China 2014CB846101

Title: S100B modulates functional connectivity of key regions for human scene/place recognition

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Abstract: Spatial navigation is crucial for living, and PPA (the parahippocampal place area), OPA (the occipital place area) and RSC (the retrosplenial cortex) have been demonstrated playing pivotal role in human spatial navigation, especially in scene/place recognition. Previous studies have shown that the S100B gene is causally related to spatial navigation performance and affects local neural activation of these regions during place-recognition and navigation tasks. The present study further asked whether S100B modulates inherent functional connectivity of these regions. Using PPA, OPA and RSC as seed regions, the present study calculated voxel-wise functional connectivity across the brain using rs-fMRI (resting-state functional magnetic resonance imaging) data obtained from a large sample of young healthy participants (N = 243), generating a set of connectivity maps reflecting the strength of the functional connectivity between a given voxel and each of the seed regions. We first examined the spatial correspondence between each of these rs-fMRI functional connectivity maps and the S100B gene expression map in postmortem brains from the Allen Brain Atlas. Then, we identified brain regions whose functional connectivity with any of the seed regions was modulated by individual serum level of S100B and S100B gene polymorphisms. The results revealed that (1) Regional S100B expression was negatively correlated with regional strength of functional connectivity with PPA and RSC. (2) Significant correlations were found between individual S100B serum level and functional connectivity with the seed regions in various cortical and subcortical regions. (3) These correlations mainly located in the putamen, the paracingulate gyrus and the

cingulate gyrus for PPA and RSC, and in the occipital regions for OPA. (4) Similar results emerged in correlating functional-connectivity with S100B genotypes. The present study provided the first evidence that S100B gene modulates the functional connectivity of regions critically involved in human spatial navigation, especially in scene/place recognition. These findings advanced our understanding of genetic modulation on the inherent functional connectivity in functionally specific neural networks.

Disclosures: **S. Xu:** None. **X. Kong:** None. **J. Liu:** None.

Poster

802. Prosthetic Vestibular Stimulation

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 802.01/DD1

Topic: D.07. Vestibular System

Title: Effect of stochastic mastoid vibration on perception of vestibular recognition of rotary motion

Authors: ***R. KABBALIGERE**[1], F. KARMALI[2], B. LEE[1], C. LAYNE[1];
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Abstract: Stochastic resonance (SR) is a phenomenon that is known to improve the strength of a weak signal in the presence of suitable amounts of non-zero level of external noise in non-linear sensory systems. There are numerous studies that have studied the effect of SR on sensation in the auditory, visual, proprioceptive and vestibular systems. This study tested the effect of stochastic vibration applied to the mastoids on vestibular perception of rotation in the dark, and particularly direction recognition thresholds and biases. In direction recognition paradigms, threshold represents the width of the Gaussian cumulative probability distribution and is linearly proportional to the standard deviation of the underlying noise. Bias is defined as an offset from zero and corresponds to the stimulus to which subjects respond correctly 50% of the time. Direction recognition threshold and bias for yaw rotation at 1Hz in 9 healthy subjects was measured with and without bilateral mastoid vibration. The vibratory stimulus consisted of band-passed white noise in the range of 1Hz-500Hz and maximum amplitude of 0.635 mm. The results showed that SR vibration significantly reduced bias magnitude when compared to baseline ($p=0.05$) but had no effect on recognition thresholds. Additionally, the effect of SR on bias was found to depend on the baseline thresholds. Subjects who had greater baseline thresholds were found to be more responsive to SR and showed greater reductions in bias. This finding may be related to the fixed level of the vibratory stimulus and points to the importance of

individualizing the stimulus level as a function of one's baseline thresholds. The presence of perceptual bias in healthy subjects has been linked to the imbalance in neural activities and firing rates of the left and right semicircular canals (SCCs). Our results suggest that SR vibration applied on the mastoid can be effective in reducing the asymmetry in neural activity of the SCCs and promote coordinated functioning between the SCCs.

Disclosures: R. Kabbaligere: None. **F. Karmali:** None. **B. Lee:** None. **C. Layne:** None.

Poster

802. Prosthetic Vestibular Stimulation

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 802.02/DD2

Topic: D.07. Vestibular System

Support: NIH grant R01-DC-014002

NCRR-ORIP

Wallace H. Coulter Foundation

Cochlear, Ltd

Title: Dynamics of eye movements and secondary vestibular neurons during prosthetic vestibular stimulation.

Authors: *C. PHILLIPS, L. LING, K. NIE, A. NOWACK, J. T. RUBINSTEIN, J. O. PHILLIPS;
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Abstract: Background: Recent research and development on new modalities for the treatment of vestibular loss have yielded vestibular prosthetics employing electrical stimulation of the semicircular canal (SCC) ampullae. These devices, currently under investigation in both human subjects and animal models, are effective in eliciting eye movements comparable, broadly, to those produced naturally through the vestibulo-ocular reflex (VOR). Here we examine the dynamics of eye movements elicited by such stimulation and compare them to dynamics of secondary vestibular neurons.
Methods: Rhesus monkeys were implanted unilaterally with a multichannel vestibular neurostimulator with stimulating electrodes in the perilymphatic space adjacent to the SCC ampullae. In addition, animals were implanted with 2D scleral search coils for the recording of eye movements and recording chambers with access to the vestibular nuclei. Eye movements and

secondary vestibular neurons were recorded in response to steady-state and current amplitude modulated (AM) trains of stimulation delivered to individual SCC ampullae.
Results: Steady-state stimulation elicits directionally appropriate nystagmus the velocity of which can be controlled parametrically by modulating either pulse rate or current amplitude. Short (2s) steady-state stimulation does not elicit a nystagmus with a constant velocity, but instead exhibits temporal dynamics. Sinusoidal AM stimulation produce nystagmus with a sinusoidal velocity profile. However, this velocity profile displays a phase shift and an amplitude that varies with the envelope frequency of stimulation, between 0.1 and 20 Hz. Steady state electrical stimulation of SCC afferents elicits phase locked activity of secondary vestibular neurons, that exhibit temporal dynamics.
Conclusions: These results illustrate significant differences between nystagmus elicited by prosthetic stimulation of the vestibular periphery and that elicited naturally, by rotations of the head. These results suggest that qualities of prosthetic vestibular stimulation that differ from natural stimulation have significant effects on information processing by the vestibular system.

Disclosures: **C. Phillips:** None. **L. Ling:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Intellectual property. **K. Nie:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Intellectual property. **A. Nowack:** None. **J.T. Rubinstein:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Intellectual property. **J.O. Phillips:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Intellectual property.

Poster

802. Prosthetic Vestibular Stimulation

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 802.03/DD3

Topic: D.07. Vestibular System

Support: NIH Grant NIDCD DC014002

NIH Grant NCRR RR-00166

NIH Grant ORIP RR-00166

NIH Contract HHS-N-260-2006-00005-C

Wallace H. Coulter Foundation

Cochlear Ltd.

Title: Relationship between vestibular evoked compound action potential responses and electrically elicited VOR.

Authors: A. L. NOWACK[1], L. LING[1], K. NIE[1], C. PHILLIPS[1], *J. O. PHILLIPS[2], J. RUBINSTEIN[1];
[2]Oto-HNS, [1]Univ. of Washington, Seattle, WA

Abstract: Background: Previous studies have shown that vestibular evoked compound action potentials (vECAPs) recorded from a fully implantable vestibular prosthesis provide a good measure of the activation of the vestibular afferents by biphasic pulse electrical stimuli. These recordings demonstrate long lasting electrical activation of nerve fibers in rhesus monkeys, and declining activation of over time in human subjects. However, recent studies have shown that dramatic dissociations of vestibular evoked behavior, such as the electrically evoked vestibulo-ocular reflex (eVOR), and vECAP responses can occur in some situations. For example, following ototoxic lesion of vestibular hair cells, vECAP responses decline whereas eVOR slow phase velocities increase. To further examine the relationship between vestibular evoked responses and behavior, we examined the relationship between vECAP threshold and amplitude gain, and the slow phase velocity of eye movements evoked by electrical stimulation in 10 rhesus monkeys.
Methods: Rhesus monkeys were implanted with a multichannel vestibular neurostimulator, with stimulating electrode arrays in the perilymphatic space adjacent to the ampullae of the three semicircular canals of one ear. In addition, animals were implanted with scleral coils for eye position recording. Eye movements were recorded in response to trains of biphasic stimulation delivered to individual SCC ampullae. vECAPs were recorded in response to stimulation at the same current levels in each canal. Both intracanal (stimulation and recording electrode in the same canal) and intercanal (stimulation and recording electrode in separate canals) recordings were obtained.
Results: vECAP threshold and gain showed a highly variable correlation with elicited slow phase eye velocity across canals or across animals. Canals with the most robust vECAP response were not those with the highest elicited slow phase velocities. Reduced vECAP responses did not reliably predict reduced or absent slow phase velocities. The correlation between vECAP responses and behavioral response were not stable over time in individual animals.
Conclusions: These results illustrate significant differences between elicited slow phase eye velocity and vECAP response during prosthetic vestibular stimulation, and suggest that the afferent pool sampled with the vECAP may significantly different than the full complement of afferents that are recruited to elicit the eVOR.

Disclosures: A.L. Nowack: None. **L. Ling:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); University of Washington. **K. Nie:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); University of

Washington. **C. Phillips:** None. **J.O. Phillips:** B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution; Cochlear Ltd.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); University of Washington. **J. Rubinstein:** B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution; Cochlear Ltd.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); University of Washington. F. Consulting Fees (e.g., advisory boards); Cochlear Ltd..

Poster

802. Prosthetic Vestibular Stimulation

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 802.04/DD4

Topic: D.07. Vestibular System

Support: NIDCD R01 DC9255

NIDCD R01 DC2390

Title: Single-unit activity of chinchilla vestibular afferent neurons in response to passive rotation and prosthetic electrical stimulation

Authors: *P. REN;
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Abstract: Bilateral loss of vestibular sensation due to ototoxic injury or other insults to both labyrinths is disabling. Affected individuals suffer chronic disequilibrium, increased risk of falls and unstable vision during head movements typical of common daily activities like walking and driving. The vestibular nerves are intact in many such cases, so an implanted stimulator encoding signals from a head-mounted motion sensor can excite the vestibular nerve and - if it creates the right pattern of activity on the nerve's five branches - restore sensation of head movement. However, the current spread or imprecise electrode placement can reduce MVP efficacy through spurious activation of non-target axons, resulting in misalignment between the actual and perceived axes of head motion. Effects of current spread can be inferred from misalignment of vestibulo-ocular reflex (VOR) responses, and we have used that technique fruitfully in chinchillas and rhesus monkeys. However, VOR measurements are an imprecise proxy for

current spread. In contrast, single unit recording from individual vestibular afferent neurons provides a much more precise assay of current spread and, consequently, can provide the information necessary to optimize design of electrode arrays for a vestibular implant. The goal of the present study was to characterize activity of vestibular afferents in response to passive whole-body rotation and prosthetic electrical stimulation, thereby establishing a normative data set for subsequent study of current spread within the labyrinth. We measured single-unit neuronal activity of >200 vestibular afferents in chinchillas, including >50 otolith units. Sensitivity was measured to tilts and to passive sinusoidal rotation (0.5~5Hz). Sensitivity increased as a function of rotation frequency. Vestibular afferent activity was also modulated by prosthetic electrical stimulation, with probability of firing increasing with increasing pulse amplitude and charge/phase. Activity of non-target neurons (i.e., vestibular afferents from an end organ other than the one targeted by prosthetic current delivered by a given stimulating electrode) was modulated by current spread, in qualitative agreement with model predictions.

Disclosures: P. Ren: None.

Poster

802. Prosthetic Vestibular Stimulation

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 802.05/DD5

Topic: D.07. Vestibular System

Support: Basic Science Research Program through the National Research Foundation of Korea (NRF) by Ministry of Education (2010-0020163)

Basic Science Research Program through the National Research Foundation of Korea (NRF) by the Ministry of Science, ICT & Future Planning (NRF-2013R1A2A2A04014796)

Title: The subadditive integration of neural responses to passive head rotation and galvanic vestibular stimulation in the vestibular nuclei

Authors: *G. KIM[1], E. JEON[3], K.-S. KIM[3], S. LEE[2];
[1]Inha Univ., Inchon-City, Korea, Republic of; [2]Electronic Engin., Inha Univ., InCheon, Korea, Republic of; [3]Otolaryngology-Head & Neck Surgery, Inha Univ. Hosp., InCheon, Korea, Republic of

Abstract: For the head orientation and body postural balance in three dimensional (3D) space, the vestibular system perceives the motion information with six degrees of freedom (three for angular and another three for linear motions) to designate the simultaneous changes acting on the

head. The sensed information is generally composed of multidimensional active or passive stimuli in a natural condition, and the information is known to be subadditively integrated in the central nervous areas. On the other hand, galvanic vestibular stimulation (GVS) has been widely used to directly excite the vestibular afferent neurons, but its central integration with the kinematic stimuli has not been thoroughly studied. Here, we investigated the integration of neural information caused by one of kinematic stimuli and GVS in the vestibular nuclei (VN) using a combined stimulus, which consists of horizontal head rotation (yaw) and GVS. Twenty six vestibular responses were recorded in the lateral vestibular nuclei from twenty healthy guinea pigs, using chronic extracellular recording by tungsten electrodes (5-7MΩ). All vestibular units (15 regular and 11 irregular neurons) for this study responded to both types of stimuli, horizontal head rotation and GVS. We designed three separate types of stimuli, *pure head rotation, pure GVS,* and *combined stimulus*, to excite the vestibular neurons in the VN. To assess the features of neural responses to the stimuli, a sinusoidal curve fitting was applied, and the amplitudes and baselines in the fitted sine wave were calculated. Two comparisons were conducted; one was based on the amplitudes during the head rotation and the combined stimulus while the other was based on the baselines during GVS, the head rotation and the combined stimulus. The former showed that the integrated neural information of the head rotation and GVS was reduced in the VN ($p<<0.01$, binomial cumulative distribution) indicating the information of two stimuli was subadditively integrated. The latter also demonstrated a similar result, attenuating the neural information related with baselines in the combined stimulus ($p=0.038$, binomial cumulative distribution). In conclusion, the subadditive neural integration was maintained when combining the neural responses to the kinematic stimulus and GVS in the VN.

Disclosures: **G. Kim:** None. **E. Jeon:** None. **K. Kim:** None. **S. Lee:** None.

Poster

802. Prosthetic Vestibular Stimulation

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 802.06/DD6

Topic: D.07. Vestibular System

Support: CIHR

NIH

Title: Neural correlates of transmastoid galvanic vestibular stimulation in alert primates: Linking vestibular afferent activation to perceptual, ocular and postural responses

Authors: *A. KWAN[1], D. E. MITCHELL[2], P. A. FORBES[3,4], J.-S. BLOUIN[4], K. E. CULLEN[1,2];
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Abstract: Every day we rely on our vestibular system for our sense of balance as we move around in the world. Physiologically, the vestibular sensors in the inner ear detect and convert head motion into a neural signal, which is then carried by the primary vestibular afferents to the central nervous system. Because the application of self-motion stimuli to activate the vestibular system often also results the unavoidable activation other sensory inputs (i.e., tactile and proprioceptive), investigating the vestibular system in isolation is challenging. In this context, an increasingly popular tool to artificially activate the human vestibular system is galvanic vestibular stimulation (GVS), in which electrical stimulation is applied between surface electrodes on the mastoid processes behind the ears. To date, however, while the effects of GVS, including the perception of self-motion, eye movements, and postural sway have been well described, their neuronal correlates remain unknown. Specifically, the link between the dynamics of the activation of the vestibular afferents and these GVS-responses has not been established. Here, in order to link the neuronal mechanisms mediating behavioural responses during GVS, we recorded both eye movements and vestibular afferent activity while GVS was applied between surface electrodes on the mastoid processes of alert macaques. First, we recorded eye velocity during sinusoidally modulated GVS, as monkeys fixated a target. We found that the eye movements evoked in alert macaques show similar patterns compared to those reported in humans. Notably, the gain of torsional eye velocity relative to peak GVS current amplitude remained relatively constant as a function of frequency. Next, and even more importantly, our single unit recording experiments revealed that GVS during these same paradigms similarly activated semicircular canal and otolith afferents. Strikingly, the gain and phase of regular afferents of both organs showed comparable trends (i.e., increasing) as a function of frequency, and irregular afferents of both organs showed comparable trends as a function of frequency (i.e., also increasing but gains were greater relative to those of regular afferents). Similar frequency responses were observed during broadband noise stimulation, suggesting that afferents responses to GVS were largely linear. Taken together, these results reveal the neural correlates underlying GVS-evoked perceptual, ocular and postural responses - a fundamental step into understanding the effect of this technique required to advance its clinical and biomedical applications.

Disclosures: A. Kwan: None. **D.E. Mitchell:** None. **P.A. Forbes:** None. **J. Blouin:** None. **K.E. Cullen:** None.

Poster

802. Prosthetic Vestibular Stimulation

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 802.07/DD7

Topic: D.07. Vestibular System

Support: DoD Grant W81XWH-14-2-0012-Sub01 and GW130093

Title: Customizing transcutaneous electro-cortical stimulation: An objective thresholding technique using sinusoidal galvanic vestibular stimulation and lateral body sway

Authors: *H. A. TRIER[1], S. B. DOUGLAS[1], C. ZUMARAN[1], A. L. ALCHEHAYED[1], J. M. SERRADOR[2,3], S. J. WOOD[1];
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Abstract: Galvanic vestibular stimulation (GVS) involves the application of low-intensity transcutaneous direct current stimulation to the mastoid processes or earlobes. At low levels of stimulation (≤1 mA) stochastic GVS stimulation has been shown to improve balance function, while higher levels have been used to disrupt function as an analog of clinical dysfunction. However, individual sensitivity and response to GVS varies. The present study established a protocol for determining an individual threshold level for GVS based on participants' postural sway responses. Young adult participants attended three one-hour sessions spaced evenly across one week, and in each session wore inertial motion sensors (MTi, Xsens Technologies, The Netherlands) on head and torso. A light foam board with an attached third sensor was held by participants to indicate direction and amplitude of perceived motion. A sinusoidal stimulus with frequency of 0.1 Hz and intensity of 0.1-1.7 mA was applied bilaterally across electrodes attached to each earlobe in increasing and then decreasing increments of 0.1 mA. During each three-minute trial, participants stood with their feet together and eyes closed while indicating perceived motion with the handheld sensor and verbal reports. The narrow stance width resulted in predominantly lateral sway in phase with the sinusoidal stimulus that was reliably detected from the roll position of the inertial sensors. Simultaneous subjective reports were less consistent than the postural sway measures. We propose this simple thresholding technique should be implemented using portable technologies to customize stimulation levels when employing transcutaneous electro-cortical stimulation interventions.

Disclosures: H.A. Trier: None. **S.B. Douglas:** None. **C. Zumaran:** None. **A.L. Alchehayed:** None. **J.M. Serrador:** None. **S.J. Wood:** None.

Poster

802. Prosthetic Vestibular Stimulation

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 802.08/DD8

Topic: D.07. Vestibular System

Support: NIDCD Grant R01-DC002390

CIHR

Title: Plasticity within vestibular reflex pathways: Implications for use of vestibular prostheses

Authors: *D. E. MITCHELL[1], C. C. DELLA SANTINA[2], K. E. CULLEN[1];
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Abstract: Whether it is the generation of a simple reflex behavior or an elaborate gymnastic routine, plasticity within motor pathways is required for the accurate execution of movements. Linking synaptic plasticity with changes in motor performance requires understanding how synaptic efficacy influences behavioral responses. The vestibular system plays a vital role in gaze and postural stabilization, through the vestibulo-ocular reflex (VOR) and vestibulo-spinal reflexes, respectively. Notably, the relative simplicity of vestibular pathways and their precise behavioral readout make it an excellent model system for studying the mechanisms underlying the fine tuning of motor performance. In this study, we examined the neural correlates of behavioral plasticity induced by applying temporally precise electrical stimulation to vestibular afferents in alert rhesus monkeys. To link changes in neuronal activity with changes in motor performance, we recorded eye and head movements driven by the VOR and vestibulo-spinal reflexes, respectively, as well as the activity of neurons that drive these reflexes during behaviorally relevant stimulation of the vestibular nerve. Responses of neurons in direct VOR and vestibulo-spinal pathways were decreased following behaviorally relevant patterns of vestibular nerve activation in awake behaving animals. Specifically, stimulation of the vestibular nerve resulted in a decreased efficacy of the synapse between vestibular afferents and first-order central neurons (i.e. long term depression (LTD)). The attenuation of these pathways was sufficient to cause a reduction in evoked VOR and vestibulo-spinal reflex responses. Interestingly, we found evidence of nearly instantaneous complementary changes in the strength of indirect inhibitory brainstem pathways, which worked to offset the reduced sensitivity of first-order central neurons. Therefore, rapid plasticity at the first central vestibular synapse can fine-tune motor performance, while complementary plasticity within indirect inhibitory brainstem pathways ultimately contributes to ensuring a robust behavioral output. Taken together, these findings provide evidence that vestibular prosthetic stimulation induces LTD at the synapse between vestibular afferents and first-order central neurons. Fortunately, our results also reveal

that changes at this synapse induced by stimulation are balanced by the complementary enhancement of local inhibitory pathways within the vestibular nuclei that contribute to ensuring a relatively robust behavioral performance.

Disclosures: D.E. Mitchell: None. **C.C. Della Santina:** None. **K.E. Cullen:** None.

Poster

803. Vestibular System: Central Pathways

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 803.01/DD9

Topic: D.07. Vestibular System

Support: Craig H Neilsen Foundation

Title: Distribution of vestibulosympathetic input to spinal glutamatergic interneurons

Authors: *G. C. WALTER, M.-C. PERREAULT;
Physiol., Emory Univ., Atlanta, GA

Abstract: Changes in body position during movement recruit neural circuits that help maintain balance and blood pressure. The vestibular system, via the vestibulospinal and vestibulosympathetic pathways, is thought to participate in both (Yates et al 2014). The goal of the present work is to assess the extent to which vestibulosympathetic control is mediated via spinal glutamatergic interneurons (INs). To do this we combined vestibular nerve ($VIII^{th}$ n.) stimulation and single-cell calcium imaging in ex-vivo brainstem-spinal cord neonatal preparations from vGluT2:GCaMPx transgenic mice. In these mice, $vGluT2^{+}$ INs genetically encode calcium sensors and their activity can be probed optically. Individual $vGluT2^{+}$ INs were visualized from the cut surface of the Th10 spinal segment. The current threshold (T) was defined as the minimum current intensity at which $VIII^{th}$ n. stimulation evoked calcium responses in CaGDA-preloaded sympathetic preganglionic neurons (SPNs). Only responses evoked by 2T stimulation are reported here. We analyzed vestibular-evoked responses in 240 $vGluT2^{+}$ INs (n=11). These $vGluT2^{+}$ INs were spatially distributed along the entire dorsoventral extent of Th10, with 115 located dorsally in lamina I-V and 125 located ventrally in lamina VI-X. Remarkably, while ventrally located $vGluT2^{+}$ INs were generally responsive to $VIII^{th}$ n. stimulation, dorsally located $vGluT2^{+}$ INs were not (92% vs 12% of responsive $vGluT2^{+}$ INs, respectively). Stimulation of sensory afferents in the Th10 dorsal root evoked responses in all the dorsally located $vGluT2^{+}$ INs tested (41/41, n=2), suggesting that their lack of responsiveness to vestibular inputs was genuine. Then, we wanted to determine whether vestibulospinal or vestibulosympathetic inputs were responsible for vestibular-evoked responses in the ventrally

located vGluT2^{+} INs. For this we took advantage of the difference in funicular trajectories of the vestibulospinal and vestibulosympathetic descending axons (VF+VLF vs DLF) and compared the responses of vGluT2^{+} INs to VIIIth n. stimulation before and after unilateral VF+VLF lesion (38, n=2). Compatible with *vestibulospinal* activation, we found that 35% of the vGluT2^{+} INs that responded to VIIIth n. stimulation before the lesion were no longer responsive to the stimulation after the lesion. Compatible with *vestibulosympathetic* activation, the remaining 65% still responded to VIIIth n. stimulation after the lesion. Our findings indicate that vestibular-responsive vGluT2^{+} INs are clustered in the ventral spinal cord and that a substantial proportion are involved in mediating vestibulosympathetic responses.

Disclosures: G.C. Walter: None. **M. Perreault:** None.

Poster

803. Vestibular System: Central Pathways

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 803.02/DD10

Topic: D.07. Vestibular System

Support: ATIP-Avenir grant 2015

Title: Light-sheet based whole-brain neuronal activity recording during vestibular stimulation in zebrafish larvae

Authors: *V. BORMUTH, R. CANDELIER, G. DEBREGEAS, G. MIGAULT;
Lab. Jean Perrin, Univ. Pierre Et Marie Curie, Paris, France

Abstract: Light-sheet microscopy allows cell resolved whole-brain calcium imaging at several brain scans per second in zebrafish larvae. Currently this technique is not compatible with dynamic stimulation of the vestibular system. We developed an ultra stable miniaturized light-sheet microscope that can be rotated while performing whole-brain recordings. Rotating the microscope rotates the fish and stimulates the vestibular system while imaging always the same plane in the brain. We demonstrate volumetric whole-brain neuronal activity recordings during vestibular stimulation. We mapped the brain activity with cellular resolution of the vestibule-ocular reflex.

Disclosures: V. Bormuth: None. **R. Candelier:** None. **G. Debregeas:** None. **G. Migault:** None.

Poster

803. Vestibular System: Central Pathways

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 803.03/DD11

Topic: D.07. Vestibular System

Support: EY12814

DC04260

R03DC014542

Title: Evolution of spatiotemporal dynamics from otolith sensory afferents to cortex

Authors: ***S. LIU**[1], J. LAURENS[1], R. CHAN[1], X. YU[1], D. DICKMAN[1], G. C. DEANGELIS[2], D. E. ANGELAKI[1];
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Abstract: Sensory signals are transformed as neural activity is relayed from sensors through pre-thalamic and thalamic nuclei to cortex. To explore how temporal dynamics and directional tuning are sculpted in hierarchical vestibular circuits, we compared response properties of macaque otolith afferents with those in vestibular and cerebellar nuclei, as well as five cortical areas (parieto-insular vestibular cortex, visual posterior sylvian area, ventral intraparietal area, dorsal medial superior temporal area, and frontal pursuit area) to identical motion stimuli. Transient translational stimuli were presented along 26 headings in 3D, including all combinations of azimuth and elevation in increments of 45°. To characterize spatiotemporal response properties, we developed 3D tuning models where the temporal profiles of the velocity (V), acceleration (A) and jerk (J) component of the motion stimulus were multiplied by independent spatial tuning curves. Neural responses were fit with models of increasing complexity incorporating one ('V', 'A', 'J' models), two ('VA', 'VJ', 'AJ' models) or three ('VAJ' model) components. We found that 52% of otolith afferents were best fit by the A model and 30% by the AJ model, whereas only 19% were best fit by the VAJ model. This indicates that acceleration responses are dominant in otolith afferents. In contrast, 7% of (including vestibular/cerebellar nuclei and the 5 cortical areas) were best fit by the V model, 19% and 11% by the VA and VJ models, and 59% by the VAJ model , indicating that velocity responses were common in central cells. These analyses reveal that a remarkable spatio-temporal transformation takes place between the otolith afferents, which carry cosine-tuned linear acceleration and jerk signals that are spatially aligned, and their targets in the brainstem and cerebellum, where neurons exhibit non-linear, mixed selectivity for multiple temporal components of the stimulus. Furthermore, the velocity, acceleration and jerk components of response for central neurons

often show dissimilar spatial tuning, being encoded in a strongly non-linear and non-separable manner . Our analysis also shows that little further processing occurs downstream, such that similar spatio-temporal properties are found in brainstem/cerebellar nuclei and multiple cortical areas. These results suggest that the first synapse represents a key signal transformation, shaping how self-motion is represented in central vestibular circuits and diverse cortical areas.

Disclosures: **S. Liu:** None. **J. Laurens:** None. **R. Chan:** None. **X. Yu:** None. **D. Dickman:** None. **G.C. DeAngelis:** None. **D.E. Angelaki:** None.

Poster

803. Vestibular System: Central Pathways

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 803.04/DD12

Topic: D.07. Vestibular System

Support: N_HKU735/14

Title: Modulatory role of orexin on synaptic transmission in the central vestibular system

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Abstract: Orexin is known to modulate synaptic plasticity in the hippocampus and contribute to social memory in adult rodents. While orexin neurons in the lateral hypothalamus project to the vestibular nucleus (VN), the role of orexin in the maturation of vestibular functions remains unexplored. We hypothesized that orexin modulates synaptic transmission in the VN, regulating the expression of vestibular-related behaviors during postnatal development. Our immunohistochemical results showed that orexin receptors and orexin-immunopositive neurons are present in the VN. Also, pharmacological perturbation of orexin receptors in the VN of neonatal rats led to impairment in developmental acquisition of vestibular-related behaviors, such as air-righting reflex. To understand the role of orexin on synaptic transmission in the VN, we employed *in vitro* whole-cell patch-clamp technique to study the action of orexin on the excitability of neurons in the medial vestibular nucleus (MVN) of rats at postnatal day 14. Treatment with orexin led to reductions in both the amplitude and frequency of miniature inhibitory postsynaptic current (mIPSC). This suggests that orexin decreases presynaptic release of inhibitory transmitters and postsynaptic depolarization within the MVN. Notably, we found that agonist of orexin 2 receptor reduced the frequency but not amplitude of mIPSC. All in all, we demonstrated that orexin suppresses synaptic inhibition on MVN neurons. We further

investigated whether orexin-modulated mIPSC is mediated by $GABA_A$ receptors or glycine receptors. With the use of bicuculline and strychnine, we observed that orexin decreased mIPSC mediated by $GABA_A$ receptors, but not glycine receptors. Taken together, our findings provide us with fundamental knowledge about the modulatory role of orexin in GABAergic transmission in the VN and its impact on postnatal refinement of neural circuit for vestibular-related behavior.

Disclosures: Y. Jiang: None. **T. Lam:** None. **C. Ma:** None. **D. Shum:** None. **J. Wang:** None. **Y. Chan:** None.

Poster

803. Vestibular System: Central Pathways

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 803.05/DD13

Topic: D.07. Vestibular System

Support: CIHR

Title: Temporal whitening of natural self-motion stimuli by early vestibular pathways

Authors: *K. E. CULLEN[1], D. E. MITCHELL[2], A. KWAN[3], J. CARRIOT[4], M. J. CHACRON[2];
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Abstract: Understanding how the brain generates appropriate behavior and accurate perception in response to incoming sensory signals remains a fundamental challenge in neuroscience. The common wisdom is that neural coding strategies are adapted to the statistics of the sensory signals found in the natural environment. Specifically, early sensory pathways are thought to efficiently process natural stimuli by matching their tuning properties to their statistics, thereby removing redundancy and thus maximizing information transmission. If this is the case, neural tuning should be inversely proportional to stimulus power, such that the resulting neural response is independent of frequency (i.e. “whitened”). To date, however, there has been no experimental demonstration that such a match exists. Here we show for the first time how whitening is achieved by sensory pathways. Specifically, we recorded from vestibular neurons during natural self-motion and found that whitening occurs sequentially, beginning at the level of the sensory periphery, and is then further refined centrally. Notably, individual neurons at the first central stage of processing suggested exceptional whitening that could not be explained solely by considering their tuning properties. We found that the apparent whitening observed for central neurons was due to a close match between their comparatively high resting discharge variability

and their high-pass tuning, and self-motion statistics. Our results therefore show that neural variability contributes to the "whitening" observed in the response spectra for natural vestibular stimuli, and suggest that this is the case for other sensory systems.

Disclosures: K.E. Cullen: None. **D.E. Mitchell:** None. **A. Kwan:** None. **J. Carriot:** None. **M.J. Chacron:** None.

Poster

803. Vestibular System: Central Pathways

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 803.06/DD14

Topic: D.07. Vestibular System

Support: NIH Grant T32 DC011499

NIH Grant K08 DC013571

Title: Central vestibular neurons integrate inputs from limb and labyrinth in an additive manner

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Abstract: The maintenance of balance is an inherently multimodal process. Vestibular and proprioceptive afferent information is processed by the central nervous system and used to generate an estimate of body position and movement in space that shapes corrective postural reflexes to external perturbations. Our group recently demonstrated in decerebrate and conscious cat preparations that hindlimb somatosensory inputs converge with vestibular afferent input onto neurons in multiple CNS locations that participate in balance control. While it is known that head position and limb state modulate postural reflexes, the combined influences of the two inputs on the activity of vestibular nucleus (VN) neurons is unknown. In the present study, we compared the responses of VN neurons to vestibular and hindlimb stimuli delivered separately and together in conscious cats. Extracellular single-unit recordings were obtained from neurons in the caudal aspects of the VN complex. Sinusoidal whole body rotation in the roll plane was used as the search stimulus. Units responding to the search stimulus were tested for their responses to 10° ramp-and-hold roll body rotation (vestibular stimulation), 60° extension hindlimb movement, and both movements delivered simultaneously. Composite response histograms were fit by a model of low and high pass filtered limb and body positon signals using least squares nonlinear

regression. Most neurons that responded to vestibular and limb stimulation did so in an additive fashion. VN neurons that exhibit these integrative properties likely participate in adjusting vestibulospinal outflow in response to limb state.

Disclosures: D.M. Miller: None. **C.D. Balaban:** None. **W.M. DeMayo:** None. **G.H. Bourdages:** None. **B.J. Yates:** None. **A.A. McCall:** None.

Poster

803. Vestibular System: Central Pathways

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 803.07/DD15

Topic: D.07. Vestibular System

Title: Monosynaptic viral tracing reveals direct inputs to mouse efferent vestibular neurons

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Abstract: *Background:* Many sensory modalities are modulated by efferent input from the central nervous system (CNS), allowing central influence of sensory inflow. One prominent example of this is the efferent vestibular system, despite intensive physiological investigation though, the underlying mechanisms and purpose of central nervous control of the peripheral vestibular labyrinth remain hypothetical. Previous work has demonstrated that activation of the cholinergic efferent vestibular nucleus (EVN) (located in the brainstem) directly modulates peripheral vestibular end organs including hair cells as well as vestibular primary afferent fibres. While more recent investigations have exposed facets of the underlying physiological and anatomical properties of the EVN, a lack of understanding regarding EVN circuit dynamics makes it impossible to link vestibular efferent activity to behaviour. *Objective:* Here we sought to determine the context within which the EVN is activated by tracing the monosynaptic inputs to this group of neurons. *Methods:* We used monosynaptic rabies tracing to determine the direct inputs to EVN neurons. In mice (n = 3) expressing Cre under the control of the choline acetyl transferase (ChAT) promotor we expressed the rabies glycoprotein (G) selectively in EVN neurons. Following G expression, we injected glycoprotein-deficient rabies (RABVdeltaG) virus expressing a fluorescent protein into the horizontal and posterior semicircular canals in the inner ear of the same animal. Histological analysis was performed to identify the direct inputs to EVN neurons. *Results:* We observed direct inputs from neighbouring vestibular nuclei including the medial and lateral vestibular nuclei, as well as from regions of the reticular formation and other parts of the brainstem. *Conclusions:* The identification of direct monosynaptic inputs to mouse EVN neurons with rabies virus will allow us to expand hypothesis regarding EVN function. In

addition, this method will allow us to manipulate EVN neurons, or their inputs, via electrical, chemical or optogenetic methods providing a means to systematically explore the context-dependent modulation of peripheral vestibular function.

Disclosures: M.A. Mathews: None. **A. Murray:** None. **A.J. Camp:** None.

Poster

803. Vestibular System: Central Pathways

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 803.08/DD16

Topic: D.07. Vestibular System

Support: NIH Grant DC006429-06S1

Title: Convergence of linear acceleration and yaw rotation signals in the vestibular nucleus

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Abstract: Linear acceleration signals carried by vestibular afferents innervating the utricle and yaw rotation velocity signals carried by afferents originating from semi-circular canals converge upon neurons in the vestibular nucleus. The majority of non-eye movement neurons in the vestibular nucleus receive these convergent signals. Canal-otolith interactions have been shown to be non-linear in these neurons, but the mechanisms that produce these convergent responses are poorly understood. Earlier studies of convergent responses have not allowed systematic, independent manipulation of the frequency and amplitudes of the translational and rotational signals. The goal of the present study is to characterize the convergent responses. Awake, behaving macaques were placed on a turntable mounted on a horizontal sled. The rotation and translation motors were independently controlled. First, the unimodal responses to sinusoidal translational and rotational stimuli were characterized. Then, responses to combined stimuli (2 or 0.3 Hz translation at 0.1g with 2, 0.5, or 0.3 Hz superimposed rotation at 30, 60 or 90°/s) were then compared to the unimodal responses in the time and frequency domains. The discrete Fourier transform was applied to Kaiser-filtered instantaneous firing rates to identify magnitude and phase of the translation and rotation frequency components of the convergent response. It was determined that convergent responses are sub/super additive dependent upon stimulus intensity and acceleration directional heading. Frequency components of each stimulus mode were present (e.g. the 2 Hz translation and 0.5 Hz rotation) in the convergent response, as well as interactions (e.g. 1.5 and 2.5 Hz components), suggesting a nonlinear, multiplicative combination. Response phase to each stimulus mode were often different between unimodal and

convergent trials. These data provide tests of models for convergent interactions, such as simple gating, addition, coincidence detection, and divisive normalization. The divisive normalization model was extended into the time domain to model instantaneous firing rates. The magnitudes of frequency components present in the convergent responses were best modeled by divisive normalization; however, the phases of the components in the convergent responses were not easily explained using any of the existing simple neural models.

Disclosures: B. Abbatematteo: None. **L.H. Carney:** None. **M. Wei:** None. **S.D. Newlands:** None.

Poster

803. Vestibular System: Central Pathways

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 803.09/DD17

Topic: D.07. Vestibular System

Support: N_HKU 735/14

Title: Behavioral expression of orexin-modulated transmission in the vestibular nucleus of postnatal rats

Authors: *U. LAM[1], C. MA[1], D. SHUM[1], J. WANG[2], Y. CHAN[1];
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Abstract: Orexin is known to participate in body balance and motor coordination via modulating synaptic transmission in the central vestibular system of adult animals. We hypothesize that orexin also regulates the maturation of vestibular functions during postnatal development. To test whether neonatal perturbation of orexinergic synapses in the vestibular nucleus (VN) exerts any effect on the acquisition of vestibular-related behaviors, we blocked or activated orexin receptors in the VN of postnatal day (P) 1 rats by implanting drug-containing Elvax slice onto the dorsal surface of VN for slow release of the drug to the underlying VN. Pharmacological intervention was achieved by loading the slices with orexin, orexin receptor antagonist (SB334867) or orexin receptor agonist ([Ala11, D-Leu15]-orexin-B). Specific behavioral tests including negative geotaxis (a graviceptive response), surface righting and air righting were performed on these rats at different postnatal stages until adulthood. Neonatal treatment with orexin receptor antagonist accelerated acquisition of negative geotaxis, surface righting, as well as air righting in the course of early postnatal development. In contrast, neonatal treatment with orexin or its receptor agonist delayed acquisition of negative geotaxis and surface righting. Adult rats pretreated at neonatal

stage with orexin receptor agonist or antagonist were further tested for (i) spatial navigation by dead reckoning test; (ii) motor coordination by rotarod test and balance beam test. Treatment with orexin receptor antagonist enhanced the performance of dead reckoning while treatment with agonist impaired the performance of both dead reckoning and motor coordination. Taken together, our findings demonstrated that orexinergic modulation in the VN impacts developmental refinement of neural circuit for vestibular-related behaviors. [Supported by N_HKU735/14]

Disclosures: **U. Lam:** None. **C. Ma:** None. **D. Shum:** None. **J. Wang:** None. **Y. Chan:** None.

Poster

803. Vestibular System: Central Pathways

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 803.10/EE1

Topic: D.07. Vestibular System

Support: BMBF grant 01GQ1004A

BMBF grant 01GQ1004B

Title: Convergence properties of sparse codes adapted to natural head motion

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Abstract: Sparse representations of natural stimuli have been shown to be useful models of neuronal population codes in a variety of sensory systems. Here we investigate whether the same principles can be applied to the vestibular system. We learned a sparse code for vestibular stimulation based on 6-degree-of-freedom measurements of angular velocity and linear acceleration of the human head. The resulting set of 6-dimensional time-varying basis functions, or kernels, captures the interdependencies between rotational and translational inputs as well as temporal signal patterns. We compared the convergence properties of this set of kernels to those of neurons in the vestibular nucleus (VN) and the rostral fastigial nucleus (FN), the first points of convergence for one-dimensional linear and angular vestibular afferent motion signals. We found that several properties of the sparse code matched those of central vestibular neurons measured in physiological experiments on mammals.
The sparse code consisting of a set of 6D time-varying kernels was learned in order to efficiently

represent natural head movements using a previously described method, namely a multivariate dictionary learning algorithm. The code was trained using samples of recorded linear acceleration and angular velocity of head motion from 10 different subjects performing 7 different activities each (running, biking, walking on grass, walking on pavement, playing soccer, walking upstairs, walking downstairs) using an inertial measurement unit, the MTx from Xsens.
Similarly to VN neurons, different learned kernels predominantly represent either linear acceleration, angular velocity or both. Furthermore, we observed a distributed encoding of gravitational and inertial components of linear acceleration. This is consistent with the observation that VN and FN neurons tend to encode a linear combination of purely inertial translation and acceleration due to gravity. These findings suggest that the observed convergence properties of our sparse code are indeed a result of adaptation to natural stimulus patterns and support the hypothesis that the otolith/canal convergence of central vestibular neurons is optimized in order to efficiently encode head motion.

Disclosures: P. Hausamann: None. **S. Glasauer:** None. **M. Kleinsteuber:** None. **P. MacNeilage:** None.

Poster

803. Vestibular System: Central Pathways

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 803.11/EE2

Topic: D.07. Vestibular System

Support: DFG GR988/20-2

Title: Connectivity of the human vestibular cortex revealed by diffusion-based probabilistic fiber tracking

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Abstract: The posterior insula/retroinsular cortex including the lateral sulcus has been associated with self-motion perception, gravity-related processing and the integration of vestibular, optokinetic, proprioceptive and tactile signals. Two areas, referred to as the parieto-insular vestibular cortex (PIVC) and the posterior insular cortex (PIC), represent subareas in this human vestibular system. PIVC and PIC both respond to vestibular stimuli, but PIVC is inhibited whereas PIC is excited by visual motion. The structural connectivity of human PIVC and PIC as

not yet been investigated *in vivo*. Therefore, we investigated the cortical/subcortical connectivity of PIC and PIVC using diffusion-weighted magnetic resonance imaging (MRI) and probabilistic tractography. Anatomical T1-weighted, functional (fMRI), and diffusion-weighted (DWI) images were acquired from 16 healthy participants. A cortical and subcortical reconstruction of the anatomical images was conducted by Freesurfer. Seed regions for the tracking algorithms (PIVC and PIC) were identified in each individual brain by fMRI based on their response to caloric vestibular and visual motion stimulation, respectively. Subcortical target regions were identified in each individual brain by the Freesurfer reconstruction. Additionally, sub-divisions of the thalamus were defined by a Morel-based standard atlas. DWI were acquired along 30 diffusion orientations. Probabilistic tracking with seeds in PIVC and PIC were performed by FSL tools. Track terminations projected to the cortical surface showed that PIVC and PIC shared connections to the insular/lateral sulcus, superior temporal cortex and inferior frontal gyrus. A comparison of the connectivity showed that PIVC was more connected to the anterior insula, Heschl's gyrus and the posterior parietal regions, whereas PIC had more connections to the supramarginal gyrus and superior temporal sulcus. For both seed regions, subcortical connections were observed with vestibular nuclei of the thalamus and the putamen. However, PIVC showed stronger connectivity with the lateral pulvinar than PIC. Our findings suggest that PIVC and PIC have a unique connectivity finger print and should be considered separate areas of the cortical vestibular network.

Disclosures: **M.W. Greenlee:** None. **A. Wirth:** None. **S.M. Frank:** None. **A.L. Beer:** None.

Poster

803. Vestibular System: Central Pathways

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 803.12/EE3

Topic: D.07. Vestibular System

Support: Deutsche Forschungsgemeinschaft (GR988/20-2)

Title: Visual-vestibular processing in the human sylvian fissure

Authors: *S. M. FRANK[1], A. M. WIRTH[2], P. U. TSE[1], M. W. GREENLEE[2];
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Abstract: The processing of vestibular cues in humans is well understood on the subcortical level, however, the organization of the cortical vestibular network is less clear. A central role is assumed for the region including and surrounding the posterior part of the Sylvian fissure (also

called lateral sulcus), extending into the posterior insula. Previous functional imaging studies have reported activation in this region during vestibular stimulation and labelled the activation cluster as parieto-insular vestibular cortex (PIVC), following terminology in primates. However, the organization of the Sylvian vestibular network is likely more complex, because another area, labelled posterior insular cortex (PIC), is located in close vicinity posterior to PIVC (Frank et al. 2014). Originally, PIC has been described as a region processing visual object motion cues (e.g., Sunaert et al., 1999; Orban et al., 2003). However, recently, vestibular responses have been reported for PIC as well, suggesting that PIC is part of the vestibular network (Frank et al., 2014). To date, no study has directly compared areas PIVC and PIC in the same participants, rendering the organization of the center of human vestibular cortex unclear. Therefore, in this study (Frank et al., 2016), we defined and compared the areas known as PIVC and PIC in the same participants (n = 15), using caloric vestibular and visual object motion stimuli in functional magnetic resonance imaging (fMRI). An independent vestibular localizer with bithermic caloric stimulation and a visual object motion localizer (dynamic white random dots moved at 15°/s in one of twelve translational directions) were employed to determine locus and size of PIVC and PIC, respectively. We find that both areas respond to caloric vestibular cues, however only the multivariate activity pattern of PIVC in the right hemisphere reliably represented the direction of caloric stimulation. During visual object motion, activation in PIVC was suppressed, whereas PIC was activated. On both, single-subject and group levels, PIC appeared to be split in separate anterior and posterior clusters. Anterior PIC was located in close vicinity to PIVC, whereas posterior PIC was located closer to the posterior ending of the Sylvian fissure. Future studies should therefore consider that the central vestibular network in the Sylvian fissure of humans consists of at least two functionally and anatomically separate areas.

Disclosures: **S.M. Frank:** None. **A.M. Wirth:** None. **P.U. Tse:** None. **M.W. Greenlee:** None.

Poster

804. Vestibular System: Periphery

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 804.01/EE4

Topic: D.07. Vestibular System

Support: BMBF Grant 01 GQ 1407

NIDCD grant DC014368

Title: Response characteristics of horizontal semicircular canal afferents to behaviorally-inspired stimuli in late-stage larvae of Xenopus laevis

Authors: K. D. GENSBERGER[1], S. HÄNZI[1], M. G. PAULIN[2], H. STRAKA[1], *L. F. HOFFMAN[3];
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Abstract: Though the discharge characteristics of semicircular canal afferent neurons have been investigated in many different animal models, very few studies have endeavored to probe afferent discharge with stimuli resembling self-motion consequences of natural locomotion behaviors. In the present study we measured head kinematics of late stage *Xenopus laevis* larvae during free swimming, which provided the inspiration for the stimuli used to investigate the evoked discharge of individual afferents projecting from the horizontal semicircular canal cristae. Head kinematics during swimming were determined from video capturing short epochs in which animals were free from touching the walls of a small tank. Frame-by-frame analyses were conducted by identifying the eyes in each frame and measuring the angular deviation of the chord connecting their centroids. Stage 51-53 larvae exhibited extremely active swimming in short episodes (2 – 4 sec). Angular head movements in the yaw plane during this locomotion behavior typically ranged between 4 – 6 Hz, with peak angular velocities that reached 400°•s^{-1}. Horizontal semicircular canal afferents in these animals exhibit comparable physiologic heterogeneity as observed in other animal models, including broad diversity in spontaneous discharge rate and interspike interval coefficient of variation (CV), sensitivity, and phase. The analyses of head kinematics during natural swimming compelled our focus on higher stimulus frequencies and a variety of peak velocities during electrophysiological recordings of evoked discharge. Afferents exhibiting higher sensitivities and phase leads, associated with higher values of spontaneous discharge CV, revealed nonlinear response amplitude modulation with increasing peak velocities. Behaviorally-relevant stimulus frequencies of 2 – 4 Hz resulted in a change in response mode to phase locking, whereby further increases in peak head velocities were not accompanied by a comparable increase in peak discharge rate. The response amplitudes of afferents with lower sensitivities and phases, associated with lower spontaneous discharge CV, exhibited stable sensitivities at the stimulus magnitudes tested, indicating more linear characteristics of their response amplitudes. The responses of these afferents were more likely to remain in a frequency modulated mode at behaviorally-relevant frequencies, and more apt to encode increasing head velocity with comparable changes in discharge rate. These findings support the notion that the heterogeneity in afferent discharge characteristics subserve different roles in head movement coding.

Disclosures: K.D. Gensberger: None. **S. Hänzi:** None. **M.G. Paulin:** None. **H. Straka:** None. **L.F. Hoffman:** None.

Poster

804. Vestibular System: Periphery

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 804.02/EE5

Topic: D.07. Vestibular System

Support: UCLA Academic Senate Grant

Title: Adaptive modifications in vestibular epithelia of Egyptian fruit bats

Authors: K. R. CHOY[1], Y. N. TON[1], *W. METZNER[1], L. F. HOFFMAN[2];
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Abstract: It is widely acknowledged that bats are among the most agile of mammals by virtue of their aerial behaviors involved in obstacle avoidance and/or prey capture while maneuvering in conditions of low ambient light. While some bat species exhibit adaptations of their cochleae to accommodate the acoustic requirements of echolocation, previous investigations have revealed a notable absence of architectural adaptations of the vestibular labyrinth that would support putative demands for enhanced high frequency head movement coding that are likely associated with greater agility. This motivated the present investigation of cellular modifications within the peripheral vestibular epithelia. Through the present study we tested the general hypothesis that the vestibular periphery exhibit cellular adaptations that are consistent with enhanced capabilities for high-frequency head movement coding. This was achieved by histologic analyses of hair cells and afferent dendrites within the striolae and central zones of utricles and semicircular canal cristae (respectively) harvested from Egyptian fruit bats (*Rousettus aegyptiacus*), which were compared to similar regions in specimens from mice (*Mus musculus*). Utricular striolae and crista central zones were identified as the regions receiving afferent calyces immunolabeled with anti-calretinin (Calb2). We found that total hair cell counts in striolae from *Rousettus* and Mus were similar, though a greater number of hair cells were found in the central zones of *Rousettus* compared to those in *Mus*. Antibodies to β-3-tubulin were used to label all afferent calyces, which enabled unequivocal identification of all type I hair cells. The striolae and central zones in *Rousettus* were found to exhibit greater proportions of type I hair cells (72.5 ± 3.6% and 86.8 ± 1.2%, respectively, relative to all hair cells) compared to these regions in *Mus* (57.2 ± 2.7% and 63.5 ± 1.1%, respectively; $p<10^{-5}$). The expression of oncomodulin, a calcium-binding protein found in striolar and juxtastriolar hair cells, was found to be more extensive in utricles from *Rousettus* compared to *Mus* ($p<10^{-5}$). The expression of Kv7.4 (i.e. KCNQ4) a low-voltage activated potassium channel associated with striolar and central zone calyces, also appeared to be more extensive in neuroepithelia from *Rousettus* compared to *Mus*. These data indicate that vestibular epithelia in *Rousettus* exhibit cellular adaptations supporting enhanced capabilities for

rapid, agile head movements compared to that found in *Mus*. These adaptations are likely driven by requirements of head stabilization during flight and echolocation.

Disclosures: **K.R. Choy:** None. **Y.N. Ton:** None. **W. Metzner:** None. **L.F. Hoffman:** None.

Poster

804. Vestibular System: Periphery

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 804.03/EE6

Topic: D.07. Vestibular System

Support: The People Programme (Marie Curie Actions) of the European Union's Seventh Framework Programme (FP7/2007–2013) under grant agreement 624158

Title: Dynamics of vestibular afferents and their contribution to neck motor-unit activity during electrical vestibular stimulation

Authors: *P. A. FORBES[1,2], A. KWAN[3], B. G. RASMAN[2], D. E. MITCHELL[3], K. E. CULLEN[3], J.-S. BLOUIN[2];
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Abstract: The nervous system's ability to encode and integrate multiple streams of sensory information affords us with the ability to engage and understand the world around us. The capacity for individual sensory systems to encode natural stimuli can be described by evaluating their dynamic range of performance. For example, the spectrum of light that is visible to the human eye ranges in frequency from 430 - 770 THz, while the human ear can perceive sounds at frequencies from 20 Hz - 20 kHz. The vestibular system, which encodes rotational and translational head motion in space, is described as having a physiologically relevant range of 0-25 Hz. This corresponds with the approximate bandwidth of vestibular input (0-30 Hz) caused by head movement during natural self-motion. Recent studies, however, have demonstrated that neck muscle activity is correlated to electrical vestibular stimuli up to 75 Hz, suggesting that vestibular afferents can evoke muscle responses at higher frequencies. It may seem irrelevant to examine sensory input to muscle activity beyond the physiologically relevant range since the mechanical output of a muscle cannot effectively contribute to postural control. However, exploring the limits of system performance can provide novel insights into the mechanisms underlying neural computations. Therefore in this study, we explore the dynamic range of the vestibular sensorimotor system by recording vestibular canal afferent responses (irregular and regular) in non-human primates, as well as single motor unit activity in a neck muscle

(sternocleidomastoid) in humans (n = 8) during electrical vestibular stimulation up to 300 Hz. Stimuli for both primate and human subjects included single sinusoids from 25-300 Hz and band-limited noise currents from 0-300 Hz. We found that both regular and irregular afferents respond to input stimuli up to 300 Hz. Notably, the cycle-averaged modulation of the afferents' firing rate to electrical stimulation continues to increase beyond the physiologically relevant range of 0-25 Hz. Furthermore, as frequency increased, afferents show increased phase locking with the input current. Human neck muscle motor units similarly respond to inputs up to 300 Hz, although the correlation between motor unit firing and input stimulus is reduced above ~125 Hz. Motor unit response gains peak at 75 Hz and decrease thereafter, while phase lag decreases continually across the bandwidth. Together these results demonstrate that the vestibular system can respond to input and contribute to muscle activity at very high frequencies. This may be relevant during high frequency transient events such as those experienced during direct head impacts.

Disclosures: **P.A. Forbes:** None. **A. Kwan:** None. **B.G. Rasman:** None. **D.E. Mitchell:** None. **K.E. Cullen:** None. **J. Blouin:** None.

Poster

804. Vestibular System: Periphery

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 804.04/EE7

Topic: D.07. Vestibular System

Support: PRODEP - DSA/103.5/15/7449

VIEP-BUAP 2016

Title: The ORL-1 receptor activation inhibits the voltage gate calcium current in vestibular afferent of rat

Authors: *E. SESEÑA MENDEZ[1], R. VEGA[2], A. ORTEGA[2], E. LUIS[2], E. SOTO[2];
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Abstract: The vestibular system permanently is modulated by neuromodulators as opioid peptides both at the central and peripheral level. The nociceptin/orphaninFQ peptide (N/OFQ) peptide and its receptor opioid receptor like-1 (ORL-1) has been found to be expressed in the vestibular nuclei complex, and N/OFQ has been shown to modulate the electrical activity of the medial vestibular nucleus neuron. In this work we evaluated in the vestibular afferent neurons

isolated the effect of ORL-1 activation in the voltage-gate calcium current (ICa), in the action potential and in the electric discharge of the vestibular afferent neurons, additionally we evaluated the changes of intracellular calcium through of calcium imaging.The results shown that the perfusion of N/OFQ decreased the high voltage activated ICa (HVA) without significantly modifying the low voltage activated ICa (LVA), the inhibition of the HVA ICa component was dependent on the concentration used. The specific ORL-1 antagonist UFP101 or the preincubation of neurons with pertussis toxin completely occluded the N/OFQ inhibitory action upon the calcium current. Elsemore, the use of ω-ctx-MVIIA (specific N type Calcium channel blocker) alsooccluded the effect of ORL-1 activation. The effect of the N/OFQ on the HVA ICa was also reverted by a prepulse to +80 mV. Ours results showed that ORL-1 activation inhibits the N type ICa in the vestibular afferent neurons in a voltage-dependent manner. We thought that ORL-1 mediates a presynaptic modulation of the neurotransmitter release from the vestibular afferent terminals to the vestibular nuclei neurons, constituting a target to negatively modulate the afferent gain.

Disclosures: **E. Seseña Mendez:** None. **R. Vega:** None. **A. Ortega:** None. **E. Luis:** None. **E. Soto:** None.

Poster

804. Vestibular System: Periphery

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 804.05/EE8

Topic: D.07. Vestibular System

Support: NIH R01DC012060 (HZ)

NIH R01DC014930 (WZ)

NIH R21EY025550 (WZ)

NIH R21DC015124 (DEV)

NIH R01HL36279 (RJR)

NIH R01DK104184 (RJR)

NIH P20GM104357 (Core B, C, RJR; Pilot, FF)

Title: Vestibular hair cell loss in type 2 diabetic T2DN rats

Authors: S. WANG[1], A. ARTEAGA[1], D. S. SANDLIN[1], R. R. GUYTON[1], Y. YU[1], F. FAN[2], R. J. ROMAN[2], D. E. VETTER[3], K. T. YEE[3], W. ZHOU[1], *H. ZHU[1];
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Abstract: Patients with diabetes mellitus are 70% more likely to have dysfunctions of the vestibular system (*Agrawal et al., Disorders of Balance and Vestibular Function in US Adults Data From the National Health and Nutrition Examination Survey, 2001-2004*). The underlying mechanism, however, has not been elucidated. In the present study, we evaluated morphological changes in the vestibular end organs of T2DN rats, a new diabetic animal model that mimics the human type 2 diabetes mellitus with accelerated diabetic nephropathy. Temporal bones were collected from 16-18 month old T2DN rats (n=4) and age-matched Sprague-Dawley control rats (n=3). Cryostat sections of inner ear were prepared and stained with Cresyl Violet. Inner ear morphology was evaluated by light microscopy. Preliminary analysis revealed that there was a substantial hair cell loss in all five vestibular end organs of the T2DN rats compared to the age-matched control rats. These results suggest that type 2 diabetes mellitus causes a loss of vestibular hair cells, which may contribute to the vestibular dysfunctions seen in patients with diabetes. Ongoing studies are to further characterize the structural and functional changes of the vestibular system in the progression of diabetes. Such knowledge is essential for developing effective programs of prevention, assessment and treatment of the diabetes-induced vestibular dysfunction. (Shaoxun Wang and Alberto Arteaga contributed equally to this abstract).

Disclosures: S. Wang: None. **A. Arteaga:** None. **D.S. Sandlin:** None. **R.R. Guyton:** None. **Y. Yu:** None. **F. Fan:** None. **R.J. Roman:** None. **D.E. Vetter:** None. **K.T. Yee:** None. **W. Zhou:** None. **H. Zhu:** None.

Poster

804. Vestibular System: Periphery

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 804.06/EE9

Topic: D.07. Vestibular System

Title: Differential effect of gentamicin on inner ear hair cells and vestibular afferent dynamics in Xenopus laevis tadpoles

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Computat. Neurosci., Planegg, Germany; [4]Dept. of Neurology, Klinikum Großhadern, LMU, Ctr. for Sensorimotor Res., Munich, Germany

Abstract: Vestibulo-ocular reflexes (VOR) assist retinal image stabilization by generating compensatory eye movements in phase opposite to head movements. However, patients with Ménière's disease, suffering from vertigo, are often treated with aminoglycoside antibiotics such as gentamicin that impairs vestibular sensation. This drug causes hair cell damage and apoptosis, however, reliefs most patients from episodes of vertigo attacks. At variance with the well-described effect of gentamicin, several details about the ototoxic mechanism of this antibiotic are still unknown. Due to the experimentally more accessible amphibian compared to the mammalian inner ear and the possibility to employ semi-intact preparations for *in-vitro* morpho-physiological experimentation, we studied the consequences of gentamicin treatment in *Xenopus laevis* tadpoles. Larvae at stages 52-55 were treated with gentamicin (2, 5 and 10 μM) for 1 or 5 days prior to the electrophysiological experiments and eye movement recordings. VOR performance was evaluated by recording extraocular motor nerve discharge during passive motion with a 6-axis hexapod, which allowed separate activation of semicircular canal and otolith organs. Extraocular motor nerve recordings indicated that 1 day of gentamicin treatment reduced the semicircular canal-related activity by ~60%, while utricular-related responses remained relatively unchanged. Longer application of this drug entirely abolished all angular acceleration-induced extraocular motor discharge modulation (semicircular canal) and significantly impaired linear acceleration-induced (utricle) responses. In addition, anatomical stainings with phalloidin (stereocilia), HCS-1 (hair cells) and caspase-3 (apoptosis) revealed a gentamicin-induced disarrangement of cilial bundles and hair cell degeneration. The disruptive effect of hair cell integrity predominated in the center of the semicircular canal cupulae and along the striola of the utricular maculae. Even though *Xenopus laevis* tadpoles, as all anamniotes possess only type II hair cells, the latter differentiate into distinct subtypes with matching morpho-physiological features and regionally specific locations within the sensory epithelia. Our findings suggest that gentamicin treatment causes a partial damage and loss of vestibular hair cells with dynamic response properties and postsynaptic phasic vestibular afferent fibers. The differential influence of gentamicin in *Xenopus* tadpoles suggests a deteriorating impact of this drug of a particular population on hair cells, as in mammals, potentially allowing more insight into gentamicin-induced ototoxicity.

Disclosures: **C. Gravot:** None. **F. Branoner:** None. **A.G. Knorr:** None. **H. Straka:** None.

Poster

804. Vestibular System: Periphery

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 804.07/EE10

Topic: D.07. Vestibular System

Support: NIH Grant DC02058

Title: The vestibular calyx ending as an axon initial segment: Na^+ channels and implications for function

Authors: *A. LYSAKOWSKI[1], J. M. GOLDBERG[2];
[1]Dept. of Anat. & Cell Biol., Univ. of Illinois at Chicago, Chicago, IL; [2]Pharmacol. and Physiological Sci., Univ. of Chicago, Chicago, IL

Abstract: Our investigations of Na channel distribution with various Pan-Na_v and Na_v isoform-specific antibodies in vestibular afferents aimed to determine the Nav channel isoforms present in the axon initial segment (AIS) of various vestibular afferent classes. We have also examined their immuno-localization in the various microdomains of the calyx ending (Lysakowski et al., JNS, 2011). Electrophysiological recordings from calyx endings in different species have reported the presence of an A-current and an h-current, so we also searched for candidate molecules for these currents. Afferent class and heminodal location were determined by co-labeling with calretinin (Desai et al., JNP, 2005) and nodal and AIS marker antibodies, such as ezrin, Caspr1, beta-IV spectrin, KCNQ3, and myelin basic protein. An ancillary finding of this study was that about 80% of the time, the heminode of calyx afferents is located at or above the basement membrane in calyx afferents and at or below the same location in dimorphic and bouton afferents, providing a longer AIS for dimorphic and bouton afferents. Whether this affects afferent timing is still undetermined. The inner surface of both calyx-bearing afferent types (Domain 1) contains $Na_v1.5$, while the apical end (Domain 2) contains $Na_v1.9$ in dimorphic afferents and is truncated in calyx afferents. The outer calyx surface (Domain 3) labels with $Na_v1.2$ in dimorphic and $Na_v1.3$ in calyx afferents. $Na_v1.6$ was present at the heminodes (Domain 4) of dimorphic vestibular afferents, but not at pure calyx afferent heminodes, while $Na_v1.1$ is present in all afferents. Using various A-current candidate antibodies ($K_v1.4$, 4.2 and 4.3), we obtained light labeling of dimorphic calyces and intense labeling of dimorphic boutons with $K_v4.3$. Immunolabeling with h-current candidate antibodies (HCN1 and HCN2) produced moderate labeling with HCN2 in all calyx endings, albeit somewhat less in calyx afferents. In conclusion, calyx and dimorphic afferents appear to mostly vary in their ion channel composition and this likely has implications for their separate functions.

Disclosures: **A. Lysakowski:** None. **J.M. Goldberg:** None.

Poster

804. Vestibular System: Periphery

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 804.08/EE11

Topic: D.07. Vestibular System

Support: CONACyT grant

PROFOCIE 2015

VIEP 2016

Title: Serotonin modulation of ionic currents in the vestibular system primary afferent neurons

Authors: *E. SOTO[1], J. LIMA[2], E. LUIS[2], R. VEGA[2];
[1]Univ. Autonoma De Puebla, Puebla Pue, Mexico; [2]Inst. de Fisiología, Univ. Autónoma de Puebla, Puebla, Mexico

Abstract: The metabotropic 5-HT1B, 5-HT1D and 5-HT1F (Ahn & Balaban, 2010; Vountau & Balaban, 2013) and ionotropic 5-HT3A and 5-HT3B (Takimoto, et al., 2014) serotonin receptors have been identified in vestibular afferent neurons (VANs), suggesting that serotonin may modulate vestibular activity; however, no studies of the action of serotonin in the vestibular afferents has been carried out. The objective of this work was to determine the ionic currents modulated by serotonin in the VANs in primary culture and to determine the action of serotonin in intracellular calcium changes induced by depolarization. To define the peripheral effects of serotonin receptors in the vestibule we study the actions of serotonin on the electrical activity of cultured vestibular afferent neurons of the rat. Using whole-cell patch-clamp recording, we found that serotonin (30 μM) significantly decreased the amplitude of the inward current (attributable to Na^+ current) by 53% measured at +20 mV and the steady-state outward current by 27% measured at +30 mV. Additionally, calcium imaging recordings using the intracellular dye Fluo 4-AM, showed that serotonin (100 μM) significantly reduced the calcium responses generated by depolarization induced by perfusion of high potassium solution (20 mM). Recently, drugs such as serotonin re-uptake inhibitors have been used in the clinics for the treatment of vestibular disorders (e.g. vertigo), their effect has been interpreted in terms of their actions at the central nervous system. However, our results indicate that serotonin receptors may play an important role in vestibular afferent neuron activity modulating the inward currents of these neurons, and intracellular calcium rise caused by depolarization.

Disclosures: **E. Soto:** None. **J. Lima:** None. **E. Luis:** None. **R. Vega:** None.

Poster

804. Vestibular System: Periphery

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 804.09/EE12

Topic: D.07. Vestibular System

Title: Peripheral vestibular damage after exposure to mild, blast wave trauma

Authors: *S. LIEN, Z. MRIDHA, J. D. DICKMAN;
Neurosci., Baylor Col. of Med., Houston, TX

Abstract: The increased use of close range explosives has led to a higher incidence of exposure to blast-related head trauma. Exposure to primary blast waves is a significant cause of morbidity and mortality. Active service members who have experienced blast waves report high rates of vestibular dysfunction, such as vertigo, oscillopsia, imbalance, and dizziness. Accumulating evidence suggests that exposure to blast wave trauma produces damage to both the peripheral and central vestibular system; similar to previous findings that blast-results in damage to auditory receptors. Mice were exposed to a 63 kPa peak blast-wave over pressure and underwent behavioral assays to identify balance deficits. Furthermore, we examined the tympanic membrane of each mouse for any signs of perforation. Afterwards, we examined the vestibular receptors, central nuclei, vestibulo-ocular reflex (VOR) behavior, in dark and light, and optokinetic reflex (OKR) in mice after exposure to mild, blast wave trauma. Horizontal vestibular-ocular reflex was tested using sinusoidal motions at 0.5 Hz, 1.0 Hz, and 2.0 Hz over 20 degrees/second over 10 cycles. We also presented the mice with an optokinetic stimulus using a rotating ball containing a light source at a velocity of 20 degrees per second. Vestibular receptors and central nuclei were histologically prepared and the following measures quantified: stereocilia hair bundle counts, density of hair cells (both type I and type II) in the central and peripheral zones. The VOR gain and phase of the eye movement responses were compared for the normal (pre-blast) and the blast exposed animals. To date, we have observed perforations to the tympanic membrane, and a reduction in dark, horizontal VOR gains and alterations of phase at later time points in the animals exposed to a blast-wave over pressure. In addition, the mice had reduced light, horizontal VOR gains; however, the phase of the eye movements showed no significant alterations. We observed loss of stereocillia bundles 1 month in the cristae and otolith organs 1 month after blast-wave exposure. The mice showed decreased performance in a rotarod performance test and righting reflex test indicating some form of motor or balance deficit. Interestingly, the mice showed drastic reductions in the slow phase component of the optokinetic reflex and notable decreases in the number of fast nystagmus beats immediately after blast-wave exposure. These results suggest that blast-wave exposure can lead to peripheral vestibular damage (possibly central deficits as well) and provides some insight into causes of vestibular dysfunction in blast-trauma victims.

Disclosures: **S. Lien:** None. **Z. Mridha:** None. **J.D. Dickman:** None.

Poster

804. Vestibular System: Periphery

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 804.10/EE13

Topic: D.07. Vestibular System

Support: NIH Grant K08DC011540

Title: Mouse otolith organs in cleared temporal bone

Authors: E. TIGNOR, R. COOK, A. PERACHIO, *T. MAKISHIMA;
Univ. of Texas Med. Br., Galveston, TX

Abstract: Hypothesis: The otolith organs can be visualized within the temporal bone by modification of tissue clearing and be suitable for downstream applications. Background: Histological and anatomical studies of the mouse otolith organs are technically difficult due to small size and location embedded in the temporal bone. Two recently published protocols, SeeDB and Sca/e allow the clearing and 3-D visualization of the whole brain in mice. Our goal was to modify the two protocols to achieve 3-D visualization of inner ear organs encased in the temporal bone and use this method to measure the planar angle of the utricle to the saccule. Methods: Temporal bones were dissected from mice at various ages up to 18 months. The adult temporal bones were decalcified. After fixation in 4% paraformaldehyde in PBS, the cochlear and vestibular hair cells in the temporal bones were labeled with colorimetric dyes. Then the samples were cleared in a series of fructose solutions with increasing concentrations for the SeeDB protocol, or sucrose and urea solutions for the Sca/e protocol. Samples were viewed using light microscopy and the planar angle between the utricle and saccule measured. Results: Successful clearing of the temporal bone was achieved. The planar angle of the saccule to utricle was 80 ± 6 degrees. No difference was found between left and right or male and female temporal bones. Conclusion: Our modified version of the SeeDB and Sca/e protocols were suitable for clearing temporal bones for further downstream applications.

Disclosures: **E. Tignor:** None. **R. Cook:** None. **A. Perachio:** None. **T. Makishima:** None.

Poster

804. Vestibular System: Periphery

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 804.11/EE14

Topic: D.01. Sensory Disorders

Support: NIH DC05987

NIH DC015080

Title: Cilia genes play differing roles in aminoglycoside-induced hair cell death

Authors: T. STAWICKI[1], E. W. RUBEL[2], *D. W. RAIBLE[3];
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Abstract: Hearing loss as a result of hair cell death is a dose limiting side effect of multiple therapeutic drugs, including aminoglycoside antibiotics and chemotherapeutics. We have used genetic screening in the zebrafish lateral line system to identify novel genes involved in hair cell death and survival in response to these medications. Through screening for mutations that confer resistance to aminoglycoside-induced hair cell death we have identified a number of mutations in cilia genes, showing novel roles for these genes in hair cells. Hair cells contain a single primary cilium early in development, known as the kinocilium. This cilium is usually lost in auditory hair cells but maintained in vestibular hair cells. We found that mutations in the intraflagellar transport (IFT) genes *ift88, traf3ip, dync2h1* and *wdr35* all lead to strong resistance to neomycin-induced hair cell death. Mutations in the transition zone genes *cc2d2a, mks1,* and *cep290* lead to more moderate protection. These two classes of genes appear to play different roles in aminoglycoside-induced hair cell death. Mutations in IFT, but not transition zone genes, show a reduction in control hair cell numbers, loss of kinocilia and a reduction of neomycin uptake into hair cells. The individual IFT genes appear to differently affect hair cells as well, as mutations in *ift88, traf3ip* and *dync2h1,* but not *wdr35* show a reduction in hair cell FM1-43 uptake, a process dependent upon mechanotransduction activity. This does not appear to be due to defects in stereocilia morphology. Future work will focus on delineating the mechanisms behind the diverse roles cilia genes play in hair cells.

Disclosures: T. Stawicki: None. **E.W. Rubel:** None. **D.W. Raible:** None.

Poster

805. Visual Sensory-Motor II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 805.01/EE15

Topic: D.08. Visual Sensory-motor Processing

Title: Quantifying individual behavioral signatures in larval zebrafish

Authors: *E. A. NAUMANN, J. E. FITZGERALD, T. W. DUNN, F. ENGERT;
Harvard Univ., Cambridge, MA

Abstract: How are individual behavioral differences manifested in underlying neural circuits? In order to study such heterogeneity within a basic vertebrate visuomotor system, we performed a detailed kinematic analysis of behavioral signatures across individual zebrafish swimming in response to monocular and binocular optic flow stimuli. Using a closed-loop assay to control the visual environment precisely while monitoring behavior, we quantified kinematic variability across individual fish. While each fish effectively modulates its behavior to eye and direction-specific features of visual motion stimuli, we find that the fine details of the behavioral implementation vary substantially across individuals. Specifically, the absolute and relative frequencies of behavioral events create individual behavioral profile differences that covary across stimuli. We hypothesize that these differences are necessarily embedded within the heterogeneous activity of neurons in the pretectum and hindbrain thought to control the optomotor response. This study of behavior across individuals is crucial for our understanding of functional degeneracy within neural circuits and suggests limitations for standard models fit on average data.

Disclosures: E.A. Naumann: None. **J.E. Fitzgerald:** None. **T.W. Dunn:** None. **F. Engert:** None.

Poster

805. Visual Sensory-Motor II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 805.02/EE16

Topic: D.08. Visual Sensory-motor Processing

Title: Mismatch receptive-fields in mouse visual cortex

Authors: *P. ZMARZ, G. B. KELLER;
Neurobio., Freidrich Miescher Inst., Basel, Switzerland

Abstract: In primary visual cortex, a subset of neurons responds when a particular stimulus is encountered in a certain location in visual space. This activity can be modeled using a visual receptive field. In addition to visually driven activity, there are neurons in visual cortex that integrate visual and motor-related input to signal a mismatch between actual and predicted visual feedback. Here we show that these mismatch neurons have receptive-fields that signal a local mismatch between actual and predicted visual flow in restricted regions of visual space. These mismatch receptive-fields are aligned to the retinotopic map of visual cortex and are similar in size to visual receptive-fields. Thus, neurons with mismatch receptive fields signal local deviations of actual visual flow from visual flow predicted based on self-motion and could therefore underlie the detection of objects moving relative to the visual flow caused by self-motion.

Disclosures: P. Zmarz: None. **G.B. Keller:** None.

Poster

805. Visual Sensory-Motor II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 805.03/EE17

Topic: D.08. Visual Sensory-motor Processing

Support: NIH Grant U01NS090514

Title: An optogenetics-based approach to determine functional connectivity in the central brain of *Drosophila*

Authors: *P. T. WEIR, M. H. DICKINSON;
Caltech, Pasadena, CA

Abstract: At peripheral layers of the nervous system, mapping information flow from primary afferents to downstream neurons has been widely successful. Neuroanatomical methods enable tracing topographically organized circuits, and electrophysiology permits tracking the transformation of neuronal responses to external stimuli. In central brain regions, however, these approaches are more difficult to implement and interpret. To examine functional connectivity in a central brain circuit of the fruit fly, *Drosophila melanogaster*, we engineered flies that express the genetically encoded calcium indicator GCaMP6s in all neurons and contain the light-gated

ion channel Chrimson under UAS control. By crossing these flies to flies from various GAL4 driver lines, we can drive expression of Chrimson in genetically defined populations of neurons. In the adult progeny of such crosses, we activated the Chrimson-expressing cells with orange light while imaging activity throughout the brain, and observed light-elicited post-synaptic responses. This activity represents a map of information flow from the cell type of interest to downstream targets. By testing numerous cells types in the central complex, we are beginning to construct a connectivity diagram for circuits far from the periphery.

Disclosures: P.T. Weir: None. **M.H. Dickinson:** None.

Poster

805. Visual Sensory-Motor II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 805.04/EE18

Topic: D.08. Visual Sensory-motor Processing

Support: EY10834

EY023268

P20GM103650

Title: Action-effect contingency modulates readiness potentials

Authors: *T. VERCILLO[1], S. O'NEIL[2], F. JIANG[1];
[1]Psychology, [2]Ctr. for Integrative Neurosci., Univ. of Nevada, Reno, Reno, NV

Abstract: The temporal window between a voluntary movement and a sensory event is crucial for determining the causal relationship between action and perception. When a delay between a voluntary action and its sensory effect occurs this temporal window is compressed and the two events are bound together to preserve the sense of causality (Eagleman & Holcombe, 2002; Engbert, Wohlschlager & Haggard, 2008; Haggard et al., 2002; Sugano, Keetels & Vroomen, 2010). According to the theory of motor control, the intentional binding effect is linked to internal forward models that are based on the motor efferent copy and predict the outcome of self-produced movements (Wolpert & Ghahramani, 2000; Haggard, 2005; Tsakiris & Haggard, 2003). In support of this idea, it has been shown that the intentional binding only occurs when an action is performed with intent but not when the movement is induced by Transcranial Magnetic Stimulation (TMS). Additionally, the TMS-induced disruption of the pre-supplementary motor area (pre-SMA), a brain region involved in motor preparation and predictive mechanism, was shown to reduce the temporal binding between a voluntary action and a subsequent sensory event

(Moore et al., 2010). However, another alternative explanation for the intentional binding is that the effect might result from retrospective inferences triggered by the sensory event that follows the action (Wegner & Wheatley, 1999). In the current study, we investigated the role of the readiness potentials (Libet et al., 1983) - the pre-motor brain activity registered in SMA and the motor area of the brain - in the intentional binding effect. We recorded EEG data from 128 channels (Biosemi system) and measured the latency and the amplitude of the readiness potentials (RPs) in the Cz channel preceding the onset of the movement in a temporal window of 2 seconds. We compared RPs in an "action-effect" condition where participants performed a motor action that produced a sensory effect 200 ms later, with those measured in an "action only" condition where participants performed the voluntary movement without any sensory feedback. Our results showed different RP patterns between the two experimental conditions. The action-effect contingency significantly modulated RPs near motor areas and these modulatory effects are evident from 500 to 100 ms before the onset of the movements. Our results suggest that predictive motor processes within the motor system contribute to the intentional binding effect.

Disclosures: **T. Vercillo:** None. **S. O'Neil:** None. **F. Jiang:** None.

Poster

805. Visual Sensory-Motor II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 805.05/FF1

Topic: D.08. Visual Sensory-motor Processing

Support: Grant FP7–250013

Istituto Italiano di Tecnologia

Title: Functional properties of mirror neurons of the monkey presupplementary motor area f6

Authors: A. LIVI[1], M. LANZILOTTO[1], *M. MARANESI[2], M. GERBELLA[1], L. FOGASSI[1], G. RIZZOLATTI[1], L. BONINI[3];
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Abstract: Mirror neurons (MNs) are a class of cells originally discovered in the ventral premotor cortex of the macaque that discharge both during the execution and the observation of goal-directed motor acts, such as grasping. Recently, neurons with mirror-like properties have been described in a wide network of anatomically connected areas, including the pre-supplementary

motor area F6, where they seem to play a role in the distinction between self- and other's action. However, an extensive description of F6 MNs functional properties is still lacking.
Here we recorded single neurons activity from area F6 in three hemispheres of two monkeys during two main experimental conditions: the execution of a visuomotor task (ET) and the observation of the same task performed by an experimenter (OT). The OT was carried out in two different modes: 1) within the monkey peripersonal space, in which the monkey observed the experimenter's action presented in a subjective view (OTp); 2) in the monkey extrapersonal space, in which the monkey observed the experimenter's action from a side view (OTe). An additional control condition with a non-biological moving stimulus (NBM) was employed in order to verify the specificity of possible action observation responses in the OTe.
We recorded 359 neurons. Among them, 67 responded during action observation in the OTe, and the great majority of this subset of neurons (75%) also showed a motor response during the ET. Moreover, 46 of the 67 neurons discharging during OTe showed a marked specificity for grasping observation relative to the NBM: interestingly, 36 of them were not at all activated by the NBM. During the OTp 113 neurons showed a significant response to action observation and 39 of them discharged also during action observation in the OTe. This finding evidences a certain degree of view- and space-invariant coding of the observed action in area F6.
The results of this study support the idea that area F6 plays an important role in the action execution-observation network, and provides an additional source of information to the "core" MN areas in the parieto-frontal cortex.

Disclosures: **A. Livi:** None. **M. Lanzilotto:** None. **M. Maranesi:** None. **M. Gerbella:** None. **L. Fogassi:** None. **G. Rizzolatti:** None. **L. Bonini:** None.

Poster

805. Visual Sensory-Motor II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 805.06/FF2

Topic: D.08. Visual Sensory-motor Processing

Support: NSERC (Canada)

ORF (Canada)

CIHR (Canada)

Title: MEG shows a progressive sensory-to-motor transformation for reaching in cortical space and time

Authors: *G. BLOHM[1], H. ALIKHANIAN[2], W. C. GAETZ[3], H. C. GOLTZ[4], J. F. X. DESOUZA[5], D. O. CHEYNE[6], J. D. CRAWFORD[5];
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Abstract: Planning an accurate reaching or pointing movement towards a visual target requires a complex sensory-to-motor transformation. This includes converting an early sensory code of the target into a shoulder-centered motor plan. Despite much recent progress, it still remains unclear where, how and when this transformation is carried out in the human brain. In particular, it is unclear whether these transformations occur in a feed-forward fashion between brain areas, predicting a gradual sensory-to-motor transformation across different brain areas in the processing hierarchy; or if these transformations occur dynamically in localized regions, predicting a dynamic change from sensory to motor coding within the same brain area(s) during the task. We use high spatio-temporal resolution magnetoencephalography (MEG) in an attempt to uncover (1) which brain areas are involved in transforming visual signals into appropriate motor commands for the arm, and (2) how this transformation occurs on a millisecond time scale. Ten human subjects sat upright in the MEG apparatus and were asked to perform delayed (1500ms delay) visually-guided pointing movements towards (pro) or away from (anti) visual targets on a fronto-parallel screen. Pro- and anti-trials required opposite motor output following identical visual stimulation, which allowed distinction between the sensory goal and motor plan. A beamformer-based spatial filtering algorithm (event-related Synthetic Aperture Magnetometry) was employed to reconstruct brain activity from the MEG recordings. Using adaptive hierarchical clustering (Alikhanian, et al., 2013), we identified 16 bilateral brain regions consistently active across all 10 participants during the task. Time-frequency response analysis was employed to find significant sensory or motor coding in different frequency bands. We also computed a sensory-motor index based on alpha and beta band powers of sensory and motor coding. Together, both analyses showed brain areas purely coding sensory information in alpha and beta bands (V1/2, V3/3a and SPL). On the other end of the spectrum, PMv only showed motor coding. Interestingly, most areas displayed a progressive transition between sensory and motor coding (SPOC, AG, POJ, mIPS, VIP, IPL, STS, S1, M1, SMA, PMd and FEF) during the delay period. This demonstrates that sensory-to-motor transformations are neither carried out in a purely feed-forward fashion, nor with a single isolated brain area. Rather, our results point towards a gradual transformation in cortical space and time.

Disclosures: G. Blohm: None. **H. Alikhanian:** None. **W.C. Gaetz:** None. **H.C. Goltz:** None. **J.F.X. DeSouza:** None. **D.O. Cheyne:** None. **J.D. Crawford:** None.

Poster

805. Visual Sensory-Motor II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 805.07/FF3

Topic: D.08. Visual Sensory-motor Processing

Support: NIH R01DE011451

Title: Merging visible and invisible light in rat V1 using a cortical prosthetic system

Authors: *E. E. THOMSON, I. ZEA, Y. THENAISIE, F. WENDY, W. WINDHAM, M. NICOLELIS;
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Abstract: Rats equipped with a sensory prosthetic system that projects information from the infrared (IR) environment to somatosensory cortex (S1) readily learn to discriminate among IR sources, typically invisible to the rat. It takes approximately 4 days for them to learn to perform a simple IR discrimination task. In the present study, we investigate the consequences of projecting IR information directly to primary visual cortex (V1), a sensory area already devoted to processing electromagnetic radiation. Remarkably, when IR information is projected to V1 instead of S1, rats typically learn to discriminate IR sources on their first day of training, normally in fewer than 50 trials. We then examined the brain's ability to integrate the new IR information into its ongoing visual processing in V1. Namely, in a visual-IR integration task we presented multiple visual and IR lights simultaneously, and the animal was rewarded only for selecting those target stimuli that combined both visible and IR lights, and had to learn to ignore distractor stimuli in which only IR or only visible cues were present. Their ability to successfully perform this multimodal integration task suggests that the information from the IR prosthesis is integrated into ongoing V1 operation, rather than simply displacing or hijacking normal visual system function. This is also supported by separate experiments in which the IR prosthesis was implanted in S1, and the animals' ability to perform whisker-based tactile discriminate tasks was unimpaired.

Disclosures: **E.E. Thomson:** None. **I. Zea:** None. **Y. Thenaisie:** None. **F. Wendy:** None. **W. Windham:** None. **M. Nicolelis:** None.

Poster

805. Visual Sensory-Motor II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 805.08/FF4

Topic: D.08. Visual Sensory-motor Processing

Support: NSF-EPSCOR-1539067

NIH P20 AA017068

NIH P20 AA017068S1

NIH 1P50AA022534-01

Title: Don't look: Cerebellar and cortical activity during an antisaccade task in adolescents with FASD

Authors: *A. D. BOLANOS[1], B. A. COFFMAN[3], P. KODITUWAKKU[2], J. M. STEPHEN[3]; [1]Neurosci., [2]Pediatrics Ctr. for Develop., Univ. of New Mexico, Albuquerque, NM; [3]Neurosci., The Mind Res. Network, Albuquerque, NM

Abstract: Individuals prenatally exposed to alcohol may develop fetal alcohol spectrum disorder (FASD), which is characterized by a broad range of cognitive and behavioral deficits along with functional and structural neural anomalies. Previous studies suggest that basic sensory deficits in individuals with FASD may contribute to deficits in sensorimotor integration. Results also show atypical development of parietal and frontal cortical networks in individuals with FASD. Both cerebellar and cortical areas comprise the eye gaze network. Animal studies have demonstrated that prenatal alcohol exposure leads to cerebellar hypoplasia and human studies of children with FASD show reduced brain volume, particularly in cerebellar regions. The current study investigated the neurophysiology of the eye gaze network during an antisaccade task in adolescents with FASD compared to age-matched healthy controls (HC) using the Elekta Neuromag 306 channel magnetoencephalography (MEG). We hypothesized a difference in cerebellar, parietal, or frontal evoked response amplitude between the FASD group and HC group during antisaccades. The antisaccade task requires a saccade to the opposite visual hemifield relative to a suddenly appearing target stimulus. Eye movement was recorded and synchronized to the MEG data using an SR Research MEG-compatible eye tracker. MEG data were filtered and head movement compensation was implemented using Maxfilter. The MEG data were analyzed relative to the onset of the target. Source modeling through spatio-temporal multidipole analysis was performed on the averaged evoked response to target stimuli for correct trials. Individuals with FASD showed a significant increase in peak amplitude 104ms after target stimulus presentation in the cerebellum compared to HC. Individuals with FASD also showed a

significant increase in peak amplitude 116ms after stimulus presentation in the inferior parietal lobule compared to HC. However, behavioral performance did not differ by group. These findings suggest that individuals with FASD exhibit greater activity within the cerebellum and parietal cortex during performance of antisaccades, which may suggest increased effort. Further investigation is needed to understand the role of cerebellum in the eye gaze network to elucidate sensorimotor integration deficits in children with FASD. This project was supported in part by NSF-EPSCOR-1539067, NIH P20 AA017068, P20 AA017068S1, and 1P50AA022534-01.

Disclosures: **A.D. Bolanos:** None. **B.A. Coffman:** None. **P. Kodituwakku:** None. **J.M. Stephen:** None.

Poster

805. Visual Sensory-Motor II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 805.09/FF5

Topic: D.08. Visual Sensory-motor Processing

Support: Human Frontiers Science Program

Title: Natural saccadic eye movements of the awake, running mouse

Authors: *J. M. SAMONDS, N. J. PRIEBE;
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Abstract: Few studies have characterized the saccadic eye movements of mice despite the increasing use of the mouse as a model to study the visual system. Most eye movements for afoveate animals stabilize gaze during head movements and the lack of a fovea raises the question as to why mice make saccades. We measured saccadic eye movements in head-fixed mice running on a track ball while they were free-viewing natural images presented in front of them. Saccades were highly correlated between the eyes ($r > 0.9$). This correlation was reduced partly because the eyes tended to diverge slightly during fixations. We found that mice tend to make saccades an order of magnitude less frequently compared to primates (0.1-0.4 saccades/s). During periods of running, however, the saccade rate increased and was more comparable between mice and primates (1-2 saccades/s). Most saccades occur along the horizontal axis, as they do in other mammals (Otero-Millan et al., 2013). Saccade sizes were an order of magnitude larger in the mouse compared to primates, ranging from 5 to 30 degrees of visual angle. Both the rate and size of saccades increased as we increased the size of natural images. This range of saccade sizes largely overlaps with the known range of receptive field sizes in the primary visual cortex (V1) of mice (Niell and Stryker, 2008; Bonin et al., 2011). Such large saccadic eye

movements could act to introduce novel and independent visual information to V1 receptive fields. When we silenced the binocular visual fields in V1 by activating parvalbumin-expressing inhibitory neurons optically, we found that mice both ran and made saccades significantly less frequently. Overall, we propose that mice use horizontal saccades to scan across scenes that are correlated along the axis of running direction (e.g., along a wall) to decorrelate incoming visual information to maximize cortical information processing. Bonin V, Histed MH, Yurgenson S, Reid RC (2011) Local diversity and fine-scale organization of receptive fields in mouse visual cortex. J Neurosci 31:18506-18521. Niell CM, Stryker MP (2008) Highly selective receptive fields in mouse visual cortex. J Neurosci 28:7520-7536. Otero-Millan J, Macknik SL, Langston RE, Martinez-Conde S (2013) An oculomotor continuum from exploration to fixation. Proc Nat Acad Sci USA 110:6175-6180.

Disclosures: J.M. Samonds: None. **N.J. Priebe:** None.

Poster

805. Visual Sensory-Motor II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 805.10/FF6

Topic: D.08. Visual Sensory-motor Processing

Support: FAPESP 2014/23963-1

CNPq 458775/2014-2

FAPESP 2015/12856-2

Title: Eye movements affect the coupling between visual information and body sway of young adults

Authors: *P. F. POLASTRI ZAGO[1], M. B. BRITO[1], F. A. BARBIERI[1], R. L. MORAES[1], D. N. LIMA[1], B. C. CAVALIERI[1], J. A. BARELA[2], S. T. RODRIGUES[1];
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Abstract: Gaze behavior appears to be associated with changes in stability. However, little is known about the effects of visual mechanisms in the postural control. The aim of the study was to investigate the effect of eye movements on the coupling between visual information and body sway in young adults. Thirteen young adults (20.3 ± 1.8 years) stood in a quiet upright stance on a force platform, inside of a “moving room”, using an eye tracker device for sixteen trials of 60 seconds. The room was stationary in the first eight trials. In the following eight trials the room

was oscillated backward and forward at 0.2 Hz with amplitude of 0.65 cm. The participants remained looking forward and performed four visual tasks: free-gaze with absent target (AT); gaze directed to stationary target (ST); and moving target with certain (CT) and uncertain (UT) locations. The target was a filled circle with 3 cm of diameter displayed in the room's frontal wall. In the latter two conditions, the task required horizontal saccadic eye movements towards the target moved to right or left at 1.1 Hz. Target eccentricity was 11.5 degrees of visual angle. Dependent variables were: mean latency between horizontal saccades and visual target, number and duration of fixations, mean sway amplitude at anterior posterior (AP) direction, gain and phase between room's movement and body sway. Results showed lower number of fixations and higher fixation duration at ST task and higher number of fixations and lower fixation duration at CT compared with UT task. Only for the stationary moving room, negative mean latency revealed saccadic anticipation to the target at CT compared to UT task. Mean sway amplitude (AP) was higher during the room's movement compared with stationary room. Phase values were similar and close to zero across conditions; gain values were higher at AT task compared with UT one. These novel results suggest that gaze control changes the coupling between visual information and body sway of young adults and this effect seems dependent on the visual task challenge.

Disclosures: **P.F. Polastri Zago:** None. **M.B. Brito:** None. **F.A. Barbieri:** None. **R.L. Moraes:** None. **D.N. Lima:** None. **B.C. Cavalieri:** None. **J.A. Barela:** None. **S.T. Rodrigues:** None.

Poster

805. Visual Sensory-Motor II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 805.11/FF7

Topic: D.08. Visual Sensory-motor Processing

Support: Program for Brain and Mind - Methodist Hospital Research institute

NIH 5R00DK082644

Title: Characterizing the dynamic neural transition from sensory input to motor output - an EEG/fMRI study

Authors: ***T. T. NGUYEN**[1], T. POTTER[1], R. G. GROSSMAN[2], C. KARMONIK[2], Y. ZHANG[1];
[1]Biomed. Engin., Univ. of Houston, Houston, TX; [2]Houston Methodist Hosp. Neurolog. Inst., Houston, TX

Abstract: Brain regions associated with visual perception and motor execution have been extensively studied. However, dynamic interactions of the regions associated with the perception and processing of stimuli and the generation of willed motor responses remain poorly known. We present a multimodal neuroimaging approach to characterize neural dynamics during the transition from sensory input to willed motor output using electroencephalography (EEG) and concurrent functional magnetic resonance imaging (fMRI) recording. EEG and fMRI data were collected from three right-handed healthy participants while viewing the serial presentation of unpleasant and pleasant faces presented in random order. The subjects were instructed to squeeze their right hand if a face was perceived as emotionally unpleasant. Structural MRI was acquired for constructing subject-specific head models and defining the source spaces to perform EEG source imaging. FMRI BOLD signal activation maps revealed multiple brain regions activated by unpleasant face stimuli and willed movement of the right hand, including the bilateral visual cortices and fusiform face areas, left motor cortex and supplementary motor area, bilateral insula and posterior cingulate cortex. Activated regions of interest (ROI) were used as fMRI spatial priors to guide EEG source imaging, yielding a time-course of current density for each ROI. The sequence of time courses of current density of ROIs following the presentation of a face perceived as unpleasant was of early activation of the bilateral visual cortices followed by activation of the cingulate cortex and insula followed by left supplementary motor area and of brief left motor cortex activation followed by prolonged activation of the left motor cortex that was concurrent with the willed movement of the right hand. The findings provide information on the neural dynamics during the transition between sensory input and motor output during the generation of willed movement evoked by stimuli that evoke emotion and demonstrate the capability of EEG/fMRI multimodal imaging to examine neural activity with high spatiotemporal resolution.

Disclosures: **T.T. Nguyen:** None. **T. Potter:** None. **R.G. Grossman:** None. **C. Karmonik:** None. **Y. Zhang:** None.

Poster

805. Visual Sensory-Motor II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 805.12/FF8

Topic: D.08. Visual Sensory-motor Processing

Support: National Eye Institute Grant 5T32 EY017271-07

NIH Grant 1P50-MH103204

Center for the Neural Basis of Cognition

Title: Beta frequency coherence between PPC and PFC local field potentials in monkeys performing a memory guided saccade task

Authors: *R. J. GERTH[1,3], N. HALL[2,3], C. OLSON[3], C. COLBY[2,3];
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Abstract: The dorsolateral prefrontal cortex (PFC) and the posterior parietal cortex (PPC) of the macaque monkey are linked to each other by dense reciprocal axonal projections. Both areas contain neurons that exhibit spatially selective cue-period, delay-period and saccade-period activity during performance of a memory guided saccade task. How interconnections between the two areas contribute to their function is not yet well understood. To explore this issue, we have analyzed the coherence of local field potential (LFP) signals monitored simultaneously in PFC and PPC during performance of a memory guided saccade task. During each experimental session, we recorded with an eight-channel linear electrode array in each area. This approach permitted comparing signals recorded from multiple pairs of sites within a single session. However, it prevented systematic placement of the saccade target relative to the response field, because neurons at different sites had different patterns of spatial selectivity. We presented targets at two widely separated contralateral sites during each session and characterized spatial selectivity at each site post hoc on the basis of differential neuronal responses on trials involving the two targets.
We analyzed coherence of LFPs recorded at pairs of sites, one in PFC and the other in PPC. We focused on oscillations in the beta range (12-25 Hz). The degree of coherence depended on time during the trial and also on whether the target was at the preferred or non-preferred location. During the visual epoch, there was a decrease in coherence. In the delay epoch there was an increase in coherence. In the peri-saccadic epoch, coherence again decreased. Each effect was most pronounced during trials in which the target was at the preferred location.

Disclosures: R.J. Gerth: None. **N. Hall:** None. **C. Olson:** None. **C. Colby:** None.

Poster

805. Visual Sensory-Motor II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 805.13/FF9

Topic: D.08. Visual Sensory-motor Processing

Support: HHMI

Title: Descending control of landing in *Drosophila* is gated by behavioral state

Authors: *J. M. ACHE, S. NAMIKI, A. LEE, K. BRANSON, G. M. CARD;
HHMI/Janelia Res. Campus, Ashburn, VA

Abstract: *Drosophila* have a numerically small nervous system but are nonetheless able to perform a plethora of sophisticated behaviors in different contexts. For example, they eat, mate, escape, fly, and land when appropriate. In many cases, two completely different actions can be elicited by the same stimulus, depending on context. For example, a dark looming object on the fly's retina can elicit an escape takeoff in a walking fly, or a landing response in a flying fly. Furthermore, most behaviors are driven by a population of only about 300 descending interneurons (DNs), which connect the brain to motor areas of the ventral nerve cord. Controlling a large number of behaviors with such a small number of DNs is a challenging task, which vertebrates face as well. Using electrophysiology, optogenetics, and computer vision strategies, we show how a small population of descending neurons controls one of the most important behaviors in a fly's life - landing.

Through an extensive optogenetic activation screen, we discovered only two bilateral pairs of DNs whose activation drives simultaneous extension of all six legs. These leg extensions mimic those observed during the 'landing response', which flying flies perform when confronted with an approaching object. We recorded the activity of all four landing DNs via whole-cell patch-clamp in awake, behaving flies, while tracking leg movements using computer vision algorithms. We found that both DN types were multimodal, responding to visual and mechanosensory stimuli. Activity in landing DNs preceded leg movements, and the firing rate of the neurons was positively correlated with leg displacement magnitude. This indicates that landing DNs are not simple command neurons, which elicit a pre-programmed movement sequence in an all-or-none manner, but instead control leg motion using a rate code. Surprisingly, visual responses were sharply reduced in one landing DN type and completely eliminated in the other when the fly was not flying. Further investigation revealed that this flight-dependence of the visual response is mediated by the known flight-related neuromodulator, octopamine, in only one of the DN types, but by a different, likely internal circuit mechanism in the other.

These results suggest that the *Drosophila* nervous system ensures the landing motor pattern does not interfere with other behaviors, like walking or takeoff, by switching off the landing DNs when the fly is not flying. Such behavioral gating of DNs, in which individual neurons are switched on or off depending on the animal's behavioral state, may be a simple, general mechanism for action-selection and descending motor control.

Disclosures: J.M. Ache: None. **S. Namiki:** None. **A. Lee:** None. **K. Branson:** None. **G.M. Card:** None.

Poster

805. Visual Sensory-Motor II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 805.14/FF10

Topic: D.08. Visual Sensory-motor Processing

Support: NIH F32 MH102049

CV Starr Fellowship in Neuroscience

Title: Altered balance between top-down and bottom-up saccadic control across exploration and exploitation

Authors: *B. A. EBITZ[1], T. MOORE[3], T. BUSCHMAN[2];
[2]Princeton Neurosci. Inst., [1]Princeton Univ., Princeton, NJ; [3]Neurobio. Dept. & HHMI, Stanford Univ., Stanford, CA

Abstract: We are constantly bombarded by numerous visual stimuli, any of which could be targeted by saccadic eye movements. Some stimuli will be targeted because of top-down information (e.g. it matches a searched-for-template or is known to be rewarding). Other stimuli attract gaze in a bottom-up manner: they are visually salient due to contrast or brightness. Critically, little is known about how we combine top-down and bottom-up influences into unified eye movement decisions, much less about how we adjust the balance between these influences in different environments or to achieve different goals. In order to begin to understand these questions, we characterized how the balance between top-down and bottom-up attentional priorities changes across different decision-making regimes. In variable and uncertain environments, periods of sampling options known to be rewarding ("exploit" states) are interspersed with periods of sampling alternative, uncertain options in order to learn about the environment ("explore" states). Emerging electrophysiological and psychophysical work suggests that exploration is an indeterminate state in which choices are random. However, we find that saccadic selection is not truly random during exploration. Instead, it is influenced by bottom-up factors: task-irrelevant, visually salient stimulus features have a greater impact on gaze during periods of exploration. This shift from top-down to bottom-up control may be a computationally efficient way to allow for the discovery of novel rewards, overcoming the strong pull of reward history on gaze. It remains unclear whether exploration is associated with enhanced bottom-up control or, instead, if bottom-up control is permitted through reduced top-down influences. We anticipate that the pattern of saccadic choice and reaction time will disambiguate these possibilities. Ultimately, this work provides a model for future investigations into how top-down and bottom-up attentional priorities are balanced and adjusted, with application to work in both humans and rhesus macaques.

Disclosures: **B.A. Ebitz:** None. **T. Moore:** None. **T. Buschman:** None.

Poster

805. Visual Sensory-Motor II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 805.15/FF11

Topic: D.08. Visual Sensory-motor Processing

Support: Leverhulme Trust Grant RPG-146

Title: Using the optocollic response to determine visual perception in the homing pigeon (Columba livia).

Authors: ***J. T. ERICHSEN**[1], C. M. DILLINGHAM[2], J. A. BARNES[1], T. MEYDAN[1]; [1]Cardiff Univ., Cardiff, United Kingdom; [2]Inst. of Neurosci., Trinity Col. Dublin, Dublin, Ireland

Abstract: As their eye movements are limited, many birds respond to continuous movement of their visual world by a reflexive oscillation of their heads, analogous to OKN eye movement in primates. To elicit this optocollic response (OCR), we have placed homing pigeons in the centre of a circular arena of high-resolution monitors and then presented drifting vertical gratings while recording their head movements. If the combination of the spatial frequency and contrast of the grating is beyond their visual capabilities, the reflexive movements cease, allowing us to establish what the animals can and cannot see. The results thus far have successfully replicated a previously published spatial contrast sensitivity curve obtained by more invasive electrophysiological methods. However, our initial study of 3 males and 3 female birds suggests that the males have a much higher sensitivity to contrast at low spatial frequencies. Such a sex difference has not been found in humans, and the reason for such a dimorphism is not clear.
In addition to defining the limits of spatial vision, this psychophysical approach can permit an investigation of the effect of stimulus velocity on the OCR. We employed two paradigms in this experiment: (1) presentation of a continuously moving drifting pattern whose velocity is increased by a constant step, and (2) presenting the same velocities in a randomized order with a static pattern in between. The results from experiment 1 show that, if the step is 10^{o}/s, the OCR continues up to very high velocities (e.g. 70^{o}/s), whereas in experiment 2, OCR only became evident quickly for velocities lower than 20^{o}/s. The presentation of a higher velocity drifting pattern only elicited OCR after a prolonged “warm up” period, which became longer the higher the step change in velocity. In humans, such a delay in the development of OKN is normally only observed in young infants. These data suggest that the pigeons are only able to stabilise their view quickly when the movement of the visual world produces a retinal image shift that is

relatively slow.
This approach is clearly applicable to exploring the visual performance of any animal in which gaze stabilization is achieved by head rather than eye movements.

Disclosures: **J.T. Erichsen:** None. **C.M. Dillingham:** None. **J.A. Barnes:** None. **T. Meydan:** None.

Poster

805. Visual Sensory-Motor II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 805.16/FF12

Topic: D.08. Visual Sensory-motor Processing

Support: Poitras Foundation

Title: Marmoset viewing preferences for social stimuli

Authors: J. HYMAN[1], *R. LANDMAN[2], J. SHARMA[1], R. DESIMONE[1], G. FENG[2];
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Abstract: Eye tracking has been used for many years in humans to investigate looking patterns, especially with respect to socially salient stimuli. Eye tracking is especially advantageous because it can be used with individuals who cannot follow verbal instructions, such as infants, and is non-invasive. More recently, eye tracking has been used to investigate reliable differences between autistic and typically developing children. Differences are found in preferential looking at faces vs bodies, eyes vs mouth, biological vs non-biological motion and gaze following in response to another individual's cues. For future development of a transgenic primate model of genetic variations associated with autism, it is important to know the extent to which wild-type primate behavior is comparable to human behavior. In non-human primates, eye tracking is typically done in head-fixed animals implanted with a head holder. Here we demonstrate preferential looking patterns using head-free eye tracking in a common marmoset (*Callithrix jacchus*). Marmosets were habituated to a small transport cage with a view port for looking at a computer screen. A small video shown at various locations on the screen was used for calibration. After calibration, a variety of stimuli were shown to investigate animals' preference for images of humans, marmosets and other animals in various forms and over multiple sessions. In support of previous studies, we find marmosets prefer to look at animals rather than objects and faces rather than the rest of the body. In addition, there is preference for upright faces over inverted faces. Within faces, we find a preference for looking at eyes, followed by mouth and other features. These results suggest that looking preferences in marmosets are similar to humans

in certain respects that are relevant to autism. The absence of lengthy animal training requirements and the head-free preparation make it relatively easy to test a larger number of animals, which is useful for comparing between groups.

Disclosures: J. Hyman: None. **R. Landman:** None. **J. Sharma:** None. **R. Desimone:** None. **G. Feng:** None.

Poster

805. Visual Sensory-Motor II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 805.17/FF13

Topic: D.08. Visual Sensory-motor Processing

Support: Howard Hughes Medical Institute

Title: Internal models hold the key to prey fixation in dragonflies: evidence from a perturbative study

Authors: *M. MISCHIATI, A. LEONARDO;
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Abstract: While maneuvering to intercept prey, dragonflies continuously rotate their head to hold the prey at a fixed position on the eye. These head rotations counteract movement of the prey-image from both self-motion and prey-motion, and do so with zero delay when the prey moves at constant velocity. Such predictive control cannot result from visual reflexes, but requires forward and inverse models of the body and internal estimates or memory of prey motion.
A crucial implication of these observations is that much of head steering during interception flights is internally driven and non-visual in nature. To investigate this, we induced interception flights to computer-controlled artificial prey that were temporarily hidden from view. We used a suspended tunnel to occlude part of the prey trajectory, and positioned the dragonflies in specific perching conditions that reproduced the period of prey occlusion across flights.
When the tunnel was placed so to hide ~20% of the prey trajectory after takeoff, the dragonflies continued chasing their prey without hesitation. The accuracy of prey fixation on the eye when the prey was occluded was comparable to when it was visible. In both conditions, head rotations counteracted the body rotations that would have caused prey-image drift on the eye. Continuous visual feedback from prey motion is thus not necessary for target fixation during pursuit of constant speed prey, and internal models alone can drive the behavior.
During flight, prey-image drift from self-motion is substantially larger than that from prey-

motion, making it hard to evaluate if both are counteracted by the head during prey occlusion. We thus also analyzed prey fixation during the preparatory head movements the dragonfly makes before takeoff. In this regime there is no self-motion and we could unequivocally assess whether head rotations counteracted expected prey movement during periods of occlusion. We found no qualitative difference in prey fixation during periods of prey occlusion versus visibility, demonstrating that head movements are driven by an internal representation of the prey's speed that persists without vision for at least 70 ms.
These results highlight the salience of internal models in the prey fixation behavior of dragonflies, and establish a novel paradigm for investigating the neural implementation of these computations in an insect.

Disclosures: M. Mischiati: None. **A. Leonardo:** None.

Poster

806. Bimanual Coordination: Behavior and Muscles

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 806.01/FF14

Topic: E.04. Voluntary Movements

Title: Unimanual versus bimanual arm cycling movements - muscle activity variances.

Authors: M. MRAVCSIK[1], N. ZENTAI[1], L. BOTZHEIM[2], *J. LACZKO[1,3,2];
[1]Univ. of Pecs, Pecs, Hungary; [2]Information Technol. and Bionics, Pazmany Peter Catholic Univ., Budapest, Hungary; [3]Laboaratory of Rehabil. Technol., MTA Wigner Res. Ctr. for Physics, Budapest, Hungary

Abstract: Arm cycling movements were performed on a cycle ergometer (MEYRA, Kalletal Germany) by 19 right handed, able bodied individuals. They cycled in various crank resistance conditions (RCs) unimanually and bimanually. In our earlier study, it was found that crank resistance didn't have a significant effect on joint angle variances. Considering variances at muscle level, when cycling was performed unimanually by the right arm for a short time (10 cycles), the crank resistance didn't have a significant effect on variances (across participants and cycles) of muscle activity patterns. This study has now been extended for longer movement time (30 cycles per participants and cycling conditions). Fatigue was not a factor as the movement time was still short. It was hypothesized that 1. The crank resistance doesn't have a significant effect on variances of arm muscle activities when cycling either bimanually or unimanually. 2. There is no significant difference in variances of muscle activity patterns comparing unimanual and bimanual cycling regarding either the left or the right arm. Methods: Participants cycled with a cadence of 60 revolutions per minute. Surface EMGs were recorded from the right and left

arm's biceps, triceps, delta anterior, delta posterior. Variances (across cycles) of muscle activities (mean EMG amplitudes) were computed for each participant. Mean muscle activity variances were compared for cycling with low RC (1.16Nm) versus high RC (3.09Nm). Cycling was performed bimanually and also unimanually with the left and with the right arm. Variances obtained in low and high RCs were compared for each arm, for unimanual and bimanual cycling separately and variances obtained in unimanual versus bimanual cycling were compared for the two arms and for both RCs separately by student's t test ($p=0.05$). Results: 1.There was significant effect ($p<0.01$) of RCs on muscle activity variances both in uni- and in bimanual cycling. The variance was significantly higher during cycling against larger resistance.This was found for the right and left arm too. 2. There were significant differences in the variances comparing uni- and bimanual cycling. The variance was significantly higher when cycling was performed unimanually compared to the bimanual case ($p<0.01$). This holds in each RC, for the left and the right arm. Conclusion: These results present quantitatively that motor control of arm cycling, at muscle level, is more stable when cycling is performed against lower resistance and when cycling is executed by two arms instead of one. Opposing our expectations, the central control may not be so stable when crank resistance is increased or when arm cycling is performed by one arm.

Disclosures: **M. Mravcsik:** None. **N. Zentai:** None. **L. Botzheim:** None. **J. Laczko:** None.

Poster

806. Bimanual Coordination: Behavior and Muscles

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 806.02/FF15

Topic: E.04. Voluntary Movements

Support: JSPS KAKENHI 16J05329

Title: Kinematic analysis of bimanual coordination during food manipulation in head-fixed rats

Authors: ***M. IGARASHI**, J. WICKENS;
Okinawa Inst. of Sci. and Technol., Okinawa, Japan

Abstract: How is bimanually coordinated behavior represented in the central nervous system? Rodents have been used to understand the neural mechanism of motor control by fully taking advantage of the combination of electrophysiology and genetic tools such as optogenetics and DREADDs (Designer Receptors Exclusively Activated by Designer Drugs). Although there are the potential advantages of use of rodents, the animal has not been employed to study bimanual coordination because of limited behavioral measures of bimanual coordination. Here, we

demonstrate a novel behavioral measurement of rats' bimanual coordination under a head-fixed behavioral system. In the task, rats were trained to be head-fixed and allowed to retrieve donut-shaped sausages. Rats' bimanual eating behavior was recorded with two high-speed cameras at 200 fps. Three dimensional coordinates of their paws were reconstructed with Matlab thereby detailed kinematic analysis of paw movements became possible. Rats showed a variety of bimanual movements such as rotations, adjustments and strokes of the food. We demonstrate a cross-correlation based analysis to classify those bimanual behaviors into asymmetric and symmetric bimanual movements. We propose potential usage of the behavioral framework in the future.

Disclosures: **M. Igarashi:** None. **J. Wickens:** None.

Poster

806. Bimanual Coordination: Behavior and Muscles

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 806.03/FF16

Topic: E.04. Voluntary Movements

Support: NSF1358756

Title: Characterizing de novo learning of a feedback control policy using a novel bimanual reaching task

Authors: *J. PAKPOOR[1], A. M. HAITH[2];
[1]Neurol., Johns Hopkins Univ., Baltimore, MD; [2]Neurol., Johns Hopkins Univ. Sch. of Med., Baltimore, MD

Abstract: A central question in motor skill learning is how we acquire the ability to continuously control novel tools, such as riding a bike or playing a video game. Such skills require learning of a new feedback control policy relating sensory states to actions. Determining how new feedback control policies are acquired is complicated by the relationship between the new controller to be learned, and pre-existing controllers. In some cases, the new control policy to be learned might be similar enough to existing controllers that these can simply be recalibrated and repurposed (e.g. reaching with a 30° rotated cursor), with no need to create a brand new policy (Telgen et al., 2014, J Neurosci 34(41):13768-79). In other cases, existing controllers might directly conflict with the new controller to be learned (e.g. reaching with a mirror-reversed cursor), in which case existing control policies may interfere with learning and/or the expression of the new one. In the presence of such conflicts, it is impossible to determine whether the difficulty in performing a new task is due to an inability to learn a new feedback control policy,

or an inability to suppress a prepotent existing one.
We devised a novel bimanual cursor-control task which avoids these confounds, allowing us to unambiguously track de novo learning of a feedback control policy. In a planar bimanual reaching task, we mapped arm locations to cursor locations in such a way as to ensure that the new actions required would be orthogonal to those required at baseline; the x-location of the cursor was determined by the y-location of the left hand, and the y-location of the cursor was determined by the x-location of the right hand. Consequently, the new control policy to be learned was orthogonal to that used at baseline.
Participants found this task extremely challenging at first, but were able to gain fluid control over the cursor after practicing for four consecutive days. Path length and reaction time reduced steadily with practice, while peak velocity increased. To specifically examine feedback control, we occasionally displaced the target during movement. Early in learning, participants showed little or no systematic response to this perturbation, but with practice developed a rapid and robust feedback response. After ~4 hours of practice, participants' performance was similar to that for veridical, unimanual control, with the exception that latency of responses for the newly learned skill was 50-100 ms longer than in the unimanual condition. Thus, in the absence of interference from existing controllers, a few hours of practice is sufficient to establish a new feedback control policy.

Disclosures: J. Pakpoor: None. **A.M. Haith:** None.

Poster

806. Bimanual Coordination: Behavior and Muscles

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 806.04/FF17

Topic: E.04. Voluntary Movements

Title: The role of handedness in a multi frequency bimanual coordination task

Authors: *S. PANZER[1], M. MASSING[1], D. KENNEDY[2], C. H. SHEA[2];
[1]Saarland Univ., Saarbrücken, Germany; [2]Texas A&M Univ., College Station, TX

Abstract: Handedness is related to asymmetries in the functions of the neural structure and appears on the behavioral level on asymmetries in the manual performance. But until now the role of handedness in bimanual coordination tasks is not completely understood. Kennedy and colleagues (2015) were interested if limb dominance is associated with interference that occurred in the contralateral limb in a bimanual isometric coordination task. They showed that in dominant right handers interference in a 1:2 or 2:1 bimanual task occurred in the limb which had to produce half of the force compared to the contralateral limb, independent of the dominant

limb. The present experiment had three aims: 1st to replicate these findings in a dynamic 1:2 or 2:1 multi frequency task where performers had to move their wrists; 2nd to determine the impact of hand preference in performing the dynamic bimanual task; 3rd to determine the impact when the start position was changed from 0° to 180° or from 180° to 0°. Changing the start position required performers to start each cycle of the movement pattern with homologous muscle activation (0°) or non-homologous pattern (180°). By starting from a non-homologous pattern, the amount of possible distortions (both wrists were in the opposite direction or both limbs moving in the opposite direction) in a cycle increased. Dominant left handers (N=13; LQ = -78.94) and dominant right handers (N=16; LQ = 91.25) (determined by the Oldfield (1971) test) were required to perform a 2:1-0°, a 2:1-180°, an 1:2-0°, or an 1:2-180° (order counterbalanced) coordination pattern using Lissajous feedback (10 practice trials and 3 test trials in each condition; 30 s each). The harmonicity value was calculated to quantify the distortions in the trial-time series. The analysis demonstrated that regardless of handedness, or the different start positions, and regardless of whether the left or right wrist was moving faster, harmonicity was always lower in the slower moving wrist than in the faster moving wrist. As in the Kennedy et al. (2015) experiment, the muscle activation pattern of the faster moving wrist appeared to influence the movements of the slower moving wrist, independent if the performers were dominant left or right handed. The present results extend the previous findings to a dynamical bimanual coordination task. However, it appears that the Lissajous display minimized the effect of the different start positions, and allowed participants to produce relatively stable coordination patterns in each of the conditions. More interesting is the finding that handedness did not result in different performance patterns.

Disclosures: **S. Panzer:** None. **M. Massing:** None. **D. Kennedy:** None. **C.H. Shea:** None.

Poster

806. Bimanual Coordination: Behavior and Muscles

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 806.05/FF18

Topic: E.04. Voluntary Movements

Title: Competing demands of individual movements modulate visual control in bimanual activities

Authors: ***S. D. SARDAR**, S.-H. YEO, R. F. REYNOLDS, J. ALLSOP, T. D. PUNT;
Univ. of Birmingham, Birmingham, United Kingdom

Abstract: The control of bimanual activities is characterised by strong inter-limb coupling, even when the demands of the individual movements involved vary considerably. Such behaviour

creates a clear challenge for how attention is 'divided' based on these 'competing' demands. We measured limb and eye movements in 10 right-handed participants while they made visually-guided pointing movements to small and large targets presented on a touchscreen monitor. Movements were either, 1. unimanual; 2. bimanual congruent (same sized targets); or 3. bimanual incongruent (different sized targets). Target size and hand dominance were expected to contribute to the relative difficulty of the individual movements. While kinematic data of limb movements confirmed strong elements of coupling, asymmetries also emerged. For congruent bimanual movements, while target acquisition was synchronous and there was no directional bias in eye movements, accuracy was reduced for the non-dominant limb. For incongruent bimanual movements, further asymmetries became evident. Movements towards the small target were associated with enhanced accuracy regardless of limb dominance. However, where the small target was acquired by the non-dominant limb, eye movements were biased in this direction and the target was acquired earlier. Data highlight the complex challenges involved in the visual control of bimanual activities. Our task elicited directional biases in eye movements and asynchrony in the terminal phase of movement to optimise control. Hand dominance was critical in modulating these findings.

Disclosures: S.D. Sardar: None. **S. Yeo:** None. **R.F. Reynolds:** None. **J. Allsop:** None. **T.D. Punt:** None.

Poster

806. Bimanual Coordination: Behavior and Muscles

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 806.06/GG1

Topic: E.04. Voluntary Movements

Support: ESA (European Space Agency)

Prodex

IAP VII/19 DYSCO (BELSPO, Belgian Federal Government)

Title: Bimanual corrective responses are driven by the biomechanics of the upper limbs

Authors: *D. CORDOVA BULENS, F. CREVECOEUR, J.-L. THONNARD, P. LEFÈVRE; Univ. catholique de Louvain, Louvain La Neuve, Belgium

Abstract: Most daily tasks involve bimanual coordination, which in many cases offers redundancy in the way the two limbs can achieve task success. Although previous work highlighted the importance of biomechanics in a broad range of contexts, its impact on bimanual

control has received comparatively little attention. Here, we show that the nervous system considers biomechanical factors to optimally distribute control across limbs during a bimanual force production task as well as when correcting for external disturbances.
The task consisted in producing a 20 N force using both arms towards visual targets representing the resultant force in the horizontal plane. Visual feedback was provided by mapping the sum of forces applied on the fixed robotic interface onto cursor motion in a virtual reality display (KINARM, BKIN Tech.). The force distribution between arms was unconstrained. Eight different directions of force production were tested. In 80% of the trials, the cursor jumped perpendicularly to the target direction after crossing the midline between the start and goal targets (jumps were ±3cm or ±5cm), requiring participants to adjust the resultant force online. We extracted the baseline forces produced by each arm after stabilization at the target force during unperturbed trials. We observed that control was distributed across limbs in a way that was compatible with a bio-inspired optimal control model. In the tested joint configuration, the relative contribution of each arm to the total force was direction dependent. Indeed, the left arm contributed more for targets placed in the 2^{nd} and 4^{th} quadrants and the right arm for targets in the 1^{st} and 3^{rd} quadrants of the horizontal plane.
The results from the perturbed trials showed that the motor correction produced by each arm was dependent on the direction of the perturbation. In particular, the motor corrections were dynamically adjusted in a way that was predicted by the direction-dependent weighting of each arm extracted during stationary holding. The initial adjustments appeared as early as 140ms following the perturbation, and displayed a clear modulation accounted for by the biomechanical constraints. For instance, for a target placed in the midline towards the body of the participant and for a rightward corrective cursor movement, the relative contribution of the left arm increased and that of the right arm decreased compared to the baseline trials. For a leftward corrective movement, we observed the opposite modulation of correcting forces.
These results show that the mechanism that optimally distributes mechanical efforts across limbs takes biomechanics into account in the online compensation of a perturbation.

Disclosures: D. Cordova Bulens: None. **F. Crevecoeur:** None. **J. Thonnard:** None. **P. Lefèvre:** None.

Poster

806. Bimanual Coordination: Behavior and Muscles

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 806.07/GG2

Topic: E.04. Voluntary Movements

Support: NIH Grant R01HD059783

Title: Bilateral reflexes in shared bimanual task are asymmetric

Authors: *J. SCHAFFER[1], R. L. SAINBURG[1,2];
[1]Kinesiology, The Pennsylvania State Univ., University Park, PA; [2]Neurol., Penn State Col. of Med., Hershey, PA

Abstract: Previous research from our lab has shown that during a bilateral task, in which a single virtual object is carried by both arms, perturbation to the dominant arm produces reflexive responses in the non-dominant arm (Mutha and Sainburg, 2009). However, when the same bilateral motions are performed without a common object, bilateral reflexes responses are absent. In that study, we did not assess dominant arm responses to non-dominant arm perturbations. Given the substantial movement asymmetries between the dominant and non-dominant arms, we now ask whether such bilateral responses are symmetric.
We tested this question using a virtual object (bar) manipulation task in which both arms are required to work together while moving a shared object into a target. At the onset of occasional and unpredictable trials, a solenoid acted as a clutch preventing motion along the medial-lateral axis, which produced errors in motion of the bar. Our preliminary results suggest that reflex responses (EMG responses that occurred < 100 milliseconds following the perturbation) were elicited in the arm that did not receive the perturbation, whether the perturbation occurred on the dominant or non-dominant arm. However, contralateral responses of the non-dominant arm were substantially larger than those of the dominant arm. These findings are consistent with previous research on unimanual movements, suggesting that the non-dominant hemisphere/arm is specialized for feedback responses to unexpected changes in environmental conditions.

Disclosures: J. Schaffer: None. **R.L. Sainburg:** None.

Poster

806. Bimanual Coordination: Behavior and Muscles

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 806.08/GG3

Topic: E.04. Voluntary Movements

Title: A virtual-reality based circle drawing task to assess spatial and temporal characteristics between mirror- and non-mirror-symmetrical upper limb movements

Authors: *P.-C. SHIH[1], C. J. STEELE[1,2], A. VILLRINGER[1,3], B. SEHM[1];
[1]Dept. of Neurol., MPI for Human Cognitive and Brain Sci., Leipzig, Germany; [2]Dept. of Psychiatry, Cerebral Imaging Centre, Douglas Mental Hlth. Institute, McGill Univ., Montreal, QC, Canada; [3]Mind and Brain Institute, Charité and Humboldt Univ., Berlin, Germany

Abstract: Coordinating limbs in a meaningful way is essential for most daily tasks. Previous studies found behavioral differences between two fundamental bimanual movement patterns: moving the limbs in a mirror-symmetrical (MS) pattern was less demanding than a non-mirror-symmetrical (non-MS) pattern (Keslo et al., 1989). A better understanding of the underlying processes might help in the development of bimanual training in patients with motor impairments. Here, we developed a virtual reality(VR) based circle drawing task to assess and compare the kinematic characteristics of MS and non-MS movements. A circle drawing task, involving shoulder and elbow joints, was developed on an upper limb robotic exoskeleton device (KINARM, BKIN Technologies). Ten young right-handed adults performed a total of four bimanual conditions: two non-MS (clockwise and counterclockwise) and two MS (inward and outward) conditions. Participants were instructed to draw consistent circles in synchrony with a 0.85Hz auditory metronome. During performance, the ideal circle (radius=7cm) was displayed. Position data was collected at a rate of 1000 Hz and the spatial and temporal features of movement were compared. First, participants exhibited decreased circularity during non-MS movements compared to MS movements. Furthermore, non-MS movements showed larger deviation distances from the ideal circle, compared to MS movements (Fig1). Second, during the bilateral counterclockwise condition (non-MS), we observed a time lag between hands, with the right hand in the leading position. Taken together, our VR-based circle drawing task is sensitive for differentiating behavioral performance during different bilateral movement patterns. The observed spatial and temporal variations between MS and non-MS conditions might reflect different neural processes involved in interlimb coordination during fundamental bilateral movement patterns. In the future, studies on stroke patients will be conducted to provide knowledge on how stroke changes movement behavior, in order to benefit rehabilitation goal setting.

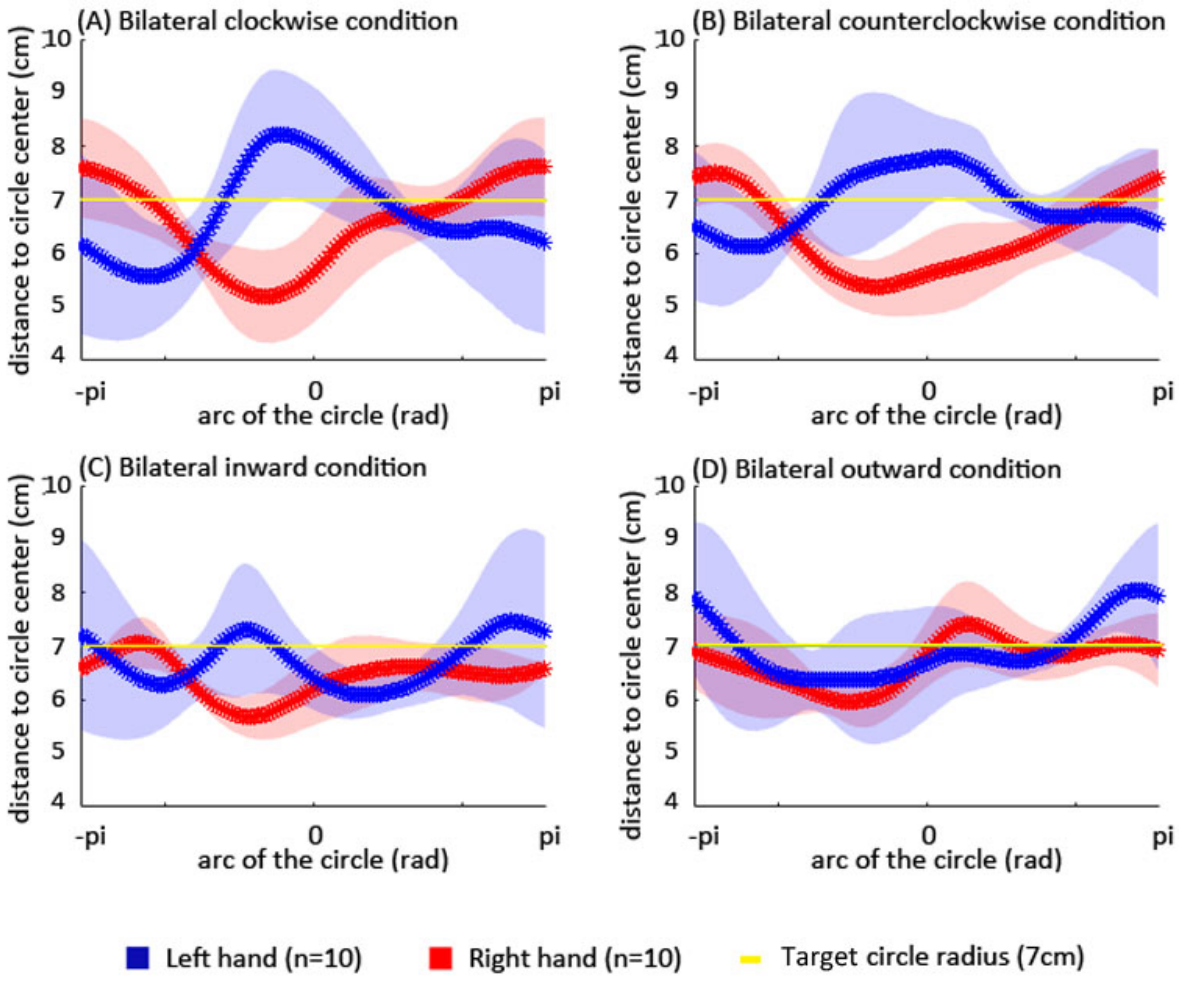

Fig 1. Deviation from target circle in different conditions. The shading indicated the standard deviation.

Disclosures: **P. Shih:** None. **C.J. Steele:** None. **A. Villringer:** None. **B. Sehm:** None.

Poster

806. Bimanual Coordination: Behavior and Muscles

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 806.09/GG4

Topic: E.04. Voluntary Movements

Title: Inter-limb reaction times depend strongly on the certainty of perturbation direction and modestly on the coordination pattern

Authors: *I. KURTZER, T. FITZGERALD, A. YASIN;
Biomed. Sci., New York Inst. of Technol. Col. of Osteo. Med., Old Westbury, NY

Abstract: Fast bimanual actions are more stable when subjects voluntarily co-activate the same muscles of the two arms versus co-activate different muscles of the two arms. This difference in motor performance partially reflects greater neural connectivity between the same muscles of the two arms versus different muscles. We predicted that differences in motor performance would also be evident for bimanual reactions to a load perturbation, faster co-activation of the same arm muscles compared to co-activation of different arm muscles. 10 healthy individuals (mean age = 25yro, 7M/3F) interacted with a programmable robot (KINARM, BKIN Technologies) which supported both arms in the horizontal plane and allowed flexion and extension of their shoulder and elbow joints. Direct vision of their arms was obscured by a metal partition and no targets or hand feedback was provided. Surface emg (Bortec AMT-8) was obtained from an elbow flexor (EF) and elbow extensor (EE) of each arm. In each trial (240 total) subjects experienced a sudden mechanical load (elbow torque = 2Nm) which could flex or extend their right elbow. Subjects were instructed to resist the perturbation of the right arm and also react with their left arm in a "mirror" or "opposite" manner. Accordingly, bimanual responses could either involve co-activation of the same arm muscles (flex both arms; extend both arms) or co-activation of different arm muscles (flex right arm/extend left arm; extend right arm/flex left). Subjects were encouraged to react as quickly as possible. Lastly, the instruction was always fixed in a block of trials - "mirror" or "opposite" - however, the perturbation direction could either be predictable or randomly alternating. When the perturbation direction was predictable, muscle onset times of the unperturbed left arm were similar for parallel activation (EF = 133 ± 6 ms; EE = 136 ± 7 ms) as reciprocal activation (EF = 127 ± 7 ms; EE = 137 ± 5 ms), $p > 0.5$. Onset times for parallel activation were significantly delayed when the perturbation direction was uncertain (EF = 194 ± 14 ms; EE = 181 ms ± 7 ms), $p < 0.001$. Moreover, the delay induced by directional uncertainty was even greater for reciprocal activation (EF = 215 ms ± 16 ms; EE = 197 ms ± 12 ms), $p < .05$. In sum, inter-limb reactions are equally fast for parallel and reciprocal activation when the perturbation direction is certain, are substantially delayed by uncertainty in perturbation direction, and are more severely delayed for reciprocal than parallel activation.

Disclosures: I. Kurtzer: None. **T. Fitzgerald:** None. **A. Yasin:** None.

Poster

806. Bimanual Coordination: Behavior and Muscles

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 806.10/GG5

Topic: E.04. Voluntary Movements

Title: The consistent nature of interference associated with the activation of homologous and non-homologous muscles

Authors: *D. M. KENNEDY, C. H. SHEA;
Dept. of Hlth. & Kinesiology, Texas A&M Univ., College Station, TX

Abstract: Recent research has indicated the neural crosstalk manifests differently during the coordination of the limbs depending on several factors including the activation of homologous or non-homologous muscles (Kennedy et al. 2014). More specifically, the results indicated a distinct pattern of interference in the forces produced by the left limb that could be associated with the activation of homologous and non-homologous muscle in the right limb during a 1:2 coordination task. The purpose of the current investigation was to determine if the pattern of interference observed in a 1:2 coordination task could be used to predict how and when interference occurred during a 1:3 coordination task and to develop an index to characterize the interference between the limbs. Participants rhythmically produced a pattern of isometric forces in a 1:2 and 1:3 multi-frequency coordination pattern using either homologous (triceps muscles of the left and right limb) or non-homologous (biceps left limb and triceps right limb) muscles. Lissajous displays were provided with a goal template and a cursor indicating the forces produced with both limbs. The template illustrated the specific pattern of force requirements needed to produce the goal coordination pattern (1:2, 1:3). Consistent with the previous investigation, the results for the 1:2 task indicated consistent and identifiable distortions in the left limb forces that could be associated with the forces produced by the right limb with a distinct pattern of interference observed with the activation of homologous and non-homologous muscles. In the homologous muscle conditions, as the right limb increased or decreased force production there were similar unintended increases or decreases in the force produced by the left limb. In the non-homologous conditions, it appears that interference occurs at the point when the right limb was initiating force production, but only while the left limb was releasing force. This interference continued from the point of muscle activation to peak force velocity. A similar pattern of results were observed for the 1:3 task. More importantly, the results indicated that interference between the limbs could be predicted based upon the activation and/or release of force in the right limb and whether homologous or non-homologous muscles were activated. The results were supported by the creation of an index that demonstrated the interference between the limbs.

Disclosures: D.M. Kennedy: None. **C.H. Shea:** None.

Poster

807. Motor Systems and Plasticity in Voluntary Movement

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 807.01/GG6

Topic: E.04. Voluntary Movements

Support: NIH Grant R01NS076589

NIH Grant R01NS090622

VA Grant I01RX000815

VA Grant I01RX001807

Craig H. Neilsen Foundation Grant 261299

NIH Grant HL69064

Title: A single session of acute intermittent hypoxia increases corticospinal excitability in humans

Authors: *L. CHRISTIANSEN[1], M. A. URBIN[1], G. S. MITCHELL[2], M. A. PEREZ[1];
[1]Dept. of Neurolog. Surgery, The Miami Project to Cure Paralysis, Univ. of Miami, Miami, FL;
[2]Ctr. for Resp. Res. and Rehabilitation, Dept. of Physical Therapy and McKnight Brai, Univ. of Florida, Gainesville, FL

Abstract: An increasing number of studies support the view that exposure to brief episodes of hypoxic air (acute intermittent hypoxia, AIH) enhances voluntary motor output in humans with and without motor disorders (for review see Gonzalez-Rothi et al., 2015; Verges et al., 2015). The neuronal mechanisms contributing to the AIH aftereffects in humans remain largely unknown. Using non-invasive transcranial magnetic stimulation we examined motor evoked potentials (MEPs, an index of corticospinal excitability) in an intrinsic finger muscle before, immediately after, and up to 75 min after 30 min of exposure to AIH or AIH_{sham} in randomized sessions separated by at least 5 days in control subjects. In the AIH protocol, participants received 15 episodes of 60-second hypoxic air (F_iO_2 =0.09) interspaced with 60-second of normoxic air (F_iO_2 =0.21). In the AIH_{sham} protocol, normoxic air (F_iO_2 =0.21) was applied during all 15 episodes. We found that MEPs size increased by 33.3±4.2% above the baseline immediately after and for up to 75 min in the AIH group ($p<0.001$). Note that oxygen saturation values decreased to 76.5±1.3% during the hypoxic episodes. In contrast, MEP size remained unchanged when subjects received AIH_{sham} at any of the times tested ($p>0.05$), and oxygen saturation remained stable at baseline levels (98.1±0.1%).We provide the first evidence that a

single session of AIH increases transmission in corticospinal projections to finger muscles in humans. AIH effects on the excitability of cortical and subcortical pathways remain to be tested.

Disclosures: L. Christiansen: None. **M.A. Urbin:** None. **G.S. Mitchell:** None. **M.A. Perez:** None.

Poster

807. Motor Systems and Plasticity in Voluntary Movement

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 807.02/GG7

Topic: E.04. Voluntary Movements

Support: NIH Grant R01NS076589

NIH Grant R01NS090622

VA Grant I01RX000815

VA Grant I01RX001807

Craig H. Neilsen Foundation Grant 261299

NIH Grant HL69064

Title: Acute intermittent hypoxia enhances synaptic-like plasticity after human spinal cord injury

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Abstract: Exposure to episodes of acute intermittent hypoxia (AIH) enhance voluntary motor output in humans with spinal cord injury (SCI; Trumbower et al., 2012; Hayes et al., 2014). It has been proposed that the beneficial effects of AIH are related to strengthening mechanisms involved in synaptic plasticity (Dale et al., 2014). To test this hypothesis in humans, we combined spike timing-dependent plasticity (STDP), a protocol that likely reflects changes in corticospinal-motoneuron synaptic efficacy, with AIH and AIH_{sham} in a crossover design in individuals with chronic incomplete cervical SCI. During STDP, transcranial magnetic stimulation over the primary motor cortex was used to elicit descending corticospinal volleys, and electrical stimulation of the ulnar nerve was used to elicit antidromic action potentials to depolarize spinal motoneurones. During AIH, participants received 15 episodes of 60-second hypoxic air (F_iO_2 =0.09) interspaced with 60 seconds of normoxic air (F_iO_2 =0.21). In the

AIH_{sham} protocol, normoxic air (F_iO_2 =0.21) was applied during all 15 episodes. Consistent with our previous results (Bunday and Perez, 2012), we found that the size of motor evoked potentials (MEPs) in an intrinsic hand muscle increased by ~20% above baseline for up to 30 min when the STDP protocol was combined with AIH_{sham}. Notably, when the STDP protocol was combined with AIH the size of MEPs increased by ~60% above baseline for up to 30 min. Our findings are the first demonstration that plasticity at corticomotoneuronal synapses is a possible mechanism contributing to AIH aftereffects following human SCI.

Disclosures: M. Urbin: None. **L. Christiansen:** None. **G.S. Mitchell:** None. **M.A. Perez:** None.

Poster

807. Motor Systems and Plasticity in Voluntary Movement

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 807.03/GG8

Topic: E.04. Voluntary Movements

Support: MRC

Wellcome Trust

Title: Classification of neurons in the motor reticular formation and their changes after a unilateral pyramidal tract lesion in primate

Authors: *B. ZAAIMI, D. S. SOTEROPOULOS, K. M. FISHER, S. N. BAKER; Newcastle Univ., Newcastle Upon Tyne, United Kingdom

Abstract: The reticular formation is the source of the reticulospinal tract, an important descending pathway in primates. We previously reported reticulospinal plasticity after a unilateral pyramidal tract lesion, when reticulospinal input to forearm flexors and intrinsic hand muscles shows a dramatic increase. Here we investigated whether sub-classes could be discerned amongst reticular neurons, and how these changed after corticospinal lesion. We recorded reticular formation neurons in five control and two lesioned monkeys. Two animals were trained to move a cursor to follow a target on screen by performing index finger flexion/extension movements. Four monkeys (including one lesioned) performed a food retrieval task requiring dexterous right hand and finger movements; one lesioned animal did not perform a dexterous hand task. 197 and 110 cells were recorded from five control and two lesioned monkeys respectively. We performed a principal component analysis of the spike width along with other measures derived from the inter-spike intervals (ISI): the mode ISI, the irregularity index (IR),

the peak of the after-hyperpolarization trajectory (AHP) assessed by an interval death-rate analysis, and the burst index. This allowed the identification of three classes of cells in the control monkeys. Cells in cluster 1 were characterized by their slow firing rate (mean mode ISI =38 ± 26 ms, cluster 2: 19 ± 7 ms, cluster 3: 22 ± 17 ms) and a strong modulation with the task. Cluster 2 contained rhythmic cells: 58% had a significant peak in their AHP trajectory. Cluster 3 had narrow spike waveforms (mean width cluster 1= 2.1 ± 1.1 ms; cluster 2= 2.4 ± 1.1 ms; cluster 3= 1.6 ± 0.8 ms), the largest burst index (mean cluster 1= 24 ± 28%; cluster 2= 20 ± 18%; cluster 3= 65 ± 23%), and the most irregular firing pattern (mean IR cluster 1= 0.73 ± 0.34; cluster 2= 0.47 ± 0.15; cluster 3= 1.09 ± 0.25). In the animal one year after a corticospinal lesion, changes in the spiking patterns of the three clusters could be observed relative to the unlesioned controls. Both the baseline firing rate and the bursting index of cluster 1 doubled. The proportion of rhythmic cells in cluster 2 reduced by 34%. Cells in cluster 3 increased their burst index and their baseline firing rate. These changes could reflect altered cortical input to the reticular formation and the increased importance of reticulospinal output for hand control after recovery, which may have produced modifications in the intrinsic properties of the cells.

Disclosures: B. Zaaimi: None. **D.S. Soteropoulos:** None. **K.M. Fisher:** None. **S.N. Baker:** None.

Poster

807. Motor Systems and Plasticity in Voluntary Movement

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 807.04/GG9

Topic: E.04. Voluntary Movements

Support: Student Undergraduate Research Fellowship from the Arkansas Department of Higher Education

Title: Rapid plasticity in human motor cortex following temporary digit fusion

Authors: *M. GARDNER, M. M. GANNON, S. M. LONG, N. A. PARKS;
Psychological Sci., Univ. of Arkansas, Fayetteville, AR

Abstract: Extensive literature has delineated remarkable effects of long-term neuroplasticity (weeks, months, or years) and topographical reorganization in sensorimotor cortex following amputation, stroke, and practice. However, very little is understood about the occurrence of early rapid functional adaptations in motor cortex representations that may mediate long-term reorganization. We investigated such short-term motor plasticity (minutes to hours) in human motor cortex by using cortical motor event-related potentials (ERPs) in a temporary “digit

fusion" paradigm. The index and middle fingers of the dominant hand were temporarily fused together with an over-the-counter topical skin adhesive. Such artificial syndactyly caused the two fused digits to move together as a single unit with use of the dominant hand. Immediately following digit fusion, we recorded motor ERPs in a simple bimanual motor response task and again approximately 45 minutes later, following a period of motor dexterity practice during which a set of fine motor tasks (Purdue peg board and marble parceling task) were repeatedly performed with the dominant and non-dominant hand. Motor potentials were also recorded in an additional control session in which subjects performed an identical set of tasks but without temporary digit fusion. Preliminary results indicate that, following practice with the fused digits, motor potentials increase in amplitude relative to the control session (or motor potentials evoked by responses given with the non-fused hand). These findings demonstrate the occurrence of rapid early functional adaptations in motor cortex following constrained motor output and are consistent with the occurrence of a mechanism of disinhibition within sensorimotor digit representations in driving such short-term motor plasticity.
Keywords: motor cortex, short-term plasticity, EEG/ERP

Disclosures: **M. Gardner:** None. **M.M. Gannon:** None. **S.M. Long:** None. **N.A. Parks:** None.

Poster

807. Motor Systems and Plasticity in Voluntary Movement

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 807.05/GG10

Topic: E.04. Voluntary Movements

Support: Austrian Science Fund (P23611)

Title: Cortical reorganization following peripheral nerve change: a functional connectivity analysis

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Abstract: *Introduction:*
Although the flexibility of the cortex to adapt to central nervous system damage is well documented, only few studies report on the cortical reorganization in response to peripheral nerve damage and no data exist concerning functional connectivity changes in primary motor cortex. Following brachial plexus avulsion, connecting the ending of the denervated

musculocutaneous to the phrenic nerve allows regaining elbow flexion. Therefore, the diaphragm motor area has to accomplish a new double function; the independent control of breathing and elbow flexion. However, although associated cortical changes are evident from activation within the diaphragm area (occuring simultaneously with arm area activations), possible network mechanisms accompanying this acquisition are unresolved (Beisteiner et al. 2011).

Methods:

Six right-handed patients (one female, aged 26-47y) with brachial plexus avulsion participated in this study. All were operated within one year before the investigation and only minor biceps innvervations of the injured arm were evident. Functional images were acquired on a 7 Tesla MAGNETOM system (Siemens, Erlangen, Germany) while performing the following tasks: (1) elbow flexion of the injured and (2) healthy arm; (3) forced abdominal respiration. For the estimation of task-based connectivity individual seed regions were derived from single-subject data and use for an ROI-to-ROI analysis. Based on our primary hypothesis individual functional connectivity estimates while performing the different tasks were calculated, specifically connectivity between primary motor arm and diaphragm areas during injured and healthy movements. The resulting estimates were Fisher z-transformed and used for further analysis.

Results:

Task-based functional connectivity exhibited higher connectivity of primary motor arm and diaphragm areas for the injured arm. In all patients movement related connectivity was found to be increased between the injured arm area and the ipsilateral diaphragm area as compared to the corresponding regions in the healthy hemisphere during healthy arm movements.

Conclusion:

Here we provide first evidence of a functional connectivity change in primary motor cortex of a healthy brain in response to a peripheral change. Results indicate the early establishment of intracortical functional connectivity between the denervated and a take-over region which may provide the decisive mechanism to regain arm movement.

Disclosures: F.P. Fischmeister: None. **E. Matt:** None. **A. Amini:** None. **R. Schmidhammer:** None. **R. Beisteiner:** None.

Poster

807. Motor Systems and Plasticity in Voluntary Movement

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 807.06/GG11

Topic: E.04. Voluntary Movements

Support: KAKENHI (26120002)

KAKENHI (25702033)

KAKENHI (26560282)

Title: Motor imagery of muscle contraction is available to induce long-lasting potentiation in indirect cortico-motoneuronal excitation in a relaxed muscle.

Authors: *S. IRIE[1], T. NAKAJIMA[1], S. SUZUKI[1], R. ARIYASU[1], T. KOMIYAMA[2], Y. OHKI[1];
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Abstract: Repetitive combined stimulation (RCS) of pyramidal tract and peripheral nerve can induce long-lasting potentiation (LLP) in indirect cortico-motoneuronal (C-M) excitation, which could be mediated by cervical interneurons (INs) in humans. However, this procedure has a limitation for clinical application, since the LLP could be induced only when the target muscle is voluntarily contracted. Therefore, we investigated if motor imagery (MI), which is known to enhance C-M excitation, can be substituted for voluntary contraction to induce LLP in the indirect C-M pathways.
Healthy volunteers (n=10), who all gave informed consent, were seated with surface electoromyogrphic recording from right biceps brachii (BB). RCS intervention (0.2 Hz, 10 min) was the same as in the previous study (Nakajima et al., Society for Neuroscience 2014). Transcranial magnetic stimulation (TMS) to the arm area of the left motor cortex was delivered with the right ulnar nerve stimulation at wrist level as a combined stimulation (CS). Interstimulus interval was set at 10 ms (TMS behind), which gave converging inputs in cervical IN systems. Stimulus strengths were determined to observe the maximum spatial facilitation in BB by the CS. As for the MI during RCS, participants were instructed to imagine performing maximal elbow flexion with sound cue signals, which was kept from 2 seconds before to 0.5 second after CS. Three types of interventions were conducted in separate experiments; (1) RCS alone, (2) RCS with MI, and (3) RCS during weak voluntary contraction of BB.
After RCS alone, motor evoked potential (MEP) in BB induced by single TMS was significantly depressed, and this depression lasted for ~60 min. Interestingly, RCS with MI induced LLP of BB MEP, which was similar to that after RCS during voluntary contraction. Furthermore, amount of spatial facilitation by CS was similarly enhanced after RCS with MI and RCS during voluntary contraction (Nakajima et al., Society for Neuroscience 2012). These findings suggest that RCS with MI could enhance indirect C-M excitation via cervical IN systems even without voluntary activation of target muscle.

Disclosures: **S. Irie:** None. **T. Nakajima:** None. **S. Suzuki:** None. **R. Ariyasu:** None. **T. Komiyama:** None. **Y. Ohki:** None.

Poster

807. Motor Systems and Plasticity in Voluntary Movement

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 807.07/GG12

Topic: E.04. Voluntary Movements

Title: Mirror visual feedback induced changes in resting state functional connectivity in a complex ball-rotation task

Authors: *V. RJOSK[1], J. LEPSIEN[1], E. KAMINSKI[1], M. HOFF[1], B. SEHM[1], C. J. STEELE[1,2], A. VILLRINGER[1,3], P. RAGERT[1,4];
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Abstract: Motor recovery after stroke depends on neural plasticity, which is impaired in the lesioned hemisphere and therefore needs to be facilitated by repetitive, intensive and task-relevant movement training in rehabilitation. Mirror visual feedback (MVF) is an encouraging approach to enhance motor performance without training in healthy adults as well as in patients with focal brain lesions. While the underlying neural mechanisms remain elusive, there is preliminary evidence that a functional modulation within and between primary motor cortices (M1) as assessed with transcranial magnetic stimulation (TMS) might be one candidate mechanism mediating the observed behavioral effects. Recently, studies using task-based functional magnetic resonance imaging (fMRI) indicated that MVF-induced functional changes might not be restricted to M1 but also include higher order regions responsible for perceptual-motor coordination and visual attention. Resting-state functional connectivity (rs-FC) represents intrinsically generated neuronal activity patterns acquired by resting-state fMRI (rs-fMRI). These patterns are temporally correlated as well as behaviorally relevant and can be used to describe plasticity-induced changes and learning-engaged cerebral regions. In the present study, we asked whether MVF induces functional network plasticity as assessed with rs-fMRI. Here, we compared the rs-FC of 17 young, healthy right-handed subjects (MG) before and after performing a complex ball-rotation task of the right hand (RH) with MVF and 18 age-matched control subjects (CG) without MVF. The primary outcome measure was the performance improvement of the untrained left hand (LH) before and after RH training. On a behavioral level, MG showed superior performance improvements of the untrained LH as compared to CG. Rs-fMRI revealed MVF-induced functional alterations in bilateral sensorimotor cortex (SM1), left anterior intraparietal sulcus (aIP) and left visual cortex (V4). A TIME (rs-fMRI pre vs. post) x GROUP (MG vs. CG) analysis revealed a significant interaction in left visual cortex (V1, V2). Furthermore, a correlation analysis revealed a linear positive relationship between MVF-induced

improvements of the untrained LH and functional alterations in left sensorimotor cortex (SM1). Our results suggest that MVF-induced performance improvements are associated with functional brain plasticity in widespread brain regions, a finding of potential interest for neurorehabilitation to depict potential target regions for non-invasive brain stimulation techniques.

Disclosures: V. Rjosk: None. **J. Lepsien:** None. **E. Kaminski:** None. **M. Hoff:** None. **B. Sehm:** None. **C.J. Steele:** None. **A. Villringer:** None. **P. Ragert:** None.

Poster

807. Motor Systems and Plasticity in Voluntary Movement

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 807.08/GG13

Topic: E.04. Voluntary Movements

Title: Characterisation of glutamatergic and $GABA_A$ mediated neurotransmission in motor and dorsolateral prefrontal cortex using paired-pulse TMS-EEG

Authors: *R. CASH[1,2,3], Y. NODA[2], R. ZOMORRODI[2], N. RADHU[2,3], F. FARZAN[2], T. RAJJI[2], R. CHEN[3], Z. DASKALAKIS[2], P. FITZGERALD[1], D. BLUMBERGER[2];
[1]Monash Alfred Psychiatry Res. Ctr., Melbourne, Australia; [2]Temerty Ctr. for Therapeut. Brain Intervention, Ctr. for Addiction and Mental Hlth., Toronto, ON, Canada; [3]Div. of Brain, Imaging and Behaviour – Systems Neurosci., Univ. of Toronto & Toronto Western Res. Institute, Univ. Hlth. Network, Toronto, ON, Canada

Abstract: Short interval intracortical inhibition (SICI) and intracortical facilitation (ICF) are non-invasive transcranial magnetic stimulation (TMS) measures of $GABA_A$ receptor mediated inhibition and glutamatergic excitatory transmission respectively. Conventionally these measures have been restricted to the motor cortex. We investigated whether SICI and ICF could be recorded from dorsolateral prefrontal cortex (DLPFC) using combined TMS and electroencephalography (TMS-EEG). We first characterized the neural signature of SICI and ICF in M1 in terms of TMS evoked potentials (TEPs) and spectral power modulation. Subsequently these paradigms were applied in DLPFC to determine whether similar neural signatures were evident. With TMS at M1, SICI and ICF led to bidirectional modulation (inhibition and facilitation respectively) of P30 and P60 TEP amplitude which correlated with MEP amplitude changes. With DLPFC stimulation, P60 was bidirectionally modulated by SICI and ICF in the same manner as for M1 stimulation, while P30 was absent. The sole modulation of early TEP components is in contradistinction to other measures such as long interval intracortical inhibition and may reflect modulation of short latency EPSPs and IPSPs. Overall the data suggest that SICI and ICF can be recorded using TMS-EEG in DLPFC providing non-invasive measures of

glutamatergic and $GABA_A$ receptor mediated neurotransmission. This may facilitate future research attempting to ascertain the role of these neurotransmitters in the pathophysiology and treatment of neurological and psychiatric disorders. *RC & YN contributed equally.

Disclosures: **R. Cash:** None. **Y. Noda:** None. **R. Zomorrodi:** None. **N. Radhu:** None. **F. Farzan:** None. **T. Rajji:** None. **R. Chen:** None. **Z. Daskalakis:** None. **P. Fitzgerald:** None. **D. Blumberger:** None.

Poster

807. Motor Systems and Plasticity in Voluntary Movement

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 807.09/GG14

Topic: E.04. Voluntary Movements

Support: Canadian Institutes of Health Research Grant MOP 62917

Title: The involvement of different motor cortical interneurons in the plasticity induction with paired associative stimulation

Authors: ***Z. NI**, C. GUNRAJ, R. CHEN;
Div. of Neurol., Krembil Neurosci Ctr. and Toronto Western Resch Inst., Toronto, ON, Canada

Abstract: Paired associative stimulation (PAS) involves pairing sensory afferent inputs induced by median nerve stimulation (MNS) with direct activation of primary motor cortex (M1) by transcranial magnetic stimulation (TMS) at specific times. TMS in posterior-anterior (PA) current direction predominantly produces early indirect (I)-waves while that in anterior-posterior (AP) current direction predominantly produces later I-waves. PAS at stimulus intervals of both 21.5 and 25 ms between MNS and TMS in the PA direction produces spike timing dependent long term potentiation (LTP) like effect in M1. Short interval intracortical inhibition (SICI) refers to the cortical inhibition where a subthreshold conditioning stimulus (CS) inhibits the motor evoked potential (MEP) generated by a superthreshold test stimulus (TS). SICI inhibits later I-wave but has little effect on early I-wave. Engagement of SICI during PAS at 25 ms interval in PA current blocks LTP induction. We hypothesize that both early and later I-waves are involved in PAS induced LTP-like effect. We tested PAS at 21.5 ms interval conditioned by SICI and PAS alone in 9 healthy subjects. In the SICI conditioned PAS, the triple-pulse (MNS-CS-TS) intervention was repeated 180 times. This was compared to a traditional PAS intervention (180 pairs of MNS-TS). Both PA and AP current directions were tested. Cortical excitability measures were repeated before intervention (baseline) and up to 60 minutes after the intervention. The measures were MEP amplitude, SICI, intracortical facilitation (ICF), long

interval intracortical inhibition (LICI) and short latency afferent inhibition (SAI). The measures were tested both in PA and AP current directions. We found that PAS alone in both PA and AP current directions produced MEP facilitation. PAS induced by AP current decreased SICI and SAI while that by PA current did not change intracortical circuits. Conditioning SICI did not alter the effects of PAS in PA direction but reduced MEP facilitation by PAS in the AP direction. The reduction in MEP facilitation was accompanied by restoration of SICI and SAI. LICI and ICF did not change with any interventional protocols. The results indicated that PAS at stimulus interval of 21.5 ms with PA directed current was mediated by early I-wave and was not affected by SICI, whereas same protocol with AP current was due to later I-waves and was blocked by SICI. We conclude that LTP-like effects induced by PAS at different current directions of TMS are mediated by separate subgroups of cortical facilitatory interneurons responsible for the generations of early and later I-waves. They have different susceptibility to cortical inhibitory circuits.

Disclosures: **Z. Ni:** None. **C. Gunraj:** None. **R. Chen:** None.

Poster

807. Motor Systems and Plasticity in Voluntary Movement

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 807.10/HH1

Topic: E.04. Voluntary Movements

Title: The influence of an acute bout of lower-limb cycling on sensorimotor integration.

Authors: *K. E. BROWN[1], J. L. NEVA[2], C. S. MANG[3], W. R. STAINES[4], L. A. BOYD[1]; [1]Physical Therapy, [3]Rehabil. Sci., [2]Univ. of British Columbia, Vancouver, BC, Canada; [4]Kinesiology, Univ. of Waterloo, Waterloo, ON, Canada

Abstract: A growing body of literature suggests that an acute bout of exercise influences the excitability of multiple cortical areas, including the prefrontal and primary motor cortices. Understanding the influence of exercise on neurophysiology is essential for developing potential interventions to optimize neural plasticity and behavioural outcomes. Moreover, sensorimotor integration is an integral part of motor learning and motor control, as incorporation of relevant somatosensory feedback to inform movement enables successful interactions with our environment. Therefore, we aimed to determine if an acute bout of aerobic exercise would alter upper-limb sensorimotor integration in young, healthy individuals. We hypothesized that an acute bout of exercise would release short-latency afferent inhibition (SAI), increase afferent facilitation (AF) and increase long-latency afferent inhibition (LAI).
Young, healthy individuals completed two sessions examining the influence of an acute bout of

lower-limb, moderate intensity cycling on primary corticospinal and primary somatosensory cortical excitability (session 1) and sensorimotor integration (session 2). In session 1, somatosensory-evoked potentials (SEPs) and motor evoked potential (MEP) recruitment curves were assessed at two time-points prior (30 minutes pre- and immediately pre-exercise) to an exercise bout and two time-points following an exercise bout (immediately post and 30 minutes post-exercise). The exercise bout consisted of a 5-minute warm up, followed by 20 minutes of cycling at an intensity set to maintain individuals within a range of 65-70% of their age-predicted maximum heart rate. In session 2, measures of sensorimotor integration (SAI, AF and LAI) were assessed twice prior to and following exercise, as in session 1.
There was no significant difference between baseline time-points, and thus the two pre-exercise time-points were collapsed to provide an average baseline value for all measures. A repeated-measures ANOVA with percent inhibition as the dependent variable for LAI revealed that there was a significant effect of time ($F_{(2,12)}$=3.941, p=0.048). Tukey's HSD tests revealed that the immediately post-exercise time-point had significantly greater inhibition than at baseline (p=0.047). There was no effect of exercise on any of the other measures.
The current dataset is the first to suggest that the neurophysiology of upper-limb sensorimotor integration may be influenced by a single bout of acute lower-limb cycling. This may have implications for neurorehabilitation approaches designed to improve sensorimotor integration as a mechanism for optimizing motor output.

Disclosures: K.E. Brown: None. **J.L. Neva:** None. **C.S. Mang:** None. **W.R. Staines:** None. **L.A. Boyd:** None.

Poster

807. Motor Systems and Plasticity in Voluntary Movement

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 807.11/HH2

Topic: E.04. Voluntary Movements

Title: Anodal transcranial direct current stimulation (tDCS) over motor cortex enhances split-belt treadmill adaptation in stroke

Authors: *X. LI[1,2], S. M. MORTON[1,2];
[1]Physical Therapy, [2]Grad. Program of Biomechanics and Movement Sci., Univ. of Delaware, Newark, DE

Abstract: Motor adaptation is a form of motor learning critical for locomotion, enabling relatively fast adjustments of walking patterns to unexpected changes in the environment. Whereas the cerebellum is known to play a major role in the initial adaptation process, recent

evidence suggests that motor cortical brain areas may be more important for consolidation and retention of motor memories. People with stroke affecting the corticospinal tract have intact locomotor adaptation but their learning is slowed and retention is poor. Transcranial direct current stimulation (tDCS) has successfully been used to induce changes in motor neuronal excitability and to induce positive behavioral changes in motor tasks in both healthy and stroke-affected individuals. However, the capability of tDCS to improve motor adaptation post-stroke has not been studied. The goal of this study was to test whether anodal tDCS could improve locomotor adaptation or its retention in people with stroke. Subjects with chronic unilateral stroke affecting the corticospinal tract participated in 2 study sessions 24 hours apart. They were assigned to receive either real or sham anodal tDCS applied over the leg representation of the lesioned hemisphere primary motor cortex (M1). During the first session, participants received tDCS while adapting their walking symmetry on a split-belt treadmill with belts set to a 2-to-1 speed ratio. Twenty-four hours later, retention was tested. Kinematic data were collected on both days using a 3D motion capture system. Preliminary results so far show that the magnitude of learning on both days is greater in the real group compared to sham, with a greater difference between groups on day 2. In addition there may be somewhat greater retention in the real group compared to sham and the rate of learning is greater in the real group on day 1, but not day 2. Overall, our results suggest that anodal tDCS over the lesioned hemisphere M1 in stroke subjects during split-belt adaptation may increase both the rate and magnitude of locomotor learning and improve its retention. We postulate that lower limb M1 activity is beneficial for locomotor adaptation and retention processes.

Disclosures: X. Li: None. **S.M. Morton:** None.

Poster

807. Motor Systems and Plasticity in Voluntary Movement

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 807.12/HH3

Topic: E.04. Voluntary Movements

Support: NIH Grant EY022987

Title: Rats gone wild: How seminatural rearing of laboratory animals shapes behavioral development and alters somatosensory and motor cortex organization

Authors: *D. F. COOKE[1,2], M. K. L. BALDWIN[1], M. S. DONALDSON[1], J. HELTON[2], D. S. STOLZENBERG[2], L. KRUBITZER[1,2];
[1]Ctr. Neurosci, [2]Psychology, UC Davis, Davis, CA

Abstract: The mammalian neocortex and the behavior it generates are highly adaptable. Few species exemplify this better than rats, which for thousands of years have thrived everywhere that humans have settled; traveling in our ships, living in our houses and cities, and eating our food despite an unending campaign of cats, traps, and poisons. Such adaptability to various climates, habitats, food sources, and predators is due, in part, to well-established sensitivity of the mammalian cortex to environmental conditions during development. This early experience can shape sensory and motor cortical maps, leading to behavior adapted to the local environment. Most studies of this process are necessarily restricted to laboratory animal models reared in a relatively deprived environment. Here we take a different approach and investigate how early natural environmental experiences shape neocortical development. We compare control rats reared in standard laboratory cages with genetically identical rats reared in an outdoor, seminatural environment: large wire mesh enclosures (9.75 X 2.5 X 2.5 m) roughly 3000 times the size of a standard rat cage. These field pens, located in a nature reserve, expose rats to weather (e.g. 12.8-43.3 °C, 4-100% humidity), day/night length and sun/moon light level conditions, as well as the sights, sounds, and smells of wild animals, including predators. A dirt floor populated by wild plants and invertebrates permits burrowing and hunting, while the mesh walls and introduced branches promote climbing. These are atavistic behaviors typical of wild rats and require sensorimotor processing entirely absent in standard laboratory cages. 24-h video recordings were made with overhead infrared cameras in the enclosure and the burrow box from which social behaviors were scored across the lifetime. Electrophysiological sensory mapping and intracortical microstimulation in adult anesthetized animals were used to examine the organization of somatosensory and motor cortex. Our preliminary data indicate that seminatural rearing shifts the timing of neurobehavioral development as well as adult exploratory, social, and cognitive behaviors. These behavioral alterations are associated with changes in the representation of movements in motor cortex, with relatively more cortical area devoted to the representation of trunk and tail movements at the expense of neighboring movement domains. Such data are critical for understanding how distinct phenotypes emerge from a single genotype based on differential early experience.

Disclosures: D.F. Cooke: None. **M.K.L. Baldwin:** None. **M.S. Donaldson:** None. **J. Helton:** None. **D.S. Stolzenberg:** None. **L. Krubitzer:** None.

Poster

807. Motor Systems and Plasticity in Voluntary Movement

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 807.13/HH4

Topic: E.04. Voluntary Movements

Support: FAPESP

CNPq

UNICID

Title: Participation of medial prefrontal cortex in plasticity induced by acrobatic exercise training

Authors: ***S. R. MOTA-ORTIZ**, P. N. DIAS, C. R. PIRES, W. F. DE OLIVEIRA, R. S. PIRES;
Univ. Cidade De São Paulo, São Paulo, Brazil

Abstract: Acrobatic training in animals promotes synaptogenesis in regions of the cerebellum and motor cortex, as well as behavioural changes, such as increasing the task performance, indicating an increase in the acquisition of motor skills. Several studies showed that many areas of the cerebral cortex are primarily involved in the processing of sensory information or the planning and execution of motor commands. During the learning process, there are changes in the structure and function of neural cells and their connections, namely learning promotes plastic changes, such as growth of new endings and synaptic buttons, growth of dendritic spines and increased functional synaptic areas. Our aim was to analyze the participation of the prefrontal cortex in plastic mechanisms promoted by acquisition of a new complex motor skill after bilateral neurochemical lesions in the mPFC of rats submitted to different time of acrobatic training. Eighteen animals were divided into 2 groups, namely Control (C) and mPFC lesion (L), and each one was subdivided into short acrobatic training (AC1, n=10) and long acrobatic training (AC4, n=8). The AC moved through a circuit of obstacles 5 times/day, 3 days/week for 1 and 4 weeks. At the end of the training, their brains were removed for immunohistochemistry assays to analyze the expression of a marker of recent neuronal activity (Egr-1) in the primary and secondary motor cortex, dorsolateral and dorsomedial striatum. Statistical analyses were performed using one-way ANOVA with the Bonferroni *post hoc* test. Our data revealed that mPFC lesion induced distinct neural mobilization in the brain areas analyzed after short and long-term of acrobatic training. In the control groups, our data revealed that AC4 (C+AC4) induced Egr-1 decreases in the secondary motor cortex (ca. 26%, $p<0.05$), dorsomedial and dorsolateral striatum (ca. 68% and ca. 69%, $p<0.0001$; respectively) compared to (C+AC1), and didn't change in the primary motor cortex. In addition, our results showed that short-term AC in the mPFC lesion group (L+AC1) induced Egr-1 decreases (ca. 38%, $p<0.05$) in the secondary motor cortex and Egr-1 increases in dorsomedial and dorsolateral striatum (ca. 32%, $p<0,05$; ca. 29%, $p<0,05$; respectively) compared to control group (C+AC1). Long-term acrobatic in the mPFC lesion group (L+AC4) induced Egr-1 decreases (ca. 38%, $p<0.05$) in the secondary motor cortex and Egr-1 increases in dorsomedial and dorsolateral striatum (ca. 32%, $p<0,05$; ca. 29%, $p<0,05$; respectively) compared to control group (C+AC4). In conclusion, our data suggest that mPFC cortex modulated motor cortex and striatum differentially within the learning of complex motor skill.

Disclosures: **S.R. Mota-Ortiz:** None. **P.N. Dias:** None. **C.R. Pires:** None. **W.F. de Oliveira:** None. **R.S. Pires:** None.

Poster

807. Motor Systems and Plasticity in Voluntary Movement

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 807.14/HH5

Topic: E.04. Voluntary Movements

Support: American Heart Association Post-doctoral Fellowship (AY)

National Science Foundation Graduate Research Fellowship (DBS)

DARPA/ARO Contract # W911NF-14-2-0043

Title: Targeted cortical reorganization using optogenetics in non-human primates

Authors: D. B. SILVERSMITH[1], *A. YAZDAN-SHAHMORAD[2], P. SABES[2];
[1]Bioengineering Grad. Program, UCB-UCSF, San Francisco, CA; [2]Physiol., Univ. of California San Francisco, San Francisco, CA

Abstract: Brain stimulation has shown promise for neural rehabilitation after injury. However, current stimulation based therapies are non-specific. A proposed mechanism for targeted reorganization is spike timing dependent plasticity (STDP): the relative timing of pre- and post-synaptic activity determines synaptic plasticity. We used optogenetic stimulation with STDP-based protocols to investigate the feasibility of inducing specific cortical reorganization.
We used a large-scale optogenetic interface that enables surface stimulation of excitatory neurons (AAV5-CamKIIa-C1V1-EYFP) and simultaneous electrocorticographical (ECoG) recording from primary somatosensory (S1) and motor (M1) cortices in two macaques. Stimulation in S1 and M1 evokes a direct response in the stimulated area followed by a delayed, indirect response in the other cortical area. To probe functional connectivity between S1 and M1 we measured the relative amplitude of the direct and indirect responses. We determined connectivity changes following two simple stimulation protocols: 1) single-site pulse trains in one cortical area and 2) paired pulse trains separated by a brief time delay across two cortical areas.
These stimulation patterns induced measureable cortical plasticity within 50 minutes. Single-site stimulation significantly increased connectivity between cortical areas; this result is consistent with STDP since indirect responses occur within 3-5ms, well within the potentiation window of STDP. Furthermore, using paired stimulation across cortical areas we were able to manipulate

the relative timing of light-evoked responses. We chose stimulation sites so that the direct response from the leading site overlapped with the indirect response from the lagging site. For large time delays (100ms) the sites acted independently, and increased connectivity was seen for both sites. When the delay was short (10ms), consistent with single-site stimulation, we saw a significant increase in connectivity for the leading site. However, there was a significant decrease in connectivity for the lagging site because the post-synaptic activity from this site occurred 13-15ms before the pre-synaptic activity, which is within the depression window of STDP.
Using optogenetic stimulation and ECoG recordings, we selectively strengthened and weakened existing connections across sensorimotor cortex in a manner consistent with STDP. This demonstrates the feasibility of driving targeted, bi-directional cortical plasticity with optogenetic stimulation and without spike-based recording; an ability that would likely find many applications for neural rehabilitation.

Disclosures: D.B. Silversmith: None. **A. Yazdan-Shahmorad:** None. **P. Sabes:** None.

Poster

807. Motor Systems and Plasticity in Voluntary Movement

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 807.15/HH6

Topic: E.04. Voluntary Movements

Title: An acute bout of exercise modulates interhemispheric inhibition in primary and non-primary motor-related areas.

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Abstract: The potential for aerobic exercise to modulate cognition, behaviour and cortical excitability is becoming of great interest to researchers and clinicians. Recently, work from our lab and others have shown that the excitability of the primary motor cortex (M1) is modulated by a single session of exercise. Specifically, a single session of lower-limb cycling exercise modulates M1 intracortical inhibitory [1] and facilitatory circuitry [1], cerebellar inhibition [2] and transcallosal inhibition within M1 in non-exercised upper-limb representations. This suggests that exercise may alter multiple networks of intrahemispheric and interhemispheric cortical circuits. Interhemispheric inhibition (IH) can be elicited from M1 and non-M1 areas such as primary somatosensory cortex (S1), dorsal premotor cortex (PMd) and the dorsolateral prefrontal cortex (DLPFC) to the contralateral M1 using dual-coil paired pulse transcranial magnetic stimulation (TMS) [3]. However, it is not known how IHI elicited from non-M1 areas

may be modulated after an acute bout of cycling exercise. The purpose of this study was to investigate the effects of a single bout of moderate exercise on IHI between M1 and non-M1 cortical regions. Dual-coil paired pulse TMS was used to measure IHI between M1 and non-M1 regions to the contralateral M1 of the non-exercised first dorsal interosseous (FDI) muscle representation. IHI was measured between right (non-dominant) hemisphere M1, S1, PMd and DLPFC to the contralateral (dominant) M1. For M1 and PMd, IHI was measured with a 10 ms (IHI-10) interstimulus interval (ISI) and a 50 ms (IHI-50) ISI to determine the potential distinct phase of IHI modulation, whereas S1 and DLPFC was only measured with a 50 ms ISI [3]. IHI was measured two time points before (baseline and pre-exercise) and one time point immediately after exercise (post-exercise). Healthy young participants performed moderate intensity cycling exercise was performed for 20 min at 65-70% of age-predicated maximum heart rate on a stationary ergometer. Preliminary results suggest that M1 IHI-50 was decreased and DLPFC IHI was enhanced post-exercise. These results suggest a decreased inhibition between M1, confirming previous work from our lab, and an increased inhibition from DLPFC after exercise. This potentially indicates that cycling exercise can concurrently modulate multiple interhemispheric circuits connected to M1. Recruitment for this study is ongoing.
[1] Singh et al. (2014) *BMC Sports Sci, Med and Rehabil*, 6:23.
[2] Mang et al. (2016) *Neural Plasticity*, doi: 10.1155/2016/6797928.
[3] Ni et al. (2009) Cerebral Cortex, 19:1654-65.

Disclosures: **J.L. Neva:** None. **K.E. Brown:** None. **L.A. Boyd:** None.

Poster

807. Motor Systems and Plasticity in Voluntary Movement

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 807.16/HH7

Topic: E.04. Voluntary Movements

Support: NIDILRR - Field-Initiated Program 90IF0090-01-00.

Title: Changes in cortical activity induced by an intervention using electromyography-driven functional electrical stimulation in individuals with moderate to severe chronic stroke

Authors: ***K. B. WILKINS**[1], C. CARMONA[2], J. DROGOS[2], J. SULLIVAN[2], J. P. A. DEWALD[2], J. YAO[2];
[2]Physical Therapy and Human Movement Sci., [1]Northwestern Univ., Chicago, IL

Abstract: Introduction: Individuals with moderate to severe chronic stroke usually lack control of their paretic hand, which may be partially due to damage to the ipsilesional corticospinal tract.

Previous evidence shows that cortical activity related to the paretic arm movements commonly shifts to the contralesional hemisphere as a function of shoulder abduction in individuals with moderate to severe stroke. This suggests that with increasing task demands, subjects no longer can rely on residual ipsilesional corticospinal tract resources, and instead increasingly rely on the contralesional hemisphere. In this study, we investigated the changes in cortical activity related to hand control induced by an intervention using a newly developed electromyography-triggered neuromuscular electrical stimulation system - ReIn-Hand that allows our targeted population to use their paretic hand in a task-specific intervention. Methods: Six individuals with moderate to severe chronic stroke participated in a 7-week intervention, 3 sessions per week. In each session, subjects used the paretic arm to perform 20-30 trials of reaching, grasping, and releasing a jar with the assistance of the ReIn-Hand device. Pre- and post-intervention, 160 channel electroencephalography (EEG) was measured when participants performed paretic hand opening with the arm resting on a haptic table or lifting up against 50% of maximum voluntary shoulder abduction force (MVF). Cortical activity was reconstructed based on subject-specific head models, and then used to quantify a Laterality Index (LI = (ipsilesional-contralesional)/(ipsilesional+contralesional)) with -1 to +1 indicating complete contra- or ipsilesional activity in the sensorimotor cortices. Results: Following the intervention, subjects showed improved range of motion, sensation, and grip strength at the hand. A 2-way (intervention and loading) repeated measure ANOVA showed that the intervention had a significant effect on LI ($F=11.8$, $p=0.018$). The post-hoc paired t-test showed that cortical activity related to paretic hand opening significantly shifted from the contralesional hemisphere to a more ipsilesional pattern for both the table condition and the 50% MVF condition. These results demonstrate that a ReIn-Hand assisted intervention could increase the use of remaining corticospinal resources from the ipsilesional hemisphere, resulting in a more typical activation pattern commonly seen in healthy individuals and well-recovered stroke subjects. This shift may serve as an indicator for improved functional gains of the paretic upper limb.

Disclosures: K.B. Wilkins: None. **C. Carmona:** None. **J. Drogos:** None. **J. Sullivan:** None. **J.P.A. Dewald:** None. **J. Yao:** None.

Poster

807. Motor Systems and Plasticity in Voluntary Movement

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 807.17/HH8

Topic: E.04. Voluntary Movements

Support: DFG RE 2740/3-1

Title: Contribution of BDNF to spontaneous and modified recovery after stroke in a rat model

Authors: *B. FRITSCH, L. TOMETTEN, M. R. CURADO, J. REIS;
Univ. of Freiburg/ Neurocenter, Freiburg, Germany

Abstract: Neuroplastic changes apparent during motor training and after brain injury have been shown to critically depend on neurotrophins, e.g. BDNF. Moreover, noninvasive electrical brain stimulation, specifically anodal tDCS, is capable of enhancing learning processes (Reis et al. 2009) and effects are also dependent on BDNF (Fritsch et al. 2010). Here, we hypothesized that an immediate increase of BDNF expression after stroke will be beneficial for motor recovery and a later decrease may hamper the possibility to undergo neuroplastic changes after stroke. Furthermore, we hypothesized that anodal tDCS applied to the lesioned motor cortex can beneficially influence BDNF levels. We planned to clarify in rats whether body fluids (blood plasma, cerebrospinal fluid) are indicative of BDNF protein content in cerebral tissue. First, we investigated BDNF protein concentration in cerebral tissue, CSF and plasma of rats 2, 4, 8, and 24 hours as well as 7 and 14 days after photothrombotic stroke or sham surgery. Second, we extended the experiments to include the investigation of anodal tDCS-effects on stroke lesion size and BDNF levels. The ELISA was optimized by a fluorometric technique with a detection limit of 1 pg BDNF protein/mg total protein. BDNF protein concentration was increased in the stroke and peri-stroke cerebral tissue as early as 2 hours post stroke and further increased over the time course reaching a maximum at 24 hours post stroke. This increase was not seen in the contralesional hemisphere. BDNF levels returned to close to normal levels by day 14 post stroke. This time course paralleled the time course of recovery measured by the mNSS stroke severity scale and the adhesive removal test. BDNF protein tissue concentration in the peri-stroke area did not correlate with BDNF protein concentration in CSF or plasma. Anodal tDCS applied to the primary motor cortex (M1) at a current density clearly below lesion thresholds (8A/m2) enhanced cerebral BDNF protein concentration under the stimulated area (M1 and striatum) but not in the neighboring cortex (S1) or distant brain regions, when applied 2 hours post stroke. tDCS applied 24 hrs post stroke, where BDNF levels were maximally increased, did not further enhance protein content. tDCS applied at day 7 post stroke only slightly elevated BDNF protein. Whether this intervention also changes the time course of recovery is currently under investigation. Our preliminary conclusion is that BDNF protein tissue levels are indicative of the course of motor recovery after stroke. Interventions affecting this relation, such as noninvasive brain stimulation using tDCS, may hold the potential to positively modify the recovery phase.

Disclosures: **B. Fritsch:** None. **L. Tometten:** None. **M.R. Curado:** None. **J. Reis:** None.

Poster

807. Motor Systems and Plasticity in Voluntary Movement

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 807.18/HH9

Topic: E.04. Voluntary Movements

Support: DFG RE 2740/3-1

Title: Anodal transcranial direct current stimulation enhances intra-limb motor transfer

Authors: F. A. ROTTMANN, M. R. CURADO, B. FRITSCH, *J. REIS;
Univ. of Freiburg, Freiburg, Germany

Abstract: Stroke is a major cause of impaired upper limb motor function. Many patients suffer from severe paralysis of both forearm and hand while to some degree motor function of the proximal upper limb remains intact. In this proof-of-concept study we asked whether proximal isometric motor training with the triceps muscle improves distal fine motor function of the ipsilateral hand (motor transfer) and vice versa and if such a transfer effect can be enhanced by applying transcranial direct current stimulation (tDCS) to the motor cortex contralateral to the trained limb. We modified the sequential isometric Pinch Force Task (SVIPT, Reis er al 2009), a visuomotor task, for execution with either triceps or hand. Skill of the training body part (triceps or hand) and skill of the transfer body part (hand or triceps) was determined by an adjusted mathematical Model based on the change of the speed accuracy tradeoff.
Adult, healthy participants were randomized into two groups to investigate a transfer from proximal (triceps) to distal (hand) OR distal (hand) to proximal (triceps) upper limb. Before training each participant's baseline skill of the transfer effector was measured. Training with either triceps or hand lasted for approximately one hour. During training participants received either anodal tDCS or sham tDCS over the contralateral motor cortex (M1). A separate group did not undergo any training to measure the repetition effect on transfer effector performance only.
We found a significant improvement of hand motor skill after triceps training, i. e. transfer from proximal to distal. No such transfer was detected from distal to proximal (i.e. triceps). However, anodal tDCS enhanced transferred skill in both groups.
From this study in healthy subjects it is tempting to speculate that patients with upper limb paralysis may benefit from combining tDCS with rehabilitation exercises of the arm. Further studies with patients are planned.

Disclosures: **F.A. Rottmann:** None. **M.R. Curado:** None. **B. Fritsch:** None. **J. Reis:** None.

Poster

807. Motor Systems and Plasticity in Voluntary Movement

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 807.19/HH10

Topic: H.01. Animal Cognition and Behavior

Support: Hartmann-Müller foundation

SNSF

Title: Learning specific VTA activation in a skilled reaching task

Authors: *S. LEEMBURG, T. CANONICA, A. LUFT;
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Abstract: Dopaminergic terminals in the primary motor cortex (M1) mainly originate in the ventral tegmental area (VTA). Dopamine release from these terminals is essential for the acquisition of motor skills. While motor skill learning requires multiple brain functions, it is unclear which behavioral element triggers VTA activation. Here, we used immunofluorescence for tyrosine hydroxylase (TH) and c-fos in combination with the retrograde tracer FastBlue to investigate learning- and reward-related activation of VTA neurons projecting to M1. After tracer injection, one group of rats was trained to perform a single pellet reaching (SPR) task for 3 days. Reward control rats (RC) received food rewards whenever SPR rats successfully retrieved a pellet. Cage control animals (CC) were kept in training cages for equal amounts of time as the other groups, but did not receive any pellets. While c-fos expression in dopaminergic neurons was increased in both SPR and RC rats, only SPR specifically activated M1-projecting dopaminergic neurons in the trained hemisphere of the caudal VTA. Moreover, animals that were showed extremely poor performance on the reaching task did not show increased dopaminergic activation. Non-dopaminergic VTA neurons are unaffected by both SPR and reward. These results indicate that the dopaminergic VTA-M1 projection is involved in successful motor skill learning and is functionally distinct from projections mediating food rewards.

Disclosures: **S. Leemburg:** None. **T. Canonica:** None. **A. Luft:** None.

Poster

807. Motor Systems and Plasticity in Voluntary Movement

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 807.20/HH11

Topic: E.04. Voluntary Movements

Support: NIH

Title: Enhanced motor recovery by vagus nerve stimulation requires cholinergic innervation in a rat model of ischemic stroke.

Authors: *A. D. RUIZ[1], S. HAYS, 75080[2], A. BERRY[2], S. VALLEJO[2], L. BARRON[2], X. CARRIER[2];
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Abstract: Stroke is a debilitating neurological insult that affects approximately 795,000 people in the U.S. each year. Following a stroke, many patients are left with impairment in upper extremity function, even after intensive rehabilitation therapy. Recent studies indicate that vagus nerve stimulation (VNS) paired with rehabilitative training significantly enhances recovery of forelimb function in models of ischemic stroke, intracerebral hemorrhage, and traumatic brain injury. Nevertheless, the mechanisms that underlie VNS-dependent enhancement recovery are largely unknown. The cholinergic nucleus basalis (NB) is a critical substrate in cortical plasticity, and several studies suggest that VNS activates cholinergic circuitry. Previous studies demonstrated that cholinergic innervation of the motor cortex is required for VNS-dependent enhancement of cortical plasticity. In this study we examine whether cholinergic innervation is required for VNS-dependent enhanced recovery in a rat model of ischemic stroke. A cohort of rats was trained to proficiency on the isometric force task, an automated and qualitative measure of forelimb function and then received a cortical ischemic lesion to impair the trained forelimb. Rats then received injections of the highly selective immunotoxin IgG-192-saporin into the nucleus basalis to deplete cortical cholinergic innervation (NB-) or control injections (NB+). Two weeks after stroke and immunolesion, rats underwent rehabilitative training for 6 weeks with or without VNS paired with forelimb movement. At the conclusion of behavioral testing, pseudorabies virus labelling was performed to assay anatomical plasticity in motor circuits controlling the forelimb. Preliminary findings indicate that VNS-dependent enhancement of stroke recovery requires cholinergic innervation.

Disclosures: **A.D. Ruiz:** A. Employment/Salary (full or part-time): University of Texas At Dallas, Texas Biomedical Device Center, Vulintus. **S. HAys:** A. Employment/Salary (full or part-time): University of Texas at Dallas, Texas Biomedical Device Center. **A. Berry:** None. **S. Vallejo:** None. **L. Barron:** None. **X. Carrier:** None.

Poster

807. Motor Systems and Plasticity in Voluntary Movement

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 807.21/HH12

Topic: E.04. Voluntary Movements

Title: Interhemispheric pathway modulation between homotopic sites in rat primary motor cortex (MI) leads to expression of new motor output in the ipsilateral forelimb

Authors: *A. L. CURRY[1,2], V. PELLICER-MORATA[4], B. MORSHED[3], S. NARAYANA[5], R. S. WATERS[4];
[2]Biomed. Engin., [3]Electrical & Computer Engin., [1]Univ. of Memphis, Memphis, TN; [4]Anat. and Neurobio., [5]Pediatrics, Univ. of Tennessee Hlth. Sci. Ctr., Memphis, TN

Abstract: Introduction: Intracortical microstimulation (ICMS) of forelimb representation in rat primary motor cortex (MI) evokes muscle contractions and/or movements only in the contralateral forelimb. An interhemispheric connection exists between homotopic forelimb representations in MI, but ICMS fails to evoke motor responses in the ipsilateral forelimb. We reported that chronic stimulation of the interhemispheric pathway between forelimb homotopic regions in somatosensory cortex (SI) enhanced the pathway, and led to new input in ipsilateral SI from the ipsilateral forelimb. Here, we examined the generality of interhemispheric pathway enhancement to assess whether chronic stimulation of the pathway between homotopic sites in MI evokes new motor responses in the ipsilateral forelimb. Methods: A carbon fiber electrode was inserted into MI and ICMS, consisting of a train of 13 pulses, was delivered to layer V to identify a site evoking movement in the contralateral forelimb. A second electrode was inserted in the opposite MI and used to find a site yielding a similar motor response in the contralateral forelimb. One of the electrodes (stimulating electrode) delivered single pulse stimulation and the second electrode (recording electrode) in opposite MI was used to record evoked response to establish a connection between homotopic motor sites. Once confirmed, single pulse stimulation was continually delivered to the stimulating electrode to evoke responses and enhance the pathway in the contralateral MI. At 15 min intervals, ICMS was delivered through the stimulating electrode and motor responses were reexamined in the periphery. If ICMS led to bilateral motor responses, inactivation of the interhemispheric pathway was carried out by applying a cooling probe to the cortical surface in the enhanced hemisphere. Lesions were made following recording to mark locations of stimulation and recording sites. Results: 1. ICMS delivered to homotopic MI initially evoked motor responses only in the contralateral forelimb. 2. Chronic single pulse stimulation enhanced the interhemispheric pathway between homotopic MI sites. 3. After 30-60 min of chronic stimulation, ICMS evoked motor responses in both contralateral and ipsilateral forelimbs. 4. Ipsilateral movement was abolished by inactivation of the enhanced MI, while the motor response in the contralateral forelimb was unaffected.

Conclusion: Interhemispheric enhancement modulates neuronal activity in SI and MI and results in expression of new functional responses. These stimulation parameters can be translated to transcranial magnetic stimulation (TMS) to improve efficacy in stroke treatment in humans.

Disclosures: A.L. Curry: None. **V. Pellicer-Morata:** None. **B. Morshed:** None. **S. Narayana:** None. **R.S. Waters:** None.

Poster

807. Motor Systems and Plasticity in Voluntary Movement

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 807.22/HH13

Topic: E.04. Voluntary Movements

Title: The storm within me: Multiple sclerosis exacerbations vaticinate meteorological events

Authors: *P. BATTA[1], A. R. HIRSCH[2];
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Abstract: Objective:
Change in weather with associated change in temperature has been described to exacerbate multiple sclerosis (MS), however exacerbation of MS symptoms prior to weather change has not heretofore been described.
Methods: Case 1:
A 60 year old right handed female presented with a 20 year history of MS. Since the onset, she observed that one-day prior to an approaching storm her symptoms invariably worsen. This would consist of worsening leg pain and weakness, requiring her to become wheelchair bound. This will persist for 6 hours after the storm is over. She affirms Uhthoff's phenomenon. A cousin and nephew, who also suffer from MS also notice a similar ability to predict the weather.
Results:
Abnormalities in Neurological Examination: Mental status examination: disheveled. Short-term memory: 5 digits forwards, 2 digits backwards. Recent memory: able to recall none of 4 objects in 3 minutes without improvement with reinforcement. Unable to spell world backwards, to interpret similarities or proverbs. Poor ability to calculate. Reflexes: 3+ bilateral lower extremities. Clock Drawing Test: 1 (abnormal).
Conclusion:
Uhthoff's phenomena (hot bath test) is well described in MS (Humm 2004), however the worsening of symptoms prior to weather change has not been reported. Possible mechanisms include meteorological induced anxiety and depression with associated exacerbation (Ackerman

1998). Alternatively, the barometric change could be affecting another region of her body (sinuses), which then may cause a pain/pressure mediated secondary effect of anxiety or depression, which further precipitates weakness and pain. Other possible mechanisms include misattribution, selective recall, or a misreporting due to psychological needs for acceptance by examiner, similar to the Hawthorne effect (observer effect) (Adair 1984). With the approaching storms there could be a change in internal temperature, which then preferentially affects areas of demyelination (Kudo 2014). Electromagnetic stimulation has been shown to cause a variety of symptoms including sleep disorders, headaches, nervousness, fatigue, and concentration difficulties (Röösli 2004). Storms cause substantial electromagnetic flux. Possibly, such meteorological electrical discharge could be the origin of her symptoms. This may be less likely since it is unclear how much electromagnetic variability occurs one day prior to the storms presentation. It is worth querying those with epoch associated neurological disorders as to linkage with meteorological events.

Disclosures: P. Batta: None. **A.R. Hirsch:** C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Smell and Taste Treatment and Research Foundation. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Smell and Taste Treatment and Research Foundation.

Poster

807. Motor Systems and Plasticity in Voluntary Movement

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 807.23/HH14

Topic: E.04. Voluntary Movements

Title: Plastic changes in pyramidal neurons in layer V of the rat motor cortex in an experimental model of motor activity.

Authors: *M. N. VÁZQUEZ HERNÁNDEZ[1], D. C. GONZÁLEZ-TAPIA[1], N. I. MARTÍNEZ-TORRES[1], D. GONZÁLEZ-TAPIA[2], I. GONZÁLEZ-BURGOS[1];
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Abstract: Nerve cells express plastic changes as response to novel or adverse conditions. Plasticity can be expressed as formation, elimination or strengthening of synaptic connections resulting from changes in the afferent stimulation. Dendritic spine plasticity has been widely studied in models related to cognitive processes. However, in psychoneural processes unrelated to cognition have not been sufficiently investigated. In this study, plastic changes of dendritic

spines of pyramidal neurons of layer V of the motor cortex were evaluated in a model of motor activity. Sprague-Dawley adult male rats were used. These were distributed in three experimental groups (E1, E2, and E3) and were subjected to a paradigm of motor activity in a Treadmill for 7 days (15 min / day). The E1 group performed the activity in constant conditions, while E2 (speed) and E3 (inclination) were subjected to different conditions of motor performance. After performing the activity, the motor cortex of experimental animals and controls were impregnated with the Golgi technique and the numerical density and spine type proportions were quantified. Pyramidal neurons of the three groups of experimental animals showed a higher spine density compared to controls. Likewise, E2 showed higher density than E1 and E3 and there was no difference between the latter two. Moreover, a higher proportion of thin spines was observed in the groups E1 and E2, and the same was observed in E3 with respect to E1. The proportion of mushroom spines was higher in E2 and E3 in respect to control group, and this was also observed in E2 when compared to E1 and E3. These findings suggests that motor activity causes plastic changes in dendritic spines of pyramidal neurons in layer V of the motor cortex, and that the thin and mushroom spines could play a different role to that attributed in cognitive processes.

Disclosures: **M.N. Vázquez Hernández:** None. **D.C. González-Tapia:** None. **N.I. Martínez-Torres:** None. **D. González-Tapia:** None. **I. González-Burgos:** None.

Poster

807. Motor Systems and Plasticity in Voluntary Movement

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 807.24/HH15

Topic: E.04. Voluntary Movements

Support: FAPESP

CAPES

CNPq

UNICID

Title: Different types of exercise induce distinct changes in the expression of synaptic proteins in the brain areas of aged rats

Authors: ***C. R. SCARANSI, ESQ**[1], R. M. S. GUTIERREZ[1], D. O. LUSTOSA[1], C. C. REAL[2], L. R. G. BRITTO[2], R. S. PIRES[1];
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Abstract: With aging, there is a decline in sensorimotor control, cognitive deficits, decline in fine motor control, gait and balance, and increased variability and slowness of movement. These impairments favor the risk of falls reducing the ability of the elderly to perform their activities of daily living (ADLs) and maintain independence. On the other hand, exercise can generate neuroprotective effects, prevent and protect brain function especially during aging.The objective of this study was to investigate the effect of acrobatic exercise (AC) and treadmill exercise (TE) on the expression of synaptic proteins synapsin I (SYS) and synaptophysin (SYP) in the prefrontal cortex, motor cortex, striatum and cerebellum of aged rats. Twenty-one male Wistar rats, 18 months old, were divided into 3 groups: sedentary (SED n=7), treadmill exercise (TE n=7) and acrobatic exercise (AC n=7). The rats were trained 3 days/week for 8 weeks. The AC moved through a circuit of obstacles 5 times/day, and TE was conducted at a speed of 8m/min for 40 min. Two months after starting the training, their brains were removed for Western blotting assays to quantify SYS and SYP expression. Statistical analyses were performed using one-way ANOVA with the Tukey *post hoc* test. Our data revealed that the different types of exercise promote distinct changes in the brain areas analyzed. In the prefrontal cortex only AC exercise induced an increase in SYP expression (ca. 21%, p=0.05) compared to SED, and SYS increase in relation to SED (ca. 38%, p=0,001) and TE (ca. 19%, p=0.01). In the motor cortex, both AC and TE induced an increase of SYP (ca. 30%, p=0.001; ca. 52%, p=0.001; respectively), and SYS (ca. 58%, p=0.01; ca. 65%, p=0.001; respectively) compared to SED. In the striatum, TE induced a decrease in the SYP expression (ca. 35%, p=0.05) compared to SED, and AC exercise generated a SYS reduction in relation to SED (ca. 21%; p=0.05) and TE (ca. 19%, p=0.05). In the cerebellum, AC exercise induced a decrease of SYP (ca. 32%, p=0.05) and SYS (ca. 34%, p=0.001) compared to SED group, and TE induced a SYS decrease (ca. 18%, p=0.05) in relation to SED. In conclusion, our data revealed that both types of exercise promoted distinct plastic changes in brain areas, with an increase SYP and SYS expression in the cortex and decrease in the striatum and cerebellum, suggesting a participation of the AC and TE in the LTP and LTD mechanisms, and highlighting the importance of starting exercises during aging. In addition, complex motor skill exercise (AC) was able to induce neuroplasticity changes mainly in the prefrontal and motor cortex, that are impaired with aging.

Disclosures: **C.R. Scaransi:** None. **R.M.S. Gutierrez:** None. **D.O. Lustosa:** None. **C.C. Real:** None. **L.R.G. Britto:** None. **R.S. Pires:** None.

Poster

807. Motor Systems and Plasticity in Voluntary Movement

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 807.25/HH16

Topic: E.04. Voluntary Movements

Support: FAPESP

CAPES

CNPq

UNICID

Title: Activity-dependent changes in the AMPA glutamate receptor subunits in the motor cortex and prefrontal cortex during aging rats

Authors: *R. M. S. GUTIERREZ[1], C. C. REAL[2], P. C. GARCIA[2], C. R. SCARANSI[1], L. R. G. BRITTO[2], R. S. PIRES[1];
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Abstract: Exercise has been shown to be effective to reduce the damage caused by aging, by improving memory, cognition and motor function. In addition, it increases plasticity and learning and has a protective effect. However, little is known about the effects of different types of exercises on the expression of glutamate receptors that can be the neural substrate of those effects. The objective of this study was to investigate the effect of acrobatic exercise (AC) and treadmill exercise (TE) on the expression of AMPA-type glutamate receptor subunits (GluA1 and GluA2/3) in the areas involved in planning and motor learning, and motor performance of adult and aged rats submitted to two months training. Forty-two male Wistar rats, with 21 aged (18 months old) and 21 adults (7 months) were divided into 6 groups: sedentary adult (SED A, n=7), adult exercise treadmill (TE A, n=7), adult acrobatic exercise (AC A, n=7), sedentary elderly (SED E, n=7), exercise treadmill elderly (TE E, n=7) and acrobatic exercise elderly (AC E, n=7). The rats were trained 3 days/week for 8 weeks. The AC moved through a circuit of obstacles 5 times/day, and TE E speed at 8m/min and the TE A at 10m/min for 40 min. Two months after starting the training, their brains were removed for Western blotting assay to quantify the GluA1 and GluA2/3. Statistical analyses were performed using two-way ANOVA with the Tukey *post hoc* test. Our data revealed that the exercise promotes changes in the motor cortex but did not so in the prefrontal cortex. In the motor cortex, the TE E induced an increase of GluA1 compare to almost all groups studied (SED E - ca. 71%, p=0.0001; SED A - ca. 57%, p=0.0001; AC E - ca. 44%, p=0,001, and TE A - ca. 45%, p=0.001). The TE E induced GluA2/3 increases in relation to the SED E (ca. 33%, p=0.05) and SED A (ca. 47%, p=0.001). Aged rats have shown TE and AC motor performance improvement, whereas adult rats have shown performance improvement in AC training. In conclusion, we have found that increasing expression of AMPA-type glutamate receptors in the motor cortex was activity-dependent and could be mitigating aged motor and learning deficits. Despite of the absence of changes of GluA1 and 2/3 expression in the prefrontal cortex after AC training, a new motor skill was acquired.

Disclosures: R.M.S. Gutierrez: None. **C.C. Real:** None. **P.C. Garcia:** None. **C.R. Scaransi:** None. **L.R.G. Britto:** None. **R.S. Pires:** None.

Poster

807. Motor Systems and Plasticity in Voluntary Movement

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 807.26/HH17

Topic: E.07. Rhythmic Motor Pattern Generation

Title: Spatial and polarity precision of concentric high-definition transcranial direct current stimulation.

Authors: *D. Q. TRUONG[1], M. ALAM, 10031[2], N. KHADKA[3], D. ADAIR[5], M. BIKSON[4]; [1]Biomed. Engin., City Col. of New York, CUNY, New York, NY; [2]Biomed. Engin., City Col. of New York, New York, NY; [3]Biomed. Engin., [4]City Col. of New York, City Univ. of New York, New York, NY; [5]City Univ. of New York, New York, NY

Abstract: Transcranial Direct Current Stimulation (tDCS) is a non-invasive neuromodulation technique that applies low amplitude current via electrodes placed on the scalp. Rather than directly eliciting a neuronal response, tDCS is believed to modulate excitability – enhancing or suppressing neuronal activity in regions of the brain depending on the polarity of stimulation. The specificity of tDCS to any therapeutic application derives in part from how electrode configuration determines the brain regions that are stimulated. Conventional tDCS uses two relatively large pads (>25 cm^2) whereas High-Definition tDCS (HD-tDCS) uses arrays of smaller electrodes to enhance brain targeting. The 4x1 concentric ring HD-tDCS (one center electrode surrounded by four returns) has been explored in application where focal targeting of cortex is desired. Here, we considered optimization of concentric ring HD-tDCS for targeting: the role of electrodes in the ring and the ring's diameter. Finite element models predicted cortical electric field generated during tDCS. High resolution MRIs were segmented into seven tissue/material masks of varying conductivities. Computer aided design (CAD) model of electrodes, gel, and sponge pads were incorporated into the segmentation. Volume meshes were generated and the Laplace equation ($\nabla\cdot(\sigma\nabla V)= 0$) was solved for cortical electric field, which was interpreted using physiological assumptions to correlate with stimulation and modulation. Cortical field intensity was predicted to increase with increasing ring diameter at the cost of focality while uni-directionality decreased. Additional surrounding ring electrodes increased uni-directionality while lowering cortical field intensity and increasing focality; though, this effect saturated and more than 4 surround electrode would not be justified. Using a range of concentric HD-tDCS montages, we showed that cortical region of influence can be controlled while balancing other design factors such as intensity at the target and uni-directionality. Furthermore, the evaluated concentric HD-tDCS approaches can provide categorical improvements in targeting compared to conventional tDCS. Hypothesis driven clinical trials, based on specific target engagement, would benefit by this more precise method of stimulation that could avoid potentially confounding brain regions.

Disclosures: **D.Q. Truong:** None. **M. Alam:** None. **N. Khadka:** None. **D. Adair:** None. **M. Bikson:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Soterix Medical.

Poster

807. Motor Systems and Plasticity in Voluntary Movement

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 807.27/II1

Topic: E.02. Cerebellum

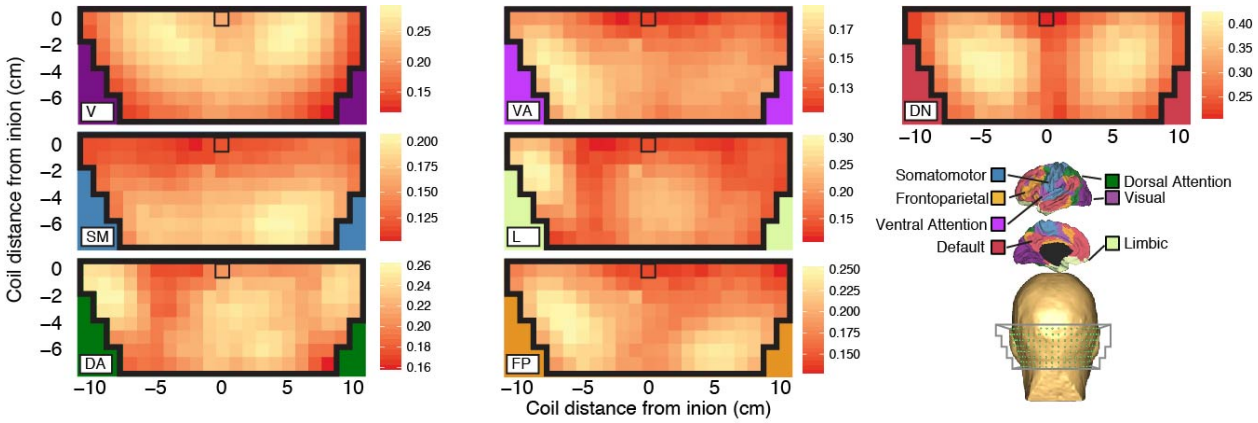
Support: Sidney R. Baer Jr. Foundation

Title: Cortical network targets of cerebellar transcranial magnetic stimulation

Authors: ***M. A. HALKO**[1], M. DANNHAUER[2], R. MACLEOD[2], D. BROOKS[3], A. PASCUAL-LEONE[1];
[1]Neurol., Beth Israel Deaconess Med. Ctr., Boston, MA; [2]Univ. of Utah, Salt Lake City, UT; [3]Northeastern Univ., Boston, MA

Abstract: *Background*: The classical view of the cerebellum suggests that it is exclusively a motor structure. However, recent imaging investigations (Buckner et al 2011; Brissenden et al 2016) have demonstrated its active involvement with non-motor networks in the brain. Recent investigations into the use of noninvasive brain stimulation upon the cerebellum have implicated cerebellar role in cognition (Halko et al 2014). However, it is unknown which networks are impacted by cerebellar transcranial magnetic stimulation (TMS), nor optimal coil positions to elicit a response. Thus, we investigated the potential impact of TMS of the cerebellum using a magnetic field model and models of human cerebellar-cortical connectivity
Methods: a single subject model was used to position 150 potential coil positions upon the posterior of the scalp, using the inion as a reference point. These field models were combined with a functional connectivity parcellation of the cerebellum to determine idealized stimulation positions for cerebellar networks.
Results: Topographic maps revealed unique coil positions for the stimulation of motor and non-motor cortex. Winner-take-all analysis revealed coil positions lateral to the inion optimally stimulate the default network (5cm lateral, 4 cm inferior to inion). Coil positions at the midline, inferior to the inion optimally stimulate the dorsal attention network. (0cm lateral, 4 cm inferior to inion). Figure 1 demonstrates predicted magnetic field upon each cerebellar network as function of coil position. Analysis of motor stimulation effects indicates the deep cerebellar nuclei receive greater magnetic field relative to cerebellar motor cortex.
Conclusions: These findings provide locations that can optimally stimulation non-motor cortex,

which are consistent with experiments which have measured functional connectivity after cerebellar stimulation (Halko et al 2014). Our approach is validated by the optimal stimulation positions for inducing cerebellar inhibition (Ugawa et al 1996). Further experimental validation of these models is necessary.



Disclosures: **M.A. Halko:** None. **M. Dannhauer:** None. **R. MacLeod:** None. **D. Brooks:** None. **A. Pascual-Leone:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Inventor of several issued and pending patents on the real-time integration of transcranial magnetic stimulation with electroencephalography and magnetic resonance imaging. F. Consulting Fees (e.g., advisory boards); Serves on the scientific advisory boards for Nexstim, Neuronix, Starlab Neuroscience, Neuroelectrics, Axilum Robotics, Magstim Inc., and Neosync.

Poster

807. Motor Systems and Plasticity in Voluntary Movement

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 807.28/II2

Topic: E.07. Rhythmic Motor Pattern Generation

Support: Medical Research Council

Canadian Institute of Health Research

Title: Effect of unidirectional iTBS with simultaneous directional high-definition tDCS on primary motor cortex excitability

Authors: *S. TREMBLAY, R. HANNAH, V. RAWJI, J. C. ROTHWELL;
Sobell Dept. of Motor Neurosci. and Movement Disorders, Univ. Col. London, London, United Kingdom

Abstract: Introduction. Recent findings suggest that manipulating shape and directionality of the stimulus waveform produced by transcranial magnetic stimulation (TMS) allows more control over the targeted neural populations (Goetz et al. Brain Stimul, 2016). In the present study, we tested the hypothesis that the effect of intermittent theta burst stimulation (iTBS) on primary motor cortex (M1) excitability can be optimised via the use of a near-rectangular monophasic pulse. In addition, we investigated if the concomitant application of a novel high-definition directional transcranial direct current stimulation (tDCS) paradigm could modulate the sensitivity of the target neurons. **Methods.** *Experiment 1.* We stimulated the dominant hand representation of M1 in 20 healthy subjects using an approximately square wave pulse generated by a controllable pulse parameter TMS (cTMS-3; Rogue Resolutions Ltd.). iTBS was delivered conventionally (Huang et al. Neuron, 2005) using a posterior-anterior directed pulse (PA). tDCS (1mA; 190 s) was applied during iTBS. Two 3.14 cm^2 circular electrodes were positioned 3.5cm posterior (anode) and anterior (return) to the TMS hotspot along the orientation of the TMS coil (PA-tDCS). The study consisted of two randomized sessions (iTBS with PA-tDCS vs Sham tDCS). M1 excitability was monitored using PA- and anterior-posterior (AP)-directed MEPs twice before iTBS, and every 10 min for 30 min after iTBS. *Experiment 2.* 7 healthy volunteers from Experiment 1 participated in a third session that was identical apart from the reversal of tDCS current direction (AP-tDCS). **Results.** iTBS + Sham tDCS yielded to a significant increase of both PA and AP average MEP amplitude (+21 and +19%, respectively). When PA-tDCS was applied simultaneously, average normalised MEP amplitude showed a 15% increase for PA and 11% increase for AP. Pilot data suggested that AP-tDCS abolished the effect of iTBS on both PA and AP MEP amplitudes (-9 and -14% respectively). **Conclusion.** Our results suggest that directional tDCS applied concurrently with unidirectional iTBS can boost or abolish the effect of iTBS depending of the direction of the electric field applied over M1. Mechanisms underlying this modulatory effect of tDCS may involve subthreshold polarisation of neurones which in turn make them more or less susceptible to the superimposed TMS. These findings are highly relevant to the field of brain stimulation as they suggest that combining both novel stimulation paradigms can optimise the amplitude of cortical excitability changes.

Disclosures: S. Tremblay: None. **R. Hannah:** None. **V. Rawji:** None. **J.C. Rothwell:** None.

Poster

808. Gait: Muscle Activity, Exercise, and Biomechanics

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 808.01/II3

Topic: E.06. Posture and Gait

Support: NSF Grant BCS-1230311

Title: Dependence of neurofeedback control on walking speed in humans

Authors: *F. EHTEMAM[1], T. KIEMEL[2];
[2]Kinesiology, [1]Univ. of Maryland, College Park, MD

Abstract: The central nervous system controls the speed of walking by modulating muscle activities. A steady-state muscle activity is the change in the activation of a muscle as a function of phase of the gait cycle averaged over several cycles at a constant speed. It has been shown before that the steady-state muscle activities are directly dependent on walking speed. In contrast, the study of transient muscle activities has not received much attention. A transient muscle activity is the change in the activation of a muscle in response to perturbations. The purpose of this study was to explore the dependency of transient muscle activities to the speed of walking. Five healthy adults walked on a treadmill in a virtual reality environment at four different speeds (0.98 ms^{-1}, 1.12 ms^{-1}, 1.25 ms^{-1} and 1.38 ms^{-1}). Visual perturbations were used to give the subjects the perception of self-motion and elicit transient responses which were captured by electromyography (EMG). To calculate the steady-state activation profiles, EMG signals were averaged over all gait cycles. To derive transient muscle activation profiles, harmonic transfer functions were used and phase-dependent impulse response functions (IRFs) were calculated. The effect of speed was only significant ($p<0.05$) for Tibialis anterior (TA). The effect of measure (steady-state vs. transient) was significant ($p<0.001$) for all muscles. No significant interaction effect was observed between speed and type of measure. The significant effect of the type of measure on muscle activations could be attributed to the difference in the nature of the steady-state and transient responses. Steady-state activations represent the activity over entire trials while transient responses are dependent to the phase of stimulus and fade away after the first two cycles following perturbations. We expected to see a main effect of speed on steady-state activities in all muscles. The lack of such effect could arise from the smaller range of speed tested here compared to previous studies.

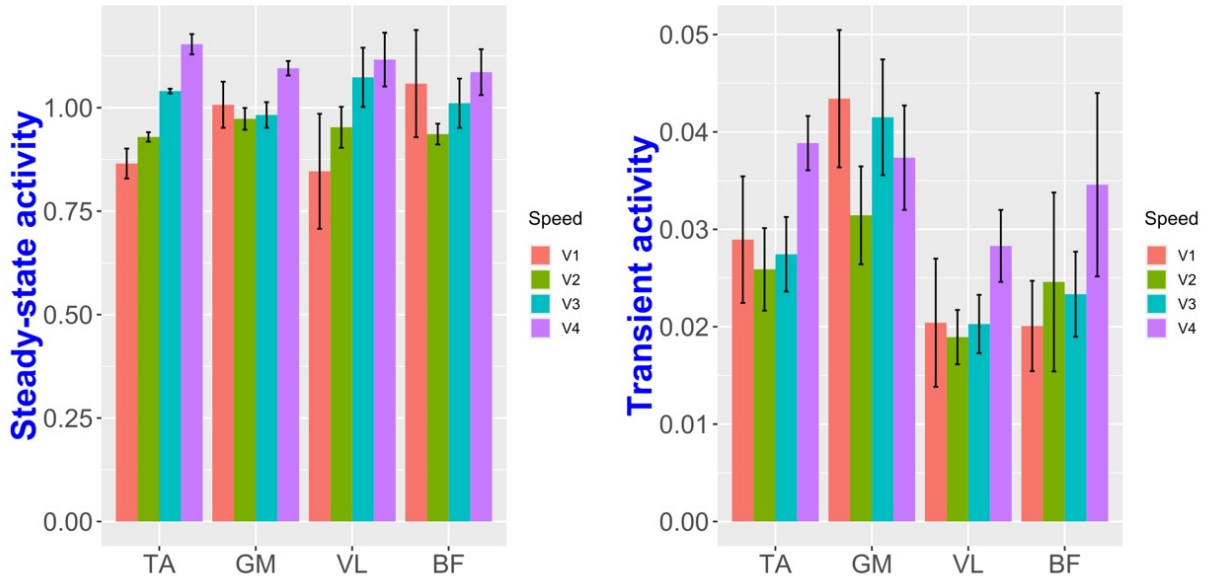


Figure 1. Steady-state (left) and transient (right) muscle activities at four different speeds (V1 = 0.98 ms^{-1}, V2 = 1.12 ms^{-1}, V3 = 1.25 ms^{-1} and V4 = 1.38 ms^{-1} for Tibialis anterior (TA), Gastrocnemius medialis (GM), Vastus lateralis (VL) and Bicep femoris (BF). Each bar shows the RMS of muscle activation signal for a combination of speed and muscle. Error bars show the standard error of the mean for the data averaged across subjects

Disclosures: F. Ehtemam: None. **T. Kiemel:** None.

Poster

808. Gait: Muscle Activity, Exercise, and Biomechanics

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 808.02/II4

Topic: E.06. Posture and Gait

Support: JSPS KAKENHI Grant no. 16K16482

Title: Simulation of adaptive interlimb coordination during locomotion on split-belt treadmill using a rat hindlimb neuromusculoskeletal model

Authors: *S. FUJIKI[1], A. SHINYA[2], T. FUNATO[3], K. TSUCHIYA[2], D. YANAGIHARA[1]; [1]The Univ. of Tokyo, Tokyo, Japan; [2]Kyoto university, Kyoto, Japan; [3]The Univ. of Electro-Communications, Tokyo, Japan

Abstract: During waking on a split-belt treadmill, humans show instantaneous and slowly adapted interlimb coordination. It is reported that humans with severe damages in the cerebellum

did show the instantaneous modifications in temporal gait parameters and in step length but did not show the subsequent slow adaptation. Although the cerebellum is known as the key contributor to motor learning, it is still unclear which sensory information is essential and how the motor commands are improved during adaptation in split-belt walking. In this study, we developed a nervous system model generating adaptive locomotor behavior based on the physiological findings. To investigate how the model contributed to its adaptive behavior in a split-belt walking, we conducted the forward dynamic simulation using a rat hindlimb musculoskeletal model, which was developed in our previous work. The skeletal model is composed of a trunk and hindlimbs and each limb has seven muscles. The nervous system model is composed of three parts. 1) motor command generator; Based on the concept of muscle synergy, it produces periodic motor command for locomotion in a feedforward fashion. 2) phase resetting by sensory information; When locomotion is disturbed by the treadmill and the actual foot contact timing is different from the usual timing (or prediction from past experience), the phase of the motor command immediately shifts to the start of stance phase. 3)motor learning; When the phase shift occurs repeatedly, the original motor command is gradually modulated based on the error between the actual and predicted foot contact timings. To reduce the error, only the temporal patterns (that is, firing timing) of the muscle synergy are modulated. For the treadmill configuration, at first, we set tied configuration (TC), where the two belts move at same speed, and then we suddenly changed to split-belt configuration (SC), where the two belts move at different speeds. After that, we returned it to TC. During the first TC, the relative phase between the left and right limbs was anti-phase. At the early stage of SC, it rapidly shifted downward from anti-phase. After a while, it gradually returned to anti-phase. At the early stage of the second TC, it rapidly shifted upward beyond anti-phase. After that, it gradually returned to anti-phase. These trends are similar to those in humans. These findings suggest the possibility that our neuromusculoskeletal model captures the essential aspects of instantaneous and slowly adapted interlimb coordination during split-belt walking.

Disclosures: **S. Fujiki:** None. **A. Shinya:** None. **T. Funato:** None. **K. Tsuchiya:** None. **D. Yanagihara:** None.

Poster

808. Gait: Muscle Activity, Exercise, and Biomechanics

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 808.03/II5

Topic: E.06. Posture and Gait

Support: JSPS KAKENHI 15K16498

Title: Improvement of sprint cycling performance by trans-spinal direct current stimulation

Authors: *S. SASADA[1], T. ENDOH[2], T. ISHII[3], T. KOMIYAMA[4,3];
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Abstract: Running speed in a short-distance sprint gradually decreases after reaching the maximum. The deterioration of sprint motor performance could be account for by a decrease in descending commands from the central nervous system to active muscles. Trans-spinal direct current stimulation (tsDCS) has been used to modulate the excitability of spinal neural circuits and enhance descending commands induced by electrical stimulation of the motor cortex. Therefore, it seems likely that tsDCS could improve sprint motor performance by inducing a positive plastic change in the excitability of spinal neural circuits to activate leg muscles. To test this premise, we investigated how sprint motor performance was modulated after tsDCS. tsDCS was applied using 2 electrodes (35 cm^2): one was located over the vertebral column (Th11 to L1) and delivered anodal or cathodal electrical stimulation, and the other was located on the right shoulder as a reference. The stimulus intensity was 3 mA, and was gradually increased/decreased over 15 s. Subjects were tested for sprint cycling performance for 30 s, following tsDCS for 15 min at rest. Change in cycling power was calculated by measuring changes in cadence. For all subjects, the maximum anaerobic power was first measured, and the optimal load for middle power training was calculated by a built-in program (COMBI, POWER MAX VII, Japan). The calculated load for each subject was used for the test cycling performance.
Power during sprint cycling over 30 s was significantly increased after cathodal tsDCS. The improvement with cathodal stimulation was notable at 10 to 20 s from the start. In contrast, there was no significant change in peak power. Anodal stimulation had no significant effect on power. The improvement of power in sprint cycling suggested that cathodal tsDCS could enhance descending commands via excitability modulation of spinal neural circuits. This stimulus method could be promising to extract potential sprint performance.

Disclosures: **S. Sasada:** None. **T. Endoh:** None. **T. Ishii:** None. **T. Komiyama:** None.

Poster

808. Gait: Muscle Activity, Exercise, and Biomechanics

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 808.04/II6

Topic: E.06. Posture and Gait

Support: VR(MH) Grant 11554

VR(MH) Grant 21076

Title: Kinematics of forward and backward walking in the mouse

Authors: M. G. VEMULA, G. N. ORLOVSKY, T. G. DELIAGINA, *P. V. ZELENIN; Karolinska Inst., Stockholm, Sweden

Abstract: Locomotion can be adapted to different behavioral goals. It can be performed in different directions, with different body configuration, speed, gait, etc. Open field and treadmill forward locomotion of intact mice has been studied in detail previously. In contrast, backward locomotion has never been studied. The aim of the present work was to compare kinematics of forward walking (FW) and backward walking (BW) of mice in different situations. With this purpose, we video recorded mice during FW and BW and analyzed hindlimb kinematics on 3 setups: 1) in a tunnel, 2) on a treadmill, 3) on an air ball with the animal's head fixed. During FW and BW, mice could walk with 3 different body configurations that differed in the hip height and the horizontal range of toes movements relative to the hip (these 2 parameter being correlated): 1) high hip symmetrical steps, 2) lower hip caudal steps, 3) lower hip rostral steps. During BW, stepping was always rostral. During FW we observed any configuration in the tunnel, symmetrical or rostral stepping on the treadmill, and symmetrical or caudal stepping on the ball. The cycle duration and stride length varied in a wide range and did not depend on the setup both for FW and BW. The swing duration did not depend significantly on the cycle duration both for FW and BW. On average the BW swing was twice shorter than the FW swing. The phase profile of hip joint angle was generally simple: swing flexion and stance extension during FW, swing extension and stance flexion during BW. However, the hip angle changes slightly preceded the swing/stance changes during FW but were slightly delayed during BW. The phase profiles of knee and ankle joint movements strongly depended on the body configuration. They were coordinated to keep the hip approximately at the same height during stance and to make the functional leg length minimal when the toes were passing under the hip during swing. Also we analyzed the interlimb coordination. We observed the same symmetrical gate (diagonal walk) during FW. In contrast, the gate during BW was less stable and could vary: lateral walk, diagonal walk, or trot. A possible structure of the locomotor CPG generating FW and BW, is discussed.

Disclosures: M.G. Vemula: None. **G.N. Orlovsky:** None. **T.G. Deliagina:** None. **P.V. Zelenin:** None.

Poster

808. Gait: Muscle Activity, Exercise, and Biomechanics

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 808.05/II7

Topic: E.06. Posture and Gait

Support: NIH Grant NS090751

NIH Grant HD048741

Title: Leveraging energetics of walking to change gait symmetry

Authors: ***R. T. ROEMMICH**[1,2], K. A. LEECH[1,2], A. J. GONZALEZ[1], A. J. BASTIAN[1,2]; [1]Motion Analysis Lab., Kennedy Krieger Inst., Baltimore, MD; [2]Neurosci., Johns Hopkins Univ. Sch. of Med., Baltimore, MD

Abstract: Humans prefer to move in ways that minimize energy cost. This is particularly apparent during walking, where energy is a key determinant of many gait features (e.g., speed, step length, step width, cadence). Here we determined if we could leverage energetics to change gait symmetry, which has clinical relevance for neurologic populations.

We collected kinematic and oxygen consumption data from young adults (n=44) as they walked on a treadmill. In Experiment 1, we tested subjects on two separate days. On day 1, the subjects walked at five different speeds – their preferred speed (~1.3 m/s) as well as, 0.5, 1.0, 1.5, and 2.0 m/s – for five minutes each. They then walked at their preferred speed while seeing continuous feedback of their ankle locations and a series of stepping targets. They used the feedback and targets to perform five different walking patterns – no limp, small left or right limp, large left or right limp – for five minutes each. We confirmed that energy cost was lowest near the preferred speed and when steps were equal; energy cost increased as subjects deviated from their preferred speed and when they limped.

On day 2, we activated a controller that changed the treadmill speed based on how much the subject limped, and tested which pairing the subjects found most comfortable. The pairings were designed to make the lowest energy cost occur at a non-preferred speed with a small limp. To walk at either their preferred speed or without a limp, subjects had to incur a high energy cost. Specifically, to walk at their preferred speed, subjects had to walk with a large limp; to walk without a limp, they had to walk very slowly (0.5 m/s). Our results showed that most subjects indeed chose to walk with a small limp at a non-preferred speed. Importantly, this means that they did not prioritize walking at their preferred speed or without a limp, but chose their walking pattern based on energetics.

We then wondered if walking for an extended distance would influence whether subjects were willing to limp, even if it remained the most energy-efficient way to walk. In Experiment 2, the protocol was identical to day 2 from Experiment 1 except subjects were required to walk for one

kilometer using the pattern they deemed most comfortable. Most subjects chose to walk the kilometer using the pattern commonly selected in in Experiment 1 - walking with a small limp at a non-preferred speed.
Energy plays an important role in determining how we walk. Here we find that we can leverage the energy cost of walking to change gait symmetry. Specifically, we show that the healthy nervous system will readily change gait symmetry to improve the efficiency of walking.
Supported by NIH grants NS090751 to RTR and HD048741 to AJB.

Disclosures: R.T. Roemmich: None. **K.A. Leech:** None. **A.J. Gonzalez:** None. **A.J. Bastian:** None.

Poster

808. Gait: Muscle Activity, Exercise, and Biomechanics

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 808.06/II8

Topic: E.06. Posture and Gait

Support: NIH Grant R01NS073717-01

Title: Mobile technology sensors detect reduction in turning velocity off medication compared to on in Parkinson's disease patients

Authors: *M. MILLER KOOP, S. OZINGA, J. L. ALBERTS;
Dept. of Biomed. Engin., Cleveland Clin., Cleveland, OH

Abstract: Objective: To use inertial measurement unit (IMU) data from a mobile device, iPad or iPhone, to quantify PD patients' gait and turning behavior, on and off anti-PD medication, during the Timed-Up-and-Go (TUG) test.
Background: The performance during the four distinct phases of TUG, Sit To Stand, gait, turning, Turn to Sit is traditionally collapsed into one metric: overall time to completion. Recent studies using inertial sensors have developed pivotal algorithms and metrics to quantify the individual phases of TUG; and using sensors on the torso and limbs, and have developed metrics that are sensitive to detecting PD movement abnormalities. In this study, a combination of new and existing algorithms were developed to analyze IMU data from a consumer electronics mobile device to determine if differences were present in PD patients completing the TUG test on and off anti-PD meds.
Methods: An iPad/iPhone mobile application was developed that utilized the embedded IMU to gather acceleration and rotational data to characterize patient's center of mass movement in the medial-lateral and anterior-posterior planes and trunk rotation. Thirty-three PD patients were

tested on and off (12 hours) anti-PD medication. Cadence (steps/sec), average velocity during turning (deg/sec), turn duration (sec), and total trial time (sec) were primary outcomes. A paired t-test or a Wilcoxon signed rank test was used to assess significant differences between on and off testing conditions. All reported p-values were corrected to account for multiple comparisons (Bonferroni, N=4).
Results: Average turning velocity was significantly slower when off medication compared to on (8.3%; p=0.011). Turn duration showed a trend to increase off meds compared to on, but lost significance when corrected (5.7%, p=0.067). Total trial time (p=0.2), and cadence (p=1.4) were not significantly different between on and off evaluations.
Conclusion: A quantitative measure of movement, in particular turning, from a mobile device provides a low cost, easy to use tool that detected a significant difference in movement from PD patients on and off medication during TUG whereas trial time did not. This result supports recent studies and shows the value of analyzing the separate behaviors of TUG individually with quantitative measures that have previously been linked to increased fall rates in PD patients.

Disclosures: M. Miller Koop: None. **S. Ozinga:** None. **J.L. Alberts:** None.

Poster

808. Gait: Muscle Activity, Exercise, and Biomechanics

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 808.07/II9

Topic: E.06. Posture and Gait

Support: Canada Foundation for Innovation (New Opportunities Fund)

Title: Age-dependent alterations in muscular control of sit-to-stand strategies with dynamic knee extensor fatiguing exercise

Authors: M. A. BRYANTON[1,4], *M. BILODEAU[2,4,1,3];
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Abstract: Background: Reduced knee extensor (KE) performance with aging has been shown to be a predictor of sit-to-stand (STS) performance as near maximal efforts have been shown in older populations to complete this task. In addition, strength limitations due to declining muscle reserves with aging have the potential to impact the muscle control strategies utilized when rising from a seated position. Aim: The purpose of this investigation was to evaluate the effects of reduced KE force output due to isolated fatiguing exercise, on STS muscular compensatory strategies in young and older adult participants. Methods: Eleven young (mean age = 27.4 ± 4.5

yrs) and eleven older (mean age = 68.4 ± 4.1 yrs) adults were asked to perform STS repetitions before and after dynamic KE fatiguing contractions (60 °/sec) at two intensities (80% and 50% of maximum KE torque) until they could no longer maintain the desired output. Surface electromyography was used to measure muscular efforts (expressed as a percentage of the maximum voluntary isometric contraction) and temporal characteristics (time of onset and peak activity relative to seat-off) of the tibialis anterior (TA), soleus (SOL), medial gastrocnemius (GAS), vastus lateralis (VL), rectus femoris (RF), bicep femoris long head (BF) and gluteus maximus (GMax) muscles. Results: We found increased SOL, GAS, RF and GMax efforts after KE fatigue during STS ascent in both age groups, however RF increased to a greater extent in older adults with lower KE strengths. Older participants also had higher TA, VL, RF and BF %MVIC regardless of STS condition. Discussion: These results indicate that isolated KE fatiguing exercise caused compensatory muscle strategies when ascending from a chair via increased reliance on unfatigued muscles at the ankle and hip as well as increased activity of synergist muscles. Older adults may therefore benefit from strength training of KE musculature to prevent further loss of muscle reserves in order to prolong functional independence.

Disclosures: M.A. Bryanton: None. **M. Bilodeau:** None.

Poster

808. Gait: Muscle Activity, Exercise, and Biomechanics

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 808.08/II10

Topic: E.06. Posture and Gait

Support: SDSU University Grants Program

Title: Does gradual training affect muscle coactivation during motor learning?

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Abstract: Identifying motor recruitment patterns during motor learning can lend insight into motor control strategies involved in clinical rehabilitation. Simultaneous neural recruitment of agonist and antagonist muscles, or coactivation, allows for increased stability and accuracy while learning novel dynamic movements, but increases metabolic cost. As a motor task is learned and performance improves, muscle coactivation decreases along with the metabolic cost of performing that specific movement. Balance activities and challenging walking tasks are frequently used in rehabilitation settings to increase movement efficiency. When comparing

muscle coordination patterns between experts and novices during narrow beam walking, experts are able to reduce the coactivation and number of muscles used for a given task. However, it is not known if different practice conditions are more effective in motor learning of a whole body balance task and reducing coactivation during performance of this task. The purpose of this study is to determine if different practice conditions will elicit more efficient muscle recruitment (i.e., decreased coactivation) when learning to walk on a narrow beam. Two types of practice were studied: Task Specific, where the target task is practiced repeatedly, and Gradual Training, where an easier form of the task is practiced, and then difficulty is gradually increased until the target task is reached. We hypothesized that the Task Specific training would lead to greater reductions in lower limb coactivation due to an increased error rate during practice, prompting a hastened neural response, even if task performance is similar between the two groups. Subjects performed 3-minute pre-training and post-training tests while walking on a 0.5-inch wide beam mounted on a treadmill. During the 30-minute training period, subjects in the Gradual Training group (n=4) walked on a 1.5-inch wide beam, then a 1.0-inch beam, and lastly a 0.5-inch beam for 10 minutes each. Subjects in the Task Specific group (n=4) walked only on the 0.5-inch beam during training. Surface EMG data were collected from ankle evertor and invertor muscles to calculate co-activation coefficients. Preliminary data showed similar improvements in performance after training between the two groups but a greater decrease in muscular coactivation in the Task Specific group compared to the Gradual Training group. Identifying the most effective practice conditions for decreasing muscular coactivation will inform how best to optimize motor learning for clinical practice.

Disclosures: **A. Schmaltz:** None. **A. Dillon:** None. **L. Paquette:** None. **A. Domingo:** None.

Poster

808. Gait: Muscle Activity, Exercise, and Biomechanics

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 808.09/II11

Topic: E.06. Posture and Gait

Support: CIHR

Parkinson's disease of Canada

Wings for life

Title: Functional contribution of the mesencephalic locomotor region to locomotor control

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Abstract: Recently, electrical stimulation of the Mesencephalic Locomotor Region (MLR) has been shown to improve locomotor recovery in hemi-lesioned rodents. Although the anatomical correlates of the MLR has been initially identified as the cuneiform nucleus (CnF), a cluster of glutamatergic neurons, and the pedonculopontine nucleus (PPN), a cluster of glutamatergic and cholinergic neurons, there is still an on-going debate about the exact anatomical correlate of this supraspinal locomotor center. Using adult VGluT2+ or ChAT+cre transgenic mice expressing Channelrhodopsin 2, optical cannulas were implanted chronically above the CnF or PPN, and wires were implanted in hindlimb flexor and extensor muscles for electromyographic (EMG) recordings. Kinematic and EMG recordings were performed at rest and during treadmill locomotion upon photostimulations. Photostimulations of glutamatergic CNF or PPN neurons initiated episodes of locomotion at rest. During on-going locomotion, photostimulations of glutamatergic CnF or PPN evoked short-latency excitatory responses in hindlimb flexor and extensor muscles during the swing phase, and inhibitory responses in extensor muscles during the stance phase. Interestingly, photostimulations of glutamatergic CnF neurons applied within a step cycle shortened the duration of the step cycle and extensor burst, thus resetting the locomotor rhythm and switching gaits from a slow trot to a fast gallop or full-bound. In contrast to glutamatergic populations, photostimulations of cholinergic PPN neurons failed to evoke episodes of locomotion in mice kept at rest. However, these photostimulations evoked excitatory motor responses in extensor muscles at rest and during treadmill locomotion. They also increased the duration of the step cycle and extensor burst, thus slowing-down the locomotor rhythm and consequently switching the gait from a trot to slow-walking gaits, such as lateral or out-of-phase walks. In summary, glutamatergic CnF and PPN neurons initiate and modulate the locomotor pattern, and accelerate the rhythm, while cholinergic PPN neurons decelerate it.

Disclosures: **N. Josset:** None. **M. Roussel:** None. **M. Lemieux:** None. **F. Bretzner:** None.

Poster

808. Gait: Muscle Activity, Exercise, and Biomechanics

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 808.10/II12

Topic: E.06. Posture and Gait

Support: NSERC

Title: Locomotor adaptation to push-off resistance during overground walking: ipsi- and contralateral effects.

Authors: M. BERTRAND-CHARETTE[1], J. B. NIELSEN[2], *L. J. BOUYER[1];
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Abstract: INTRODUCTION: Recent work has demonstrated that treadmill walking with a resistance applied to the ankle during swing can lead to modifications in ankle dorsiflexor control that persist after resistance removal ("aftereffects"; Blanchette et al. 2011; Barthelemy et at 2012). An initial attempt to replicate this finding during push-off at the end of stance was unsuccessful (Noel et al 2009). Several factors could explain this lack of transfer, including the different sensorimotor control of the targeted muscle groups and/or the mechanical constraints of walking on a treadmill for push-off adaptation. The primary objective of the present study was therefore to see if walking overground would provide a better environment for push-off adaptation. The secondary objective was to document the effect of unilateral resistance exposure on bilateral locomotor control. **METHODS**: 30 healthy subjects walked back and forth in an 80-meter corridor before, during, and after application of an elastic resistance at the ankle. Elastic tubing (Thera-band Silver) attached to the front of a modified ankle-foot orthosis delivered the resistance during push-off (range: 1.3-7.6 Nm). Ankle angle, Tibialis Anterior and Soleus EMGs were collected bilaterally throughout the test using wireless recordings. **RESULTS**: On the resisted side, 28/30 subjects adapted to the initial deviation in peak ankle plantarflexion (PAP) produced by the resistance. 25/30 subjects presented aftereffects (increased PAP from 13.4 ± 3.1 to 21.2 ± 3.1°, $p<0.0001$). SOL EMG showed significant aftereffects in 18/30 subjects (mean EMG increase of 41.4 ± 34.1%). TA EMG was not modified, as expected. On the non-resisted side, changes in SOL EMG were only seen at the beginning of resistance exposure, and no significant aftereffects were measured upon resistance removal. **DISCUSSION**: This pilot study shows the feasibility of modifying push-off kinematics and EMG activation using an elastic resistance applied at the ankle while walking overground. This effect is limited to the trained leg.

Disclosures: M. Bertrand-Charette: None. **J.B. Nielsen:** None. **L.J. Bouyer:** None.

Poster

808. Gait: Muscle Activity, Exercise, and Biomechanics

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 808.11/II13

Topic: E.06. Posture and Gait

Support: T32HD007414-22

HD048741

Title: Creating flexible motor memories in human walking

Authors: *K. A. LEECH[1,2], R. T. ROEMMICH[1,2], A. J. BASTIAN[1,2];
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Abstract: Savings, or faster relearning after initial learning, is a phenomenon observed across many motor learning paradigms including split-belt treadmill walking. When split-belt treadmill walking is used in rehabilitation, the belt speeds are often changed from day-to-day to provide progressive training. However, it is not known if learning is "saved" from one belt speed combination to another. Alternatively, patients may have to learn from scratch in response to each new perturbation. Here we investigated factors in initial learning that facilitate greater savings across different walking speeds.

We collected kinematic data from young adults (n=48) while they walked on a split-belt treadmill. All participants adapted to a split-belt perturbation where the belts moved at different speeds (Adaptation 1), de-adapted with the belts speeds tied, and adapted again to a second split-belt perturbation (Adaptation 2). We tested several groups where the split-belt speeds were systematically changed during Adaptation 1, but were always the same during Adaptation 2 (1.5 and 1.0 m/s, a 1.5 to 1 ratio). Different groups were tested in which we manipulated belt speed parameters during Adaptation 1 (e.g. belt speed difference, average, ratio) to test their effects on relearning in Adaptation 2.

We were surprised to find very low levels of savings when people learned from an identical 1.5 to 1 speed ratio in both Adaptations 1 and 2. Savings was much stronger when people learned a 2 to 1 ratio in Adaptation 1 prior to a 1.5 to 1 ratio in Adaptation 2. Importantly, this was the case even if the actual belt speeds were markedly different in Adaptation 1— savings occurred in groups first exposed to 1.0 and 0.5 m/s speeds or 2.0 and 1.0 m/s speeds (both 2 to 1 ratios). Thus, the *ratio* of the belt speeds in Adaptation 1 seems to be critical for savings in Adaptation 2, regardless of the actual training speeds. If the ratio is too small, savings does not occur even when the identical perturbation is repeated. No other factors manipulated in Adaptation 1 (e.g. belt speed difference or average) predicted this effect in Adaptation 2.

These findings show that adaptive learning can be stored, recalled, and used to improve performance in different conditions. Our results suggest that experiencing a larger perturbation size (ratio of belt speeds) during initial learning is the necessary ingredient to elicit savings and its transfer to new walking speeds. These findings may be useful when considering how to structure and progress locomotor learning in rehabilitation interventions.

Supported by NIH grants T32HD007414-22 to KAL and HD048741 to AJB.

Disclosures: **K.A. Leech:** None. **R.T. Roemmich:** None. **A.J. Bastian:** None.

Poster

808. Gait: Muscle Activity, Exercise, and Biomechanics

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 808.12/II14

Topic: E.06. Posture and Gait

Support: American Heart Association 15PRE21820002

Title: Step by step variability of kinematic trajectory compared when walking with a wide range of speeds in people with poststroke hemiparesis

Authors: *D. D. RUMBLE, C. P. HURT, D. A. BROWN;
Physical Therapy, Rehabil. Sci. Program, Univ. of Alabama At Birmingham, Birmingham, AL

Abstract: PURPOSE/HYPOTHESIS: Walking disability is a major concern among people with poststroke hemiparesis. One major characteristic of walking disability is slow walking speed. Recent studies have focused on factors underlying slow walking speed, such as strength and balance impairment. However, preliminary results from our laboratory suggest, with weakness and balance accounted for, certain portions of the hemiparetic gait's foot trajectory during the swing phase may be susceptible to increased step by step variability (SSV) and may play a major role in generating foot placement errors. Where a nonimpaired individual may adapt their gait to accommodate faster speeds, people poststroke may have increased susceptibility to speed-induced missteps resulting in the choice of slower speeds as a strategy to avoid unstable walking conditions. A problem with past studies was the inability to study large range of speeds that might reveal complex behaviors at very fast speeds. We used a robotic system coupled with a treadmill that assists individuals to walk at faster speeds than typically possible, by providing for-aft assist forces. We hypothesized that, at progressively faster speeds, the SSV will increase for the paretic limb but not for the nonparetic limb nor for nonimpaired individuals. METHODS: Individuals walked at progressively faster speeds as we measured step trajectory using high speed motion capture. Regression analyses was used to model the relationship between speed and SSV for the nonparetic and paretic legs of individuals poststroke, as well as the dominant leg in nonimpaired individuals. RESULTS: To date, we have recorded observations of 12 people with poststroke hemiparesis and 15 nonimpaired individuals walking at a wide range of speeds. People poststroke exhibited greater SSV in the paretic limb at terminal swing at progressively faster speeds for 9 out of 12 participants, but the non-paretic limb exhibited increased SSV only for six out of the twelve. Non-impaired individuals exhibited increased SSV in relation to speed at terminal swing for 9 out of 15 participants. DISCUSSION/CONCLUSION: The control of foot trajectory becomes more variable at faster speeds for the paretic limb more often compared to the non-paretic limb and non-impaired limb. This is possibly due to compensatory strategies that are developed to accommodate faster speed walking poststroke.

Disclosures: **D.D. Rumble:** C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); American Heart Association. **C.P. Hurt:** None. **D.A. Brown:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); KineAssist.

Poster

808. Gait: Muscle Activity, Exercise, and Biomechanics

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 808.13/II15

Topic: E.06. Posture and Gait

Title: The effects of optic flow and treadmill speed on the spatial and temporal components of gait.

Authors: *A. H. POLLACK[1], T. J. RAND[2], M. MUKHERJEE[2];
[1]Creighton Univ. Sch. of Med., Omaha, NE; [2]Univ. of Nebraska Omaha, Omaha, NE

Abstract: Introduction: Treadmill walking is commonly used in rehabilitation and research settings and has several benefits. However, lack of optic flow during treadmill walking results in conflicting sensory information which can have an effect on gait characteristics. Virtual reality can simulate overground walking by providing an optic flow that matches the individuals walking speed. However, optic flow can also be manipulated in virtual reality to better understand how an individual's gait is altered in response to incongruent visual input. Furthermore, changing treadmill speeds away from an individual's comfortable walking speed can also have an impact on their gait characteristics. The purpose of this study was to determine the effects of changing treadmill speed and optic flow speed on the spatial and temporal characteristics of gait.
Methods: Six participants free of any gait abnormalities walked on a treadmill in a virtual reality environment. Preferred walking speed was determined on the treadmill and the fast and slow speeds were calculated as double and half of the preferred walking speed respectively. This resulted in nine conditions (3 walking speeds x 3 optic flow speeds) that were randomized. Step lengths and step times were calculated for each condition and the means and coefficient of variation were calculated. A two-way ANOVA was used to determine the effect of treadmill and optic flow speed.
Results: Step length showed an effect of treadmill speed ($P = .002$) with the fast walking speed resulting in a larger step length than either preferred or slow walking. Step length variability also showed differences (P = .012) but the slow speed had increased variability compared to the fast speed. Step time showed an effect of treadmill speed ($P = .002$), with the slow walking speed

exhibiting longer step times than the preferred or fast speeds. Step time variability was also higher in the slow speed as compared to the preferred and fast speeds (P = .008).
Discussion: The spatial component of gait responded differently than the temporal component. While this may be expected due to the biological constraints of walking (slower steps take more time, faster steps become longer), what is interesting is that the variability in the spatial and temporal aspects responded differently. When looking at the spatial component of walking there was an increase in step length in the fast condition but a reduction in variability. Step times on the other hand increased during slow walking but also increased in variability. These data indicate different neural control is used for the temporal and spatial aspects of gait.

Disclosures: **A.H. Pollack:** None. **T.J. Rand:** None. **M. Mukherjee:** None.

Poster

808. Gait: Muscle Activity, Exercise, and Biomechanics

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 808.14/II16

Topic: E.06. Posture and Gait

Support: NIH Grant NS058659

NIH Grant HD032571

NIH Grant NS048844

NIH Grant EB012855

Title: Planar covariation of hindlimb elevation angles is present during walking of intact and spinal cats and in simulated locomotion of a neuromechanical model

Authors: *A. N. KLISHKO[1], M. A. LEMAY[2], I. N. BELOOZEROVA[3], S. N. MARKIN[4], I. A. RYBAK[4], B. I. PRILUTSKY[1];
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Abstract: Planar covariation of leg elevation angles has been demonstrated during various locomotor behaviors (Borghese et al. 1996) and suggested to reflect neural constraints that simplify the control of kinematically redundant leg. These constraints might be related to kinematic synergies stabilizing leg length and leg orientation during locomotion (Ivanenko et al. 2007; Klishko et al. 2014), although their mechanisms are not known. Here, we investigated

planar covariation of hindlimb elevation angles in cats during locomotor behaviors that require substantial contribution of the motor cortex (precise stepping on horizontal ladder), exclusive contribution of the spinal cord (hindlimb locomotor movements after spinal cord transection at the thoracic level) and normal level and slope (+/- 50%) walking in intact cats with presumably greater contribution of the spinal cord. In addition, we examined planar covariation of hindlimb elevation angles in level and slope walking simulated using a comprehensive neuromechanical computational model of hindlimb locomotion (Markin et al. 2016). Planar covariation of hindlimb segments was evaluated using principal component analysis (Borghese et al. 1996). The results demonstrated a high degree of planar covariation of hindlimb segment angles for all locomotor behaviors studied, including simulated level and slope walking. The orientation of the covariance plane in the space of tarsal, shank and thigh elevation angles differed however among locomotor behaviors. Time profile of the first principal component (PC1) was highly correlated with the hindlimb orientation ($r > 0.9$), whereas that of PC2 showed the highest correlation with hindlimb length although the correlation was generally much weaker ($r > 0.6$-0.9) for intact cats, and ($r>0.2$-0.9) for spinal cats. A variety of stable locomotor patterns were generated by computer simulations of level and slope walking by varying the values of the sensory feedback gains and supraspinal inputs to interneurons of the CPG. All generated locomotor patterns demonstrated a high level of planar covariation of hindlimb segment angles. We suggest that potential neural constraints responsible for the kinematic synergy of planar covariation of elevation angles during locomotion are inherent in the spinal locomotor circuitry.

Disclosures: **A.N. Klishko:** None. **M.A. Lemay:** None. **I.N. Beloozerova:** None. **S.N. Markin:** None. **I.A. Rybak:** None. **B.I. Prilutsky:** None.

Poster

808. Gait: Muscle Activity, Exercise, and Biomechanics

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 808.15/II17

Topic: E.06. Posture and Gait

Support: NIH Grant 1P20GM109090-1

Graduate Research and Creative Activity at UNO

Title: Virtual reality augments learning of the spatial component of a gait coordination task differently for each leg

Authors: ***T. J. RAND**, J. L. FUJAN-HANSEN, M. MUKHERJEE;
Univ. of Nebraska At Omaha, Omaha, NE

Abstract: During split-belt treadmill walking the sensorimotor system must adapt to a novel set of constraints. The visual input is a rich source of information that can influence the split-belt adaptive process. Magnitude and temporal structure are two aspects of variability that can provide complimentary information about a movement pattern. Exploring how these measures change in response to split-belt walking can help characterize the neuromuscular control that is involved in locomotor adaptation.
Methods: 20 participants walked on a split-belt treadmill in both tied-belt and split-belt conditions: 10 participants walked in a virtual reality (VR) environment and the other 10 walked blindfolded (BF). Three 5-minute split-belt conditions were conducted where the right belt moved at twice the speed of the left belt. A virtual moving corridor was provided to the VR participants at the speed of the slow belt. Coefficient of variation and entropy were calculated for step length and step time. The baseline values from the tied-belt were subtracted from the first split-belt trial to represent early adaptation and the last split-belt trial to represent late adaptation. These measures were calculated for 200 step lengths and times on the right and left legs.
Results: For step length the VR condition resulted in an increase in coefficient of variation (P = .007) and a decrease in entropy (P = .004) for the fast leg during early adaptation, which returned to baseline values in late adaptation. The BF group showed no change across conditions. Step time did not show differences between the VR and BF groups for either leg.
Discussion: During early adaptation the spatial component of the fast leg had greater overall variability which happened in a more ordered manner. This could indicate a freezing of the degrees of freedom while adapting to the new locomotor pattern. Interestingly this phenomenon was not seen on the slower side or when the participants were blindfolded. There was also no difference in the temporal component for either leg between the VR or BF groups. In the BF group sensory reweighting would result in a higher proprioceptive gain, which may have allowed adaptation to the split-belt walking pattern without altering the spatiotemporal characteristics of either leg. However, in the VR group the visual flow matched the slow leg but was incongruent with the fast leg. This resulted in the fast leg exhibiting altered spatial characteristics while learning to calibrate to an incongruent visual flow. These data highlight the importance of visual information on sensorimotor adaptation in a novel walking task, and suggest that VR must be created in a manner that evokes the desired response.

Disclosures: **T.J. Rand:** None. **J.L. Fujan-Hansen:** None. **M. Mukherjee:** None.

Poster

808. Gait: Muscle Activity, Exercise, and Biomechanics

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 808.16/JJ1

Topic: E.06. Posture and Gait

Support: NIDILRR Grant H133E120010

Internal Grant UAB Center on Disability Health and Rehabilitation Science

Title: Locomotor muscle activity responses to walking in an environment of reduced postural demands

Authors: *S. A. GRAHAM[1], D. A. BROWN[2];
[1]Physical Therapy, Univ. of Alabama At Birmingham, Hoover, AL; [2]Physical Therapy, Univ. of Alabama At Birmingham, Birmingham, AL

Abstract: Background
Separate central controllers for posture and locomotion are thought to act interdependently to maintain upright posture and allow effective locomotor pattern expression. We tested this theory by manipulating postural control influence relative to locomotor control. We designed an experimental apparatus that constrains trunk motion and reduces weight bearing on the limbs during treadmill walking, in order to observe short-term compensations with limb muscle activity to allow walking with reduced postural control requirements.
Purpose
We had two objectives, 1) to determine if the support apparatus minimized muscle activity related to upright trunk orientation, and 2) to investigate how locomotor muscle activity, during transition periods of the gait cycle, responds to walking tasks where postural demands are minimal.
Methods
Five nonimpaired individuals walked on a treadmill at 1.0 m/s in three conditions. First, participants walked without any support (standard walking). Second, participants walked with light steps on the treadmill surface while supported by the apparatus (minimal postural demand and locomotor effort). Third, also in the apparatus, participants targeted a magnitude of vertical force with their dominant limb, equivalent to the average peak ground reaction force (GRF) during standard walking (minimal postural demand, standard locomotor effort). We collected trunk kinematics, GRFs, and EMG data from lower-limb and trunk muscles.
Results
The support apparatus minimized degrees of trunk motion by 73% medial-lateral, 80.5% fore-aft, and 87% rotation, and decreased vertical GRF impulses to 18 ± 4% of those during standard walking. When taking light steps, external oblique and erector spinae activity were reduced to roughly half of that during standard walking. Effortful supported walking showed a general increase in vastus medialis (VM) and biceps femoris (BF) activity during the transition period before heel strike; four of five participants increased VM activity by more than 2 standard deviations (SD) from standard walking, and BF activity increased by
more than 1SD. Muscle activity prior to toe off in rectus femoris and soleus did not show consistent magnitude changes.
Conclusions
The support apparatus effectively minimized trunk muscle activity during suspended walking with light steps. When locomotor effort was required, however, limb muscle activity was increased preceding heel strike to compensate for reduced contributions from postural control

muscles. Future studies will investigate whether inappropriate postural interference is causal to impaired muscle activity patterns during walking poststroke.

Disclosures: S.A. Graham: None. **D.A. Brown:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); KineAssist.

Poster

808. Gait: Muscle Activity, Exercise, and Biomechanics

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 808.17/JJ2

Topic: E.06. Posture and Gait

Support: NSERC Grant

Student Bursary (U. LAVAL/CIRRIS)

Title: The positioning between the feet and pelvis when avoiding obstacles

Authors: *B. J. MCFADYEN[1,2], L.-P. DUGAS[2], L. J. BOUYER[1,2];
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Abstract: Biped locomotion is a complex mechanical process relying on dynamic equilibrium control. Positioning between the feet and the body is believed to be crucial for stable walking on level surfaces and a possible control variable. A good part of our locomotor experience, however, requires the adaptation to the environment to avoid or accommodate surface changes. Little is understood about foot-pelvis positioning during locomotor adaptations for obstacle avoidance. The goal of this study was to explore such geometric relationships during the approach to, and clearance of, an obstacle with unexpected changes to its position. Nine healthy young adult male participants stepped over a 19 cm high obstacle with their right leg leading. For approximately 22 percent of the trials, the position of the obstacle was unexpectedly advanced at either lead (early detection) or trail (late detection) foot contact prior to obstacle clearance forcing an adaptive reorganization of foot-body-environment geometry. Stride length, minimum foot clearance over the obstacle, and foot-obstacle horizontal proximity before and after clearance, were measured along with the relative positions between the pelvis and each foot from the two steps of approach to just after clearance. Reaction to unexpected obstacle movement was to increase step lengths and change proximity before and after crossing. Clearance was less affected for the trail foot as compared to the lead foot. Absolute foot-pelvis positions at foot contacts were different from level locomotion, although the geometric proportions of pelvic

positioning to front versus back feet in a given step were unchanged during approach. Despite changes in foot-pelvis positioning that depended on whether and when obstacle movement was perturbed, the pelvis did maintain the same anterior position to the back supporting foot at lead clearance for both early and late detection during obstacle movement. These preliminary findings show that foot-pelvis positioning is modified from level walking in order to clear obstacles, and can be quickly adapted to unexpected obstacle positions, with a possible bias to preserving a geometric reference to the back supporting foot during lead foot clearance when visual control is known to be important.

Disclosures: B.J. McFadyen: None. **L. Dugas:** None. **L.J. Bouyer:** None.

Poster

808. Gait: Muscle Activity, Exercise, and Biomechanics

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 808.18/JJ3

Topic: E.06. Posture and Gait

Support: a Grant-in-Aid for Scientific Research (B) (No. 26289063)

for Scientific Research on Innovative Areas (No. 15H01660)

Title: Synergy analysis of rat walking for elucidating the dysfunction due to neurological disorder

Authors: *R. SUZUKI[1], T. FUNATO[1], D. YANAGIHARA[2], S. FUJIKI[2], Y. SATO[1], S. AOI[3], K. TSUCHIYA[3];
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Abstract: In order to avoid the redundancy of muscles and joints, human and animals are known to move multiple muscles and joints in a coordination manner, called synergy. Synergy has a robust nature to variation in walking speeds and walking directions. Synergy changes by some neurological diseases. Multiple synergies are reported to unify after stroke and synergies are also reported to again separate slowly after the stroke (Chueng et al., PNAS, 2012). Muscle synergy of walking is also reported to change after stroke (Clark et al., J Neurophysiol, 2010). For investigating the relationship between such a synergy and stroke in detail, analyzing muscle synergy of animals with stroke is considered to be a novel method. In this research, as a preliminary step, walking synergy of intact rats were investigated.
In the experiment, intact Wistar rats bipedally walk on a treadmill with postural support. Joint

motions are measured using motion capture system, and elevation angles of body segments (foot, shank and thigh) on sagittal plane are calculated from the measured motion. EMGs of tibialis anterior, gastrocnemius, rectus femoris and vastus lateralis are measured, and they are low-pass filtered with 5 Hz. In order to extract the intersegmental coordination, singular value decomposition (SVD) is performed to the segment angles. In order to extract muscle synergies, non-negative matrix factorization (NMF) is performed to the measured EMGs.
From the analysis of segmental motion, two intersegmental coordination were extracted. Moreover, by comparing them with representative motion of walking, each coordination was found to correlate with the movement of limb orientation and length, respectively. From the analysis of EMGs, 2 muscle synergies were extracted. In one muscle synergy, flexor muscles were dominant, and extensor muscles were dominant in other synergy. The characteristic of muscle synergy was not affected by variation in walking speeds.
Through this research, we have constructed an analytical environment of the synergy of walking rats.

Disclosures: **R. Suzuki:** None. **T. Funato:** B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution; JSPS. **D. Yanagihara:** B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution; JSPS. **S. Fujiki:** B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution; JSPS. **Y. Sato:** None. **S. Aoi:** B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution; JSPS. **K. Tsuchiya:** None.

Poster

808. Gait: Muscle Activity, Exercise, and Biomechanics

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 808.19/JJ4

Topic: E.06. Posture and Gait

Title: Local dynamic stability in activations of muscle synergies during treadmill walking.

Authors: *B. KIBUSHI[1,2], S. HAGIO[3,2], M. KOUZAKI[1];
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Abstract: Walking is extremely stable motion, however stability of control may change depending on walking speeds. The maximal Lyapunov exponent has been estimated to quantify the local dynamic stability of walking motion (Dingwell and Cusumano, 2000). In terms of control, the central nervous system (CNS) needs to simplify redundant degrees of freedom with musculoskeletal system, it might be solved by control via muscle synergies in the spinal cord (Hagio et al., 2015). We hypothesized that stability in activations of muscle synergies may change depending on walking speeds. To investigate our hypothesis, we estimated maximal Lyapunov exponents in activations of muscle synergies and velocities of center of mass (COM) among various walking speeds. Our purpose was to reveal that how local dynamic stability in activations of muscle synergies change depending on walking speeds. Ten healthy men (23.3±0.9 years) walked on a treadmill at 14 various walking speeds (2.0-8.0 km/h and preferred walking speed) over 50 gait cycles. Surface electromyograms were recorded from 24 muscles in lower limb and trunk, and we used non-negative matrix factorization algorithm to extract muscle synergies (Tresch et al., 1999). Three-dimensional position of 29 retro-reflective spherical markers was measured to calculate the kinematic data. Maximal Lyapunov exponents in COM and activations of muscle synergies are calculated as the average exponential rate of divergence that results from continuously to very small perturbation (Dingwell and Marin, 2006). A positive maximal Lyapunov exponent means that an analyzed data is unstable. We calculated maximal Lyapunov exponents as short-term exponents and long-term exponents. Short-term exponents in the COM and activations of muscle synergies increased as walking speeds got faster. In addition, long-term exponents in the COM increased when walking speeds increased. However, long-term exponents in activations of muscle synergies were fixed regardless of walking speeds. These results suggest that the CNS may keep long-term instability in activations of muscle synergies even if walking speeds increase.

Disclosures: B. Kibushi: None. **S. Hagio:** None. **M. Kouzaki:** None.

Poster

808. Gait: Muscle Activity, Exercise, and Biomechanics

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 808.20/JJ5

Topic: E.06. Posture and Gait

Support: NIH Grant K12HD073945

James Zumberge Individual Research Award from the University of Southern California

Title: Perceptual, physiological and neuromechanical correlates of effort associated with step-length manipulations during split-belt walking

Authors: *N. SANCHEZ, S. PARK, J. M. FINLEY;
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Abstract: Background: During walking, most self-selected gait parameters such as speed, step length, step width, and step timing are chosen to minimize the metabolic cost of transport. Research has shown that when adapting to walking on a split-belt treadmill, a simultaneous reduction in step length asymmetry and metabolic cost occurs, however, whether convergence to step length symmetry is the energetically optimal behavior during split-belt walking remains to be seen. Here, we modified step length asymmetry using real-time visual feedback to determine the most economical strategies for walking on a split-belt treadmill.
Methods: Thirty healthy individuals walked on a dual-belt treadmill under three conditions: 1) a 5-minute BASELINE period at 1 m/s; 2) a 5-minute period walking at 1 m/s with feedback (FBK) of baseline step length asymmetry (SLA); and 3) a 5-minute split-belt walking period (SPLIT) with the left and right belts moving at 1.5 m/s and 0.5 m/s respectively. Seven different SPLIT trials were conducted, and for each trial participants were provided with visual feedback of the target SLA and their achieved SLA. SLA was specified as a percentage of stride length, with target values of 0%, +/- 5%, +/-10%, and +/-15%. Kinematics were recorded using an optical motion capture system and these data were used to calculate spatiotemporal measures of asymmetry. Joint moments, powers, and mechanical work were derived from kinematic data and ground reaction forces. Metabolic power was calculated for each SLA level from the rate of oxygen consumption and carbon dioxide production using standard techniques. We also assessed subjective measures of effort using the Borg scale of perceived exertion.
Results: Consistent with our previous findings (Finley et al., 2013), we observed a proportional increase in the metabolic cost of walking on a split belt treadmill for more negative SLAs (longer steps with slow leg). However, for positive SLAs (0 to 15%), the relationship between metabolic power and SLA was highly variable across participants: in 65% of participants, optimal metabolic power occurred for SLAs greater than zero and surprisingly, only 20% of participants experienced the lowest metabolic cost at 0%SLA. A dissociation between performance and metabolic cost was also observed: performance was worse for positive SLAs despite their lower metabolic cost. These results suggest that adaptation to walking on a split belt treadmill may not be exclusively driven by optimization of metabolic cost, but instead may result from interactions between limb mechanics, spinal pattern generators, and supraspinal circuits involved in error-based learning.

Disclosures: **N. Sanchez:** None. **S. Park:** None. **J.M. Finley:** None.

Poster

808. Gait: Muscle Activity, Exercise, and Biomechanics

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 808.21/JJ6

Topic: E.06. Posture and Gait

Support: ANR-10-IDEX-03-02

Association France Alzheimer

Title: Behavioural phenotyping using pressure sensor derived signals reveals early signs of pathological phenotype in the 3xTg mouse model of Alzheimer's disease

Authors: *M. CARREÑO[1,2,3], M. C. MENDRANO[1,3], F. MARTINS[1,3], M. BOMPART[1,3], K. LOPEZ DE IPIÑA[2], A. MOUJAHID[2], X. LEINEKUGEL[1,3];
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Abstract: Behavioural phenotyping is a required step to exploit the multitude of transgenic mouse models and potentially useful pharmacological agents made available by academic and industrial pharmaceutical research. It is based on the detection of animal movement. Pressure sensors using the piezoelectric technology can provide extremely detailed and precise information regarding animal movement that can be a nice complement to video signal to analyze laboratory animal behaviour in a variety of protocols, including freely moving in an open field. One interesting thing about such movement-related signal is that it reflects the summed activity of all the muscles of the animal. Depending on the coordination of these myriads of muscles, their mechanical piezo signature can sum up or cancel each other. This is therefore a very rich but also very complex signal that can be used to characterize the behavioural phenotype of the animals under study. We have recorded the spontaneous activity of 3xTg mice between 3 weeks and 7 months of age. Our analysis of the movement-related signal reveals early signs of the pathology and alterations of the time organization of locomotion, suggesting altered motor and cognitive control.

Disclosures: **M. Carreño:** None. **M.C. Mendrano:** None. **F. Martins:** None. **M. Bompart:** None. **K. Lopez de Ipiña:** None. **A. Moujahid:** None. **X. Leinekugel:** None.

Poster

808. Gait: Muscle Activity, Exercise, and Biomechanics

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 808.22/JJ7

Topic: E.06. Posture and Gait

Support: Grant-in-Aid for Young Scientists (B)

Title: Lesions to the olivo-cerebellar pathway disturbed a toe trajectory during stepping over an obstacle in rat

Authors: *Y. SATO[1], S. AOKI[2], D. YANAGIHARA[3];
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Abstract: In everyday life, we commonly encounter uneven terrain in which there are obstacles or stepping-stones in walking paths. In such a situation, stepping over obstacles to avoid tripping is essential for safe and smooth locomotion. Stepping over an obstacle during locomotion requires appropriate toe trajectory, to adapt for height and width of the obstacle. It is suggested that the cerebellum plays a crucial role for adaptive control of locomotion. Climbing fibers (CFs) which originate from the inferior olive (IO), these synaptic actions to the Purkinje cells are necessary for the synaptic plasticity in the cerebellum and motor learning. Previous study reported that climbing fiber responses are apparent in low frequency and are not dependent to the locomotor phases. However, perturbation induced climbing fiber responses in very high probability. Our question has been - does the deficit of IO neurons and their CFs inputs affect the obstacle avoidance during locomotion? Pharmacological lesions of the IO was induced by administration of 3-acetylpyridine in rat. In pre- and post-lesions, limb movements during overground locomotion and obstacle (heights: 2, 3, 4cm) avoidance were captured by high speed camera and were analyzed. All procedures relating to the care and treatment of animals conformed to the guidelines established by the Animal Investigation Committee of The University of Tokyo and the United States National Institute of Health. The results are as follows. 1) In the post-lesion, rats showed excessive toe elevation and shortening stride length during overground locomotion. 2) During stepping over the obstacle, rats showed severely fluctuated toe trajectory. These results indicate that olivo-cerebellar pathway is involved in not only the limb movements during overground locomotion but adaptive control of toe trajectory during stepping over the obstacle.

Disclosures: **Y. Sato:** None. **S. Aoki:** None. **D. Yanagihara:** None.

Poster

808. Gait: Muscle Activity, Exercise, and Biomechanics

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 808.23/JJ8

Topic: E.06. Posture and Gait

Title: Effects of shoe heel height and heel areas on gait

Authors: *R. UTSUMI, S. YOSHIOKA, S. FUKASHIRO;
Univ. of Tokyo, Tokyo, Japan

Abstract: High-heeled shoes are commonly worn by women, and many studies have revealed that high-heeled shoes influence the joint kinetics and kinematics during walking. However, previous studies have not referred to the influences of the aspects of shoe types, such as heel height, heel areas, straps, designs. The purpose of this study is to determine how the heel height and heel areas of high-heeled shoes influence the walking strategy without changing the other aspects. For the first experiment, seven female subjects who regularly wear high-heeled shoes (mean age 24.7 ±1.8 years old) wore 4 types of shoes: sneakers and the same sneakers with insoles of 3cm, 5cm and 7cm (S0, S3, S5 and S7).
We traced 31 markers on anatomical positions with three dimensional motion analysis system(HAWK Digital System, Motion Analysis Corp., USA / nac, Japan) and measured ground reaction forces with a force plate(Force Plate 9281E, Kisler, Switzerland). We examined influences of the heel height on kinematics at optical walking speed.
In each trail, there was no significant difference regarding walking strides and pitches. Higher heels increase angles of ankle planter flexion throughout stance phase, and increase the angles of knee flexion and hip flexion during mid-stance phase. Higher heels don't significantly affect on joint torques of ankle, knee and hip.
Secondly, to verify how shoe areas affect on walking strategy, we prepared S7 and high-heeled shoes (average heel height 7.6cm, heel areas 6.5cm^2 ,HH), and tracked kinematics dates under same condition as previous trials. The walking strides in trial wearing HH, was significantly shortened compared with the trail wearing S7.
Throughout the stance phase, when subjects were wearing HH, the angles of ankle planter flexion were increased than wearing S7.It indicates the characteristics of HH such as the smaller heel areas and stiffness of heel cause the ankle joint of planter flexion to reduce impact at heel contact.
And in wearing HH, with significant flexion of the knee joint angle, the torque of knee flexion and the torque of hip extension were increased. These results indicate that movement of COP to forward makes the knee joint angle to flex, and the hip significant extension torques prevent the hip joint from over flexion accompanied by knee flexion. Compared with S7, HH cause the lower limbs joints exert torque.

Our study indicates that, during walking, the joint angles of lower limbs are influenced mainly by heel-height and the joint torques of the lower limbs are influenced by heel areas more than by heel height. We suggest that it is important to consider the walking strategy wearing high-heeled shoes with aspects of shoes distinctly.

Disclosures: R. Utsumi: None. **S. Yoshioka:** None. **S. Fukashiro:** None.

Poster

808. Gait: Muscle Activity, Exercise, and Biomechanics

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 808.24/JJ9

Topic: E.06. Posture and Gait

Support: NIH/NICHD-R01HD082216

Title: Constraint-induced forced use the paretic leg during treadmill walking in individuals post stroke

Authors: C.-J. HSU[1], J. KIM[1], R. TANG[1], E. ROTH[1], W. RYMER[1], *M. WU[2,1];
[1]Rehabil. Inst. of Chicago, Chicago, IL; [2]Dept Physical Med. & Rehabil, Northwestern Univ. - Chicago, Chicago, IL

Abstract: Introduction: Locomotor training is a task-specific approach for stroke rehabilitation. However, an individual with post-stroke hemiparesis tends to rely more on the non-paretic leg to perform bipedal walking during locomotor training, which may limit the improvements in motor control of the paretic leg through a use-dependent motor learning mechanism. Constraint-Induced Movement Therapy has been utilized to improve the use of paretic arm by restraining the non-paretic arm. However, this paradigm has not been effectively applied to lower limb training in individuals post stroke due to the strong coupling between the two legs during bipedal gait. The purpose of this study was to examine the effects of constrain induced forced of the paretic leg during treadmill walking in individuals post-stroke. We hypothesized that applying a resistance force to the non-paretic leg during the swing phase of gait would enhance muscle activation of the hip extensors and ankle plantarflexors of the paretic leg during treadmill walking in individuals post-stroke. **Materials/Methods:** Twelve subjects with hemiparesis due to chronic (> 6 months) stroke participated in the study**.** A customized cable-driven robotic system was used to apply a controlled resistance force to the non-paretic leg at ankle. Subjects were instructed to walk on a treadmill at self-selected comfortable speed without perturbation (i.e., baseline) and 2 randomized test conditions with resistance force applied at early swing phase and late swing phase. Surface electrodes recorded the electromyograms (EMG) from 7

muscles on the paretic leg: abductor (gluteus medius), medial hamstrings, medial gastrocnemius, soleus, rectus femoris, vastus medialis and tibialis anterior. The variable of interest was the integrated EMG of each muscle. **Results:** Integrated EMG of medial hamstrings (p= 0.023) and tibialis anterior (p=0.011) significantly increased in the early swing resistance condition compared to baseline. Integrated EMG of medial gastrocnemius also tended to increase in the early swing resistance condition compared to baseline (p=0.060), and significantly greater for the condition with early swing resistance than that with late swing resistance (p= 0.012). **Conclusions:** Applying a resistance force to the non-paretic leg during the early swing phase of gait enhanced muscle activity of the paretic leg during treadmill walking. **Clinical Relevance:** This study provides initial evidence of the application of constrain induced forced use of the paretic leg during locomotor training. Results from this study may be used to develop a paradigm for improving walking function of individuals post stroke.

Disclosures: C. Hsu: None. **J. Kim:** None. **R. Tang:** None. **E. Roth:** None. **W. Rymer:** None. **M. Wu:** None.

Poster

808. Gait: Muscle Activity, Exercise, and Biomechanics

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 808.25/JJ10

Topic: E.06. Posture and Gait

Title: Application of a multilayer perceptron neural network with an iPod as a wireless gyroscope platform to classify reduced arm swing gait for people with Erb's palsy

Authors: *T. J. MASTROIANNI[1], R. LEMOYNE[2];
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Abstract: Erb's palsy involves trauma to the brachial plexus, which impairs the respective arm. One of the symptoms of Erb's palsy is reduced arm swing during gait. Symmetric arm swing is an inherent feature of healthy gait. The presence of asymmetry of arm swing while walking can potentially induce the development of compensatory mechanisms. The gyroscope signal can provide quantified insight regarding the severity of Erb's palsy reduced arm swing. An iPod equipped with a software application can function as a wireless gyroscope platform. A feature set of an asymmetric pair of arm swing during gait can be post-processed based on the gyroscope data collected while walking. Machine learning through a multilayer perceptron neural network has been successfully applied for distinguishing between an asymmetric pair due to reduced arm swing as a result of Erb's palsy.

Disclosures: **T.J. Mastroianni:** None. **R. LeMoyne:** None.

Poster

808. Gait: Muscle Activity, Exercise, and Biomechanics

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 808.26/JJ11

Topic: E.06. Posture and Gait

Title: Differential activation of the leg muscles during cycling interacts with transition to running in triathletes

Authors: ***A. J. KOVACS**[1], C. L. CAMIC[1], L. E. BRADLEY[1], P. GRIFFITH[1], E. A. DURHAM[1], T. L. MILLER[1], H. S. BAWEJA[2];
[1]Exercise and Sport Sci., Univ. of Wisconsin - La Crosse, LA Crosse, WI; [2]Col. of Hlth. and Human Services, San Diego State Univ., San Diego, CA

Abstract: Notwithstanding of their level of experience, triathletes report difficulties in transitioning to running after the intense bout of cycling. Recent evidence suggests that cycling may influence neuromuscular control of the subsequent running. Nevertheless, the specific neural mechanisms underlying this transition difficulty remain unclear. Therefore, the purpose of this study was to identify aspects of neuromuscular control that may contribute to transition difficulties experienced by triathletes. Data collection is ongoing. Currently, six competitive triathletes (ages 18-23 years) have participated in the study. All subjects performed 4 sessions over two weeks. The first two sessions (counterbalanced) were used to determine the aerobic capacity (VO_2max) and ventilatory threshold (VT) for running and cycling. The next two experimental sessions (counterbalanced) consisted of 40 minutes of cycling followed by a 10-minute run (C-R) or a 40 minute run followed by 10 minute run (R-R). Both experimental sessions were performed at the athlete's VT. Muscle activity (surface EMG) was recorded from six leg muscles only during the experimental sessions. Muscle activity was quantified as EMG amplitude, relative timing of muscle activation onset and offset, and signal-to-noise ratio (S/N). EMG amplitude for cycling was higher than that for running. EMG amplitude and timing of muscle activation were not different during post-transition running for both conditions. Regardless of conditions, the S/N stabilized within the first 5 minutes of the initial cycling (C-R) and running (R-R) bouts. Furthermore, after transition there was a differential change in S/N of the lower leg muscles when compared with the upper leg muscles only for the C-R condition, but not R-R condition. Our results suggest an initial rapid adaptation and increase in efficiency of muscle activation during the initial long bout of exercise. The difficulty in transitioning from cycling to running appears to originate from a sudden decrease in S/N for the C-R condition

when compared with the R-R condition in the lower leg muscles. In sum, our findings suggest that performing highly repetitive movements increase the task specific voluntary drive to the muscles and impedes transition to a different repetitive activity.

Disclosures: **A.J. Kovacs:** None. **C.L. Camic:** None. **L.E. Bradley:** None. **P. Griffith:** None. **E.A. Durham:** None. **T.L. Miller:** None. **H.S. Baweja:** None.

Poster

808. Gait: Muscle Activity, Exercise, and Biomechanics

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 808.27/JJ12

Topic: E.06. Posture and Gait

Title: On the combined task of walking and grasping, transporting and placing a dowel on a target in young adults

Authors: *R. MORAES[1], L. O. SANTOS[2], A. A. S. COSTA[2];
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Abstract: We investigated a dual motor task which involves the coordination of upper and lower limbs as observed during the combined task of gait and prehension. Our purpose was to investigate gait and prehension control during the dual motor task of walking while lifting and transporting a dowel to a target with different levels of manual task difficulty in young adults. Fifteen young adults performed the prehension task of lifting and transporting a dowel (4.5 cm diameter) to one of two target sizes (8 cm or 12 cm diameters) located at one of two distances from the starting point (40 or 60% of the total length of each participant's right upper limb). Participants should place the dowel closest to the target center. They performed the prehension task either walking or in upright stance (standing). We analyzed different variables related to dowel transport (from contact to release) and walking stability, using the margin of dynamic stability (MDS), at both dowel's contact and release. For the analyses of dowel transport, analyses of variance revealed several significant findings summarized in the sequence. Radial error of dowel placement relative to target center was larger for walking (0.99 cm) than for standing (0.75 cm). Dowel transport duration was longer for standing (1.06 s) than for the walking (0.73 s). Transport duration also increased for the long compared to the short distance in both tasks, but this increased was more pronounced for the standing task. Peak wrist velocity (relative to the iliac crest) was larger for standing (0.84 m/s) than for walking (0.08 m/s). In both tasks, peak wrist velocity increased from the short to the long distance, but this increase was more pronounced in the standing task. Time to peak wrist velocity increased in walking (44.0%) compared to standing (36.8%). For the MDS at both dowel's contact and release, there were

differences between tasks in both anterior-posterior (AP) and medial-lateral (ML) directions. At contact and release, AP MDS was more negative in walking (-0.267 m and -0.319 m, respectively) than in standing (-0.015 m and -0.048 m, respectively). For the ML direction, at both contact and release, MDS was larger for walking (0.058 m and 0.066 m, respectively) than for standing (0.037 m and 0.034 m, respectively). These results indicate that task affected how the dowel was transported such that error increased and transport duration decreased when walking. The increase in time to peak wrist velocity when walking suggests that participants spent less time visually correcting the dowel transport compared to the standing task. Moreover, stability in the AP direction was reduced for the walking compared to the stationary task.

Disclosures: R. Moraes: None. **L.O. Santos:** None. **A.A.S. Costa:** None.

Poster

808. Gait: Muscle Activity, Exercise, and Biomechanics

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 808.28/DP05 (Dynamic Poster)

Topic: E.06. Posture and Gait

Support: NSF Grant 1431078

Title: Active versus passive perceptual control of locomotion: The preference for ballistic movements during walking

Authors: *S. L. BARTON[1], S. STEINMETZ[1], J. S. MATTHIS[2], B. FAJEN[1];
[1]Rensselaer Polytechnic Inst., Troy, NY; [2]Univ. of Texas at Austin, Austin, TX

Abstract: During the course of walking, humans are mechanically similar to an inverted pendulum. This affords stable and efficient locomotion that emerges from the interaction between the body and the environment. Visual perception during walking appears to be used to modify the ballistic trajectory of the body for each step as necessary. This control strategy allows walkers to exploit the stability and efficiency of pendular walking during locomotion. Previously we have shown that the accuracy of foot placement during locomotion depends on the availability of visual information about the terrain during the last half of the preceding step (Matthis et al., 2013; Matthis et al., 2015). This critical control phase is the last point when the determinants of the ballistic trajectory can be modified based on visual information. We have also shown that walkers are able to respond to sudden changes in the position of a target foothold during the step. However, the adjustments depend on the timing and the direction of the perturbation. These findings suggest that the biomechanically-derived ballistic mode of walking may be preferred, even though walkers are capable of using vision during a step to adjust foot

placement. In the current study we asked whether subjects preferred to maintain an initial ballistic trajectory of the body or if they would switch to a more desirable stepping target when available. Subjects walked along a path of evenly spaced virtual stepping targets while being recorded with motion capture. One target was positioned off of the path, making it incongruent with the others and requiring a break in the regular stepping behavior. On a subset of trials, an alternative target appeared in the congruent position, offering a choice to subjects about where to step. The timing of visual information about this new target was varied as a function of the distance from the incongruent target. We found that subjects preferred to follow the ballistic trajectory of the body once it had been initiated, despite that they were capable of switching to the congruent target and that the incongruent target demanded a significant stepping deviation (35% of subject step-length). Subjects only switched to the congruent target if visual information was provided well in advance of the initiation of the step to the incongruent target, indicating a preference for relying on the ballistic trajectory of the body when executing a step. This suggests that walkers prefer to exploit their biomechanics for the production of walking, and rely on perceptual control during a step only when they can't modify their ballistic trajectory.

Disclosures: **S.L. Barton:** None. **S. Steinmetz:** None. **J.S. Matthis:** None. **B. Fajen:** None.

Poster

808. Gait: Muscle Activity, Exercise, and Biomechanics

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 808.29/JJ13

Topic: E.06. Posture and Gait

Support: CIHR MOP-110950

Title: V3 spinal interneurons are crucial in regulating weight-loading movement

Authors: *H. ZHANG, D. DESKA-GAUTHIER, Y. ZHANG;
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Abstract: V3 interneurons (INs) are a major group of glutamatergic commissural neurons located in the spinal cord. They innervate motor neurons as well as many other ventral INs and are essential for producing a robust and organized locomotor rhythm. Until now, however, the mechanisms underlying the function of V3 INs in locomotion is still unclear. To address this question, we have systematically examined the kinematics and muscle activities of the hind limbs of a mutant mouse, in which the expression of Vesicular Glutamate Transporter 2 (VGLUT2) is specifically deleted in the V3 INs. Kinematic analysis showed that mutant mice couldn't fully extend their ankle and knee joints at the later stage of the stance phase, and then

they quickly lifted their leg causing a short flexor phase, but took a long stretch to touch the ground. Therefore, there was no significant difference in the overall length of swing and stance periods between mutant and control animals, but the relative position between the rear paw and the hip joint was shifted in mutant mice, which made it less efficient for the mutant mice to propel themselves forward. Corresponding to such abnormal gaits, electromyography (EMG) recording indicated that the mutant mice couldn't maintain sustained extensor muscle activities during the stance phase. In addition, the ankle flexor muscle, TA, in mutant mice had a narrower bursting duration, while their knee extensor, VL, started earlier during swing phase than those in control mice. Furthermore, in the ladder-walking task, mutant mice had more errors on the foot placement. These results indicated that V3 INs might be involved in spinal pathways that are responsible for maintaining the muscle excitability and regulating the joint positions during walking.

Disclosures: H. Zhang: None. **D. Deska-Gauthier:** None. **Y. Zhang:** None.

Poster

808. Gait: Muscle Activity, Exercise, and Biomechanics

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 808.30/JJ14

Topic: E.06. Posture and Gait

Support: TUBITAK 2232 grant (115C086)

Title: Investigation of biologic feedback influence on knee biomechanics during running

Authors: *H. ARGUNSAH BAYRAM[1,2], M. B. BAYRAM[1,2];
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Abstract: Biologic feedback is non-invasive and commonly used in rehabilitation for the purpose of providing motivation and increasing the performance. Biologic feedback mechanisms are artificial systems, which provide additional information- audial, visual, tactile- to the patient. They favor motor learning by improving motor control in static and dynamic tasks by augmenting motor information that makes them helpful tools for improving balance, motor rehabilitation and also training.
This study aims (1) exploring the quantification of heart beat optimization and knee joint range of motion (ROM) during running on treadmill at self-selected pace while biologic feedback is provided and (2) comparing the output during the same exercise while the feedback is absent. Therefore, this investigation not only improves the benefits of rehabilitation/training on treadmill

by providing motivation but also explores the advantages of using biologic feedback in improving balance and motor control.
Fifteen healthy unprofessional runners were recruited for the study. During their first visit to the Biomechanics Laboratory, they ran on the treadmill for fifteen minutes while the feedback was absent. One week later, they performed the same exercise while visual and audial biologic feedback was available. A twin axis goniometer was plastered on the lateral side of the knee joint and the ROM was monitored continuously while the participant was running on the treadmill at a constant pace. Similarly, heart rate was monitored throughout the exercise. Gait symmetry was monitored by Gaitometer- an application available for iPhone and iPod, which uses the built-in accelerometers in the smart phone to detect and analyze the step symmetry of the user.
One subject was tested so far, and data collection is ongoing. Preliminary data showed that the ROM and heart rate were not significantly different with or without biologic feedback at the beginning of the exercise. However as the exercise duration increased, restricted ROM was obtained when biologic feedback was not provided to the participant (110 degrees vs. 98 degrees). Similarly, as the exercise duration increased, higher heartbeat was obtained when biologic feedback was not provided to the participant (162 vs. 188). The biologic feedback provided real-time gait analysis to the participant and assisted him in obtaining a more symmetric, balanced and sustainable training.

Disclosures: H. Argunsah Bayram: None. **M.B. Bayram:** None.

Poster

809. Posture: Aging, Injury, and Disease

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 809.01/JJ15

Topic: E.06. Posture and Gait

Title: Brain activation changes during balance and attention demanding tasks in older adults with multiple sclerosis

Authors: *M. E. HERNANDEZ[1], G. CHAPARRO[1], E. O'DONNELL[1], R. HOLTZER[2], M. IZZETOGLU[3], R. W. MOTL[1];
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Abstract: The present study used functional Near Infrared Spectroscopy (fNIRS) to evaluate real-time neural activation differences in the pre-frontal cortex (PFC) between older adults with multiple sclerosis (MS) and healthy older adults (HOA) during the performance of attention demanding tasks (i.e., backward recitation of alternate letters of the alphabet) while standing

(Talk) or while walking on a straight line (SLWT) on a self-paced instrumented treadmill. Ten older adults with MS and 12 HOA underwent fNIRS recording while performing the SLWT and Talk tasks with an fNIRS cap consisting of 16 optodes positioned over the forehead. As a baseline for each task, we considered walking on straight line (SLW) or standing. The results revealed that the MS group were unable or unwilling to ramp up their PFC oxygenation levels during SLWT compared to Talk tasks over the course of a 30 second trial, which is contrast with controls (Figure 1). These findings provide evidence of a decreased ability of older adults with MS to allocate additional attentional resources in balance-demanding conditions, compared to healthy controls. This study is the first to investigate brain activation dynamics during the performance of these balance and cognitively demanding tasks in older adults with and without MS.

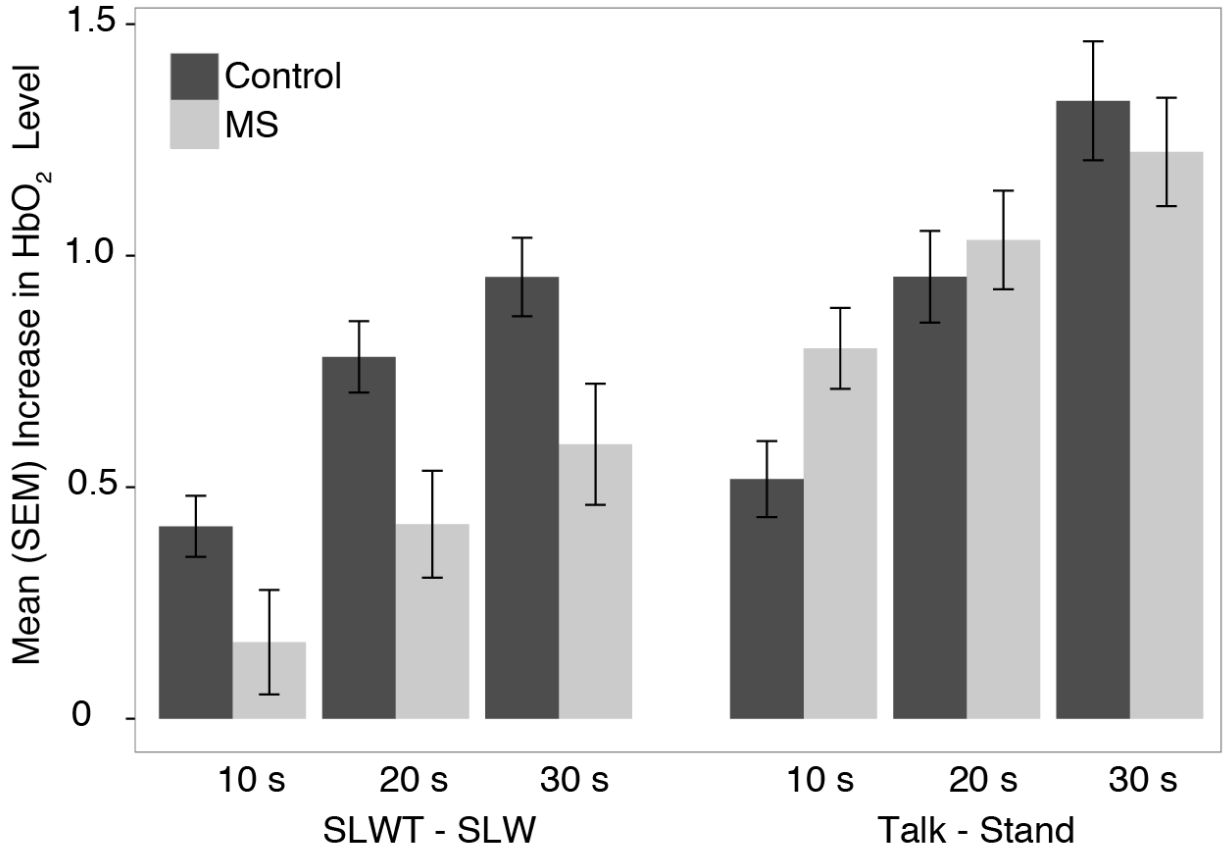

Figure 1. Mean (SEM) increase in oxygenation levels in older adults during straight line walking and talking (SLWT) relative to straight-line walking (SLW) and during talking (Talk) relative to standing on a self-paced treadmill on older adults with multiple sclerosis (MS) and healthy controls.

Disclosures: **M.E. Hernandez:** None. **G. Chaparro:** None. **E. O'Donnell:** None. **R. Holtzer:** None. **M. Izzetoglu:** None. **R.W. Motl:** None.

Poster

809. Posture: Aging, Injury, and Disease

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 809.02/JJ16

Topic: E.06. Posture and Gait

Title: Acute postural control deficits in Division I college athletes following mild concussions

Authors: *S. SORIA, M. J. RAUH, D. J. GOBLE, H. S. BAWEJA;
Sch. of Exercise and Nutritional Sci., San Diego State Univ., San Diego, CA

Abstract: Objective: The purpose of this study was to determine the extent of postural control deficits accompanying concussions in Division I collegiate athletes within 48 hours of injury. **Design:** Cross-sectional study **Setting:** University Athletic Training Department & Biomechanics Laboratory **Participants:** Preseason baseline balance testing of 519 healthy Division I college athletes was performed with the BTrackS Balance Test (San Diego, CA). Of the baselined athletes, 26 (18-23 years; 14 females) experienced a concussion during the ensuing sport season. Post-injury balance testing was performed on these concussed athletes within 48 hours of injury. Additionally, 20 healthy young adults (19-25 years; 10 females) were baselined on 2 sessions 7 days apart. **Outcome measures:** All testing consisted of three 20s trials of quiet unperturbed standing with eyes closed; feet shoulder width apart and hands on the hips. We calculated total center of pressure (COP), COP antero-posterior (AP), and COP medio-lateral (ML) sway displacements. A principle component analysis was used to calculate the 99% confidence intervals (CI) of the COP area. **Main results:** There were no preseason baseline differences in any of the balance measures between athletes and controls. However, postural displacement in all directions (AP, ML, and Total) increased significantly in athletes post-injury. Furthermore, ~80% of the increase in COP excursions was accounted for by a ~7 fold increase in the COP area post-injury. **Conclusion:** Our findings are indicative of a decrease in postural control and multisensory integration post-concussion. Future studies should investigate the long-term effects and recovery from concussions in athletes.

Disclosures: S. Soria: None. **M.J. Rauh:** None. **D.J. Goble:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Holds an equity stake in the parent company for the BTrackS Balance Plate. This conflict of interest was strictly managed by San Diego State University through a mitigation plan.. **H.S. Baweja:** None.

Poster

809. Posture: Aging, Injury, and Disease

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 809.03/JJ17

Topic: E.06. Posture and Gait

Support: A grant from the Research Institute of Industrial Technology, Toyo University

Title: A novel method for evaluating risks for fall and forgetfulness in the elderly using handwriting characteristics

Authors: *Y. HOSOKAWA[1], H. TAKATSU[1], K. WATANABE[2], T. WATANABE[3], E. TANAKA[2], T. ANME[2], H. KAWAGUCHI[1];
[1]Toyo Univ., Gunma, Japan; [2]Tsukuba Univ., Ibaraki, Japan; [3]Japan Univ. of Hlth. Sci., Saitama, Japan

Abstract: We aimed to establish a simple quantitative method for evaluating motor and cognitive performances in elderly people by analyzing their handwriting characteristics using a digital pen. This device, which digitizes handwriting with a spatial resolution of 0.3 mm and a temporal resolution of 13 ms, can be used to simultaneously acquire data from multiple users. Therefore, the digital pen is suitable for use in screening for risks associated with falls and forgetfulness in elderly people. In total, 153 elderly people (age 54-90; 34 men and 119 women) were recruited for a longitudinal study conducted over 2 years (2013 and 2014), as a part of the Joso project (Elderly People Health Empowerment Project in Joso City, Ibaraki Prefecture, Japan). This project was conducted in cooperation with Joso City, the University of Tsukuba, and Toyo University. Participants were required to complete three questionnaires: lifestyles, basic checklist, and Motor Fitness Scale. These questionnaires required drawing a figure (one-stroke sketch task) and included measures reflecting risks for fall and forgetfulness. We analyzed several handwriting characteristics of the sketch task, including stroke range, writing pressure, writing speed, and acceleration of writing speed using multivariate logistic analysis. Significant correlations were noted between handwriting pressure and scores of risks for fall ($p < 0.05$). We also found significant negative correlations between stroke range/writing acceleration and risks for fall or forgetfulness ($p < 0.05$). Thus, handwriting data can be used for simple evaluations of motor and cognitive performances in elderly people. These evaluations may help develop strategies to maintain quality of life for elderly people. The protocols used in this study were approved by the Ethics Committee of the University of Tsukuba. This work was partially supported by a grant from the Research Institute of Industrial Technology, Toyo University.

Disclosures: **Y. Hosokawa:** None. **H. Takatsu:** None. **K. Watanabe:** None. **T. Watanabe:** None. **E. Tanaka:** None. **T. Anme:** None. **H. Kawaguchi:** None.

Poster

809. Posture: Aging, Injury, and Disease

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 809.04/KK1

Topic: E.06. Posture and Gait

Support: Physical Therapy Department Research Fund, University of Michigan-Flint

Title: Center of pressure variables in dynamic functional tasks that are related to a history of falls in community dwelling older adults

Authors: K. NEWMAN, *M.-H. HUANG, A. RIGHTER;
Univ. of Michigan Flint, Flint, MI

Abstract: Age-related changes in postural control are major risk factors for falls. Many studies have investigated stabliometric variables of center of pressure (COP) in static standing. However, research on the measures of postural stability during dynamic movements to detect fall risks is limited. This study investigated whether COP parameters during a functional, dynamic movement task could identify older adults with a history of falls (fallers) and examined the effect of trial on COP. Twenty-one community-dwelling older adults volunteered; 11 were non-fallers and 10 were fallers based on self-reported history of falls in the past 12 months. All could walk >50 ft without another person's assistance and with no history of neurologic conditions. Participants reached forward to grasp a water bottle (weight 100 g) placed at 30 cm in front of the feet on the floor using the right arm, and returned to an upright posture while holding it. They were instructed to perform the task as fast as possible. Participants performed 3 trials. A force platform (AMTI OR6-5. Watertown, MA) and a motion analysis system (VICON Motion Systems Ltd. Centennial, CO) recorded ground reaction forces and body kinematics, respectively. COP variables included the displacement during and the duration of anticipatory postural adjustments (APA), maximum forward displacement, peak velocity, and trajectory smoothness measured by normalized integrated jerk (NIJ). Linear Mixed Model analyzed variables with group as between subject factor and trial as within subject factor. Tukey's LSD was used for post-hoc comparisons. Significance level was $p<0.05$.
Arm reaching movements were significantly faster in non-fallers than fallers during reaching but not returning movements ($p<0.05$). APA amplitudes were significantly smaller ($p<0.05$) and APA durations were significantly longer ($p<0.05$) in fallers (9.8 mm, 189 ms) than non-fallers (14.3 mm, 150 ms). COP trajectory smoothness was significantly reduced in fallers (NIJ=633) compared to non-fallers (NIJ=403) during the reach portion of the task ($p<0.05$), but not the return. In contrast, all groups achieved maximum COP forward displacement at comparable timings and had similar COP peak velocities. Neither the effect of trial or group by trial was significant.

During a dynamic reaching task, APA amplitudes and durations and the control of COP trajectory smoothness during movements, but not the velocities of COP are altered with a history of falls in older adults. COP variables remained consistent across trials. Further research needs to investigate the kinematic strategies with relation to the control of COP during reaching tasks in fallers and non-fallers.

Disclosures: K. Newman: None. **M. Huang:** None. **A. Righter:** None.

Poster

809. Posture: Aging, Injury, and Disease

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 809.05/KK2

Topic: E.06. Posture and Gait

Support: European Union (FP7-ICT project 610454)

Title: The video head impulse test predicts the ability to reweight vestibular information during stance in patients with vestibular disorders

Authors: *J. VAN KORDELAAR[1], J. H. PASMA[2], M. CENCIARINI[3], C. MAURER[3]; [1]Biomechanical Engineering, Inst. for Biomed. Technol. and Tech. Med., Univ. of Twente, Enschede, Netherlands; [2]Biomechanical Engin., Delft Univ. of Technol., Delft, Netherlands; [3]Neurologische Klinik, Neurozentrum, Univ. Freiburg, Freiburg, Germany

Abstract: INTRODUCTION: During stance, vestibular information is used and weighted based on its reliability. Vestibular deficits affect the reliability of vestibular information and therefore affect the ability to reweight vestibular information during stance. Vestibular information during stance mainly consists of frequencies up to 5 Hz. However, vestibular-ocular reflex (VOR) tests designed to detect vestibular deficits mainly operate in restricted frequency ranges such as 0.002 - 0.004 Hz for the caloric test, 0.1 - 1 Hz for the rotational chair test and 1 - 6 Hz for the head impulse test. In this study we investigated how these three VOR tests are related to the ability to reweight vestibular information under different sensory disturbance conditions in patients with vestibular disorders. METHODS: 11 Patients (5 female) with vestibular disorders (mean ± SD age: 59.3 ± 9.9 years) were included. All patients underwent VOR examination using videonystagmography during bilateral cold caloric test, the rotational chair test at horizontal harmonic oscillations of the chair at 0.4 Hz and the head impulse test. In addition, balance control experiments were conducted using continuous support surface rotations (SS) which followed a pseudo-random ternary sequence (PRTS). Patients stood with their eyes closed during two SS conditions: 1) 0.5 degrees peak-to-peak amplitude and 2) 1.0 degrees peak-to-peak

amplitude. System identification and parameter estimation were used to estimate balance control model parameters, including the vestibular weight W_v which indicates how much patients relied on vestibular information in each condition. Spearman correlation coefficients were calculated to establish the relation between VOR tests (caloric test, rotational chair test and head impulse test) and the difference in the vestibular weight (W_{v_diff}) between 0.5 and 1.0 degrees peak-to-peak amplitude. RESULTS: Only the head impulse test was significantly related to W_{v_diff} ($\rho = -0.67$, $p = 0.033$), indicating that patients who showed more asymmetric ocular responses to left and right head impulses showed less sensory reweighting between SS conditions during balance control. DISCUSSION: Our results suggest that out of the three VOR tests included in this study the video head impulse test is most predictive of a reduced ability to reweight vestibular information during stance in patients with vestibular disorders. The video head impulse test mainly operates in the 1-6 Hz frequency range, which is comparable to the frequency range of joint torque and body sway oscillations and could therefore explain this high association.

Disclosures: J. Van Kordelaar: None. **J.H. Pasma:** None. **M. Cenciarini:** None. **C. Maurer:** None.

Poster

809. Posture: Aging, Injury, and Disease

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 809.06/KK3

Topic: E.06. Posture and Gait

Support: RIF127D23 (W81XWH-13-C-0189)

Title: Visual-vestibular processing deficits in subacute mild traumatic brain injury

Authors: *W. WRIGHT[1], R. T. TIERNEY[1], J. K. MCDEVITT[2];
[1]Temple Univ., Philadelphia, PA; [2]East Stroudsburg Univ., East Stroudsburg, PA

Abstract: The search for reliable and valid signs and symptoms (s/s) of mild traumatic brain injury (mTBI) has lead to a growing body of evidence that individuals with long-lasting, unremitting impairments often experience visual and vestibular symptoms, such as dizziness, and postural and gait disturbances. In this study we evaluate the role of visual-vestibular processing deficits following mTBI with a focus on subacute s/s (i.e. >7 days post-injury). A battery of clinically accepted vestibular, oculomotor, and balance assessments as well as a novel virtual reality (VR)-based balance assessment device were used to assess adults with a recent concussion (n=14) in comparison to a healthy age-matched cohort (n=58). Our results show significant between-group differences when using the VR-based balance device (p=0.001) and

symptom reports collected after performing the oculomotor and vestibular tests ($p<0.05$). Specifically, the dynamic visual motion condition in the VR-balance assessment emerged as the most discriminating balance condition. From the oculomotor and vestibular signs and symptoms tests, the rapid alternating horizontal eye saccades, optokinetic stimulation, gaze stabilization, and near-point convergence were all sensitive to health status, while the BESS, King-Devick, and Dynamic Visual Acuity tests were not. When combining the VR-balance outcomes with the OKN symptoms and the convergence test in a single regression model, accuracy reached 95.8%. Using this model to calculate a receiver operating characteristic curve revealed it to have a highly significant area under the curve (AUC=0.985, $p<0.001$). In conclusion, postural and visual-vestibular tasks most closely linked to spatial and self-motion perception had the greatest discriminatory outcomes. These findings suggest that mesencephalic and parieto-occipital centers and pathways are commonly involved in mTBI.

Disclosures: W. Wright: None. **R.T. Tierney:** None. **J.K. McDevitt:** None.

Poster

809. Posture: Aging, Injury, and Disease

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 809.07/KK4

Topic: E.06. Posture and Gait

Title: Dual-tasking diverts attention from postural control in older adults

Authors: *J. ERRAM[1], B. TAYLOR[2], P. GILBERT[2], D. GOBLE[1], H. BAWEJA[1];
[1]Sch. of Exercise and Nutritional Sci., Col. of Hlth. and Human Services, San Diego, CA; [2]Col. of Sci., San Diego, CA

Abstract: Postural control is accompanied with cognitive activities that are unrelated to posture in our daily lives. Both, postural control and cognition tend to deteriorate at different rates with aging. Therefore, the purpose of this study was to compare the effect of concurrent cognitive tasks on quiet unperturbed standing in young and older adults. Currently, 22 older adults (Age range: 60-90 years; 13 females) and 12 young adults (Age range: 18-21; 5 females) have taken part in the study. The Balance Tracking System (BTrackS, San Diego, CA) force plate was used to measure the postural sway. Balance testing consisted of 4 conditions: Single-task with eyes open, single-task with eyes closed, dual-task with eyes open and verbal memory encoding, and dual-task with eyes closed and digit span encoding. Subjects performed 3 trials per condition while standing with feet shoulder width apart and hands on hips. Each trial lasted 20 seconds during which the total center of pressure (COP), anteroposterior COP, and mediolateral COP sway displacements were calculated. A principle component analysis was used to calculate the

95 and 99% confidence intervals of the area within which the COP excursions would lie. Additionally, subjects performed the verbal memory and digit span encoding tasks in a sitting position, while their balance was not being tested or challenged. The subjects' error rates on the verbal memory encoding task and digit span encoding task were then calculated 'on' and 'off' the force plates. Our preliminary results suggest that when instructed to perform a demanding dual-task with eyes closed, older adults shift their attention away from postural control and their COP excursions decrease relative to the single-task baseline with eyes closed only, where attention is explicitly directed towards postural control. However, when performing the less demanding dual-task with eyes open, older adults do not show any differences in COP displacements relative to the single-task baseline with eyes open. Therefore, our findings are indicative of an interactive relation between the efficacy of postural control and concurrent cognitive demands, which reflect opposing trends in attentional resource competition in aging.

Disclosures: J. Erram: None. **B. Taylor:** None. **P. Gilbert:** None. **D. Goble:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); receipt of intellectual property rights/patent holder. **H. Baweja:** None.

Poster

809. Posture: Aging, Injury, and Disease

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 809.08/KK5

Topic: E.06. Posture and Gait

Title: Normative data for the btracks sports balance test in school and college athletes.

Authors: *C. FRENCHIK[1], S. M. SORIA[2], M. J. RAUH[2], D. J. GOBLE[2], H. BAWEJA[2]; [1]San Diego State Univ., National City, CA; [2]San Diego State Univ., San Diego, CA

Abstract: Problems with balance and postural stability can arise from athletic injuries affecting the musculoskeletal system, vestibular system and/or brain. The BTrackS Sports Balance Test is a brief, highly objective, easily administered test of static balance. The purpose of this study was to develop normative data for this test in school and college athletes aged 10-25 years. A secondary aim examined whether development of postural sway control was influenced by gender and body mass index (BMI). 235 adolescents between the ages of 10-14 years (60 females), 2266 adolescents between the ages of 15-19 years (601 females) and 1883 young adults between the ages of 20-25 years (631 females) volunteered to participate in the study. The Balance Tracking System (BTrackS, San Diego, CA) force plate was used to assess the postural sway during quiet standing for all trials. Testing consisted of 1 familiarization and 3

experimental trials of quiet standing with eyes closed with feet shoulder width apart and hands on the hips. Each trial lasted 20 seconds during which the total center of pressure (COP) sway, COP antero-posterior sway, COP medio-lateral sway excursions, velocities and 95% CIs of the COP area were quantified. Overall, adolescents from 10-14 years of age exhibited greater postural sway when compared with 15-19 and 20-25 year old athletes. Furthermore, females exhibited lower postural sway excursion in all directions when compared with males, irrespective of age. As expected the BMI increased significantly with age but did not account for the variability in total COP excursion. Our tests relied heavily on vestibular and proprioceptive integration as they were performed only with eyes-closed. Therefore, our findings are indicative of developing multisensory integration and balance ability continuing up to the age of 14 years. Our findings extend previous studies showing females to exhibit lower postural sway than males. These normative data provide a frame of reference for interpreting the BTrackS Sports Balance Test performance in school and collegiate athletes who sustain injuries on and off the field and provide a screening guideline for return to play.

Disclosures: **C. Frenchik:** None. **S.M. Soria:** None. **M.J. Rauh:** None. **D.J. Goble:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); BtrackS, inc.. **H. Baweja:** None.

Poster

809. Posture: Aging, Injury, and Disease

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 809.09/KK6

Topic: E.06. Posture and Gait

Title: Effect of light load on balance in young and older adults

Authors: *N. R. BIRCHFIELD, N. DOUNSKAIA;
Arizona State Univ., Phoenix, AZ

Abstract: Loads are carried in backpacks by both young and older adults. It is recognized that heavy backpacks destabilize balance even in young adults. However, the effect of light load on balance remains largely unknown. The mechanical model of the body as an inverted pendulum shows that the vertical posture is essentially unstable because the body's center of mass is above the base of support. This predicts that even light load attached above the natural center of mass may destabilize the body because it lifts the total center of mass. We tested this hypothesis by examining changes in postural stability caused by light load placed on the shoulders in sixteen young and sixteen older adults. Three conditions of load were used, unloaded (baseline), and 1% and 3% of body weight distributed equally between the two shoulders. Postural stability was

assessed by testing functional reach (forward and lateral) through measuring the reach distance. Also, static balance was assessed by measuring the postural sway area using an ellipse that included 95% of the center of pressure (COP) data points. The COP data were obtained with the use of a HUMAC (CMSi, Stoughton, MA) balance board in two vision conditions: with eyes opened and closed. Reach distance was shorter in older than young adults in all three directions. Load significantly shortened reach distance compared with the baseline values in both groups, although during the forward reach only. The sway area was smaller in older than young adults. Load caused increases in sway area in young adults but no changes were detected in older adults. More close examination revealed two subgroups of older adults with 8 subjects in each. Subgroup 1 increased sway area with load similar to younger adults. In contrast, Subgroup 2 decreased sway area with load. Also, subgroup 1 had smaller sway area in the baseline condition compared with subgroup 2, suggesting that subgroup 1 on average had better balance than subgroup 2. The results suggest that even the lightest load destabilized both young and older adults. Indeed, young adults decreased reach distance, and their sway area increased. They did not compensate for the increases in sway area likely because their balance remained within safety limits. Load had a similar effect on subgroup 1 of older adults. Subgroup 2 had worse balance in the baseline condition, which prompted these older adults to reduce sway area in the loaded conditions for safety reasons. These considerations suggest that the reaction to light load attached to the shoulders may potentially distinguish older adults whose postural control starts to get compromised.

Disclosures: N.R. Birchfield: None. **N. Dounskaia:** None.

Poster

809. Posture: Aging, Injury, and Disease

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 809.10/KK7

Topic: E.06. Posture and Gait

Support: Lions Foundation

Title: Mulitfractal analysis of center of pressure in peripheral neuropathy

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Abstract: The control of balance can be impaired in persons with a peripheral neuropathy. Some of the factors contributing to the symptoms include the following: the nature of the underlying

pathophysiology; whether sensory and/or motor nerves are affected; and the duration and rate of progression of the neuropathy (NINDS, Dec. 2014). The present study is part of an effort to quantify variability in the center of pressure (CoP) in persons with a peripheral neuropathy while the subject maintains a steady balance when standing on a forceplate. The general aim is to identify and characterize the short and long range correlation and self-similarity of fluctuations over time in the CoP using a multifractal, de-trended fluctuation analysis (Kantelhardt et al., 2002), MFDFA, of time series data. For this initial work the analysis was applied to CoP data during the following conditions: in the light while fixating on a distant, straight-ahead target; in darkness (eyes closed; no cognitive task); in darkness and engaged in an attention-demanding task (counting); in the light and engaged in an attention-demanding task (looking at a distant computer screen and identifying colored circles). The preliminary results suggest possible fractal properties of the postural control system dynamics, interactions across temporal scales, and how that is manifested in peripheral neuropathy. This approach could provide further insight into some of the factors affecting the control of balance in peripheral neuropathy.

Disclosures: J.H. Anderson: None.

Poster

809. Posture: Aging, Injury, and Disease

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 809.11/KK8

Topic: E.06. Posture and Gait

Title: Activation timing of postural muscles and P300 component of event-related potential during bilateral arm flexion in oddball task with different presentation probability of target stimulus in the elderly

Authors: *C. YAGUCHI[1], K. FUJIWARA[2];
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Abstract: With rapid arm movement while standing, postural muscles of the legs and trunk are automatically activated before focal muscles of the arms (Belen'kii et al., 1967). For the elderly, the preceding activation of the biceps femoris is less observable compared to young subjects (Rogers et al., 1992; Woollacott and Manchester, 1993), and the joint movement during arm movement was smaller at the ankle than the hip (Bleus et al., 2006). These findings were demonstrated during arm flexion with the arm moving from the side of the body, in which preceding activation of the triceps surae (TS) has not been observed also for young adults (Bouisset and Zattara, 1981). In contrast, preceding activation has been observed during arm

flexion from a position with the hands suspended in front of the body (Fujiwara et al., 2011). However, the preceding activation of postural muscles in the elderly has not been investigated during this arm flexion. Furthermore, the preceding time of TS became larger in the task condition where the postural disturbance can be predictable and the preparation for postural control is sufficient (Fujiwara et al., 2011). The anticipation of target presentation can be controlled by changes of the presentation probability of target stimulus in an oddball task (Polich, 1991). Therefore, using arm flexion from the suspended position in the oddball task with different target probability, we investigated the relationship between age-related changes of anticipation function and preceding activation of postural muscles. Thirteen young and thirteen elderly adults flexed their arms to the target stimuli with 15% and 45% probabilities in auditory oddball tasks, and at their own timing. The onset time of postural muscles with respect to anterior deltoid (AD) onset and the amplitude of P300 component of an event-related potential were measured. For young adults, gastrocnemius (GcM) activated earlier than AD in all conditions, and the preceding time was shorter in 15% than in 45% or own timing. For the elderly, GcM activation preceded AD only in own timing, but not in 15% and 45% with no significant differences between them. P300 amplitude was significantly larger in 15% than in 45% for young adults. For the elderly, there was no significant difference in P300 amplitude between 15% and 45%, which were similar with that in 45% of young adults.These results indicated that the postural control pivoting at the ankle could be done also for the elderly when they can sufficiently prepare for postural disturbance as in the own-timing task, but not be done in the oddball task regardless of the target probability. This would be related to the deterioration of anticipation function with aging.

Disclosures: **C. Yaguchi:** None. **K. Fujiwara:** None.

Poster

809. Posture: Aging, Injury, and Disease

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 809.12/KK9

Topic: E.06. Posture and Gait

Support: SDSU Undergraduate Research Fellowship

Title: Implementation of BTrackS for assessment of balance in individuals with stroke

Authors: *C. GRAFF, H. S. BAWEJA, D. J. GOBLE;
Exercise and Nutritional Sci., San Diego State Univ., San Diego, CA

Abstract: Balance is necessary when performing activities of daily living such as walking, transitioning from a siting to standing position, or reaching out to grab an object. In clinical settings, balance is typically measured using functional assessments such as the Berg Balance Scale. Unfortunately, such assessments tend to be subjective and can take up to 20 minutes to perform. The Balance Tracking System (BTrackS) is a new low-cost force plate that can provide a fast (<2 min), objective and reliable alternative for balance assessment in the field of physical medicine. The purpose of this study was to demonstrate the feasibility of implementing BTrackS for the assessment of balance in individuals who have experienced a stroke. A total of 18 adults (mean age=56.4+/-12.5 years; 11 men, 7 women) with clinical diagnosis of stroke and 18 age-matched controls (mean age=56.2+/-13.0 years; 11 men, 7 women) participated in this study. Individuals with stroke were recruited from the Adaptive Fitness Clinic at San Diego State University and controls were from the local community. Each participant was balance tested while standing on the BTrackS force plate. Testing consisted of one familiarization trial and three experimental trials, each lasting 20 seconds. For each trial, participants stood as still as possible on the plate with their feet shoulder-width apart, hands to their sides, and eyes open. Balance ability was determined by the BTrackS software, which calculated the average amount of total sway across the experimental trials. As expected, BTrackS was successfully implemented for the testing of individuals with stroke. Specifically, data collected showed a significant difference in balance between participants who had a stroke compared to their age-matched controls ($p<0.05$). There was also a trend in the data ($p<0.1$) revealing that those who had more severe strokes exhibited worse balance than those who suffered a less severe strokes. BTrackS is potentially a better solution for monitoring balance changes in those individuals with stroke as it is fast, objective and reliable compared to standard functional assessments.

Disclosures: C. Graff: None. **H.S. Baweja:** None. **D.J. Goble:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Balance Tracking Systems.

Poster

809. Posture: Aging, Injury, and Disease

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 809.13/KK10

Topic: E.06. Posture and Gait

Title: Postural control with concurrent cognitive tasks in parkinson's disease patients

Authors: *M. M. BURKE, III[1], B. TAYLOR[2], J. ERRAM[3], J. V. FILOTEO[4], P. E. GILBERT[2], D. J. GOBLE[3], H. S. BAWEJA[3];

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Abstract: Dopaminergic denervation in the basal ganglia is responsible for reduced movement automaticity in patients with PD and increased reliance on attention to execute motor functions such as maintaining posture and balance. Postural control is very often accompanied with cognitive activities that are unrelated to posture and could impede postural corrections in PD patients. PD can be further classified as *Postural instability/gait dominant* (PIGD) and *Tremor dominant* (TD) phenotypes with PIGD variant being more susceptible to rapid cognitive decline when compared with TD. However, the effect of concurrent cognitive loads on postural corrections in PIGD and TD phenotypes of PD is not well understood. Therefore, the purpose of this study was to compare the effect of concurrent cognitive tasks on quiet unperturbed standing in PIGD and TD Parkinson's disease patients. Data collection is ongoing. Currently, 8 PD-PIGD patients (age range: 64-84 years; 2 females), 13 PD-TD patients (age range: 62-84 years; 3 females) and 30 healthy controls (Age range: 60-90 years; 18 females) have taken part in the study. The Balance Tracking System (BTrackS, San Diego, CA) force plate was used to measure postural sway as an indicator of balance ability. Balance testing consisted of 2 conditions: Single-task with eyes open, and dual-task with eyes open and verbal memory encoding. Subjects performed 3 trials per condition while standing with feet shoulder width apart and hands on hips. Each trial lasted 20 seconds during which the total center of pressure (COP), anteroposterior COP, and mediolateral COP sway displacements were calculated. A principle component analysis was used to calculate the 99% confidence interval of the area within which the COP excursions would lie. Additionally, subjects performed the verbal memory encoding task in sitting, while their balance was not being tested or challenged. The subjects' error rates on the verbal memory encoding task were then calculated 'on' and 'off' the force plates. Our preliminary findings suggest that postural sway excursions are amplified in PD patients (PIGD>TD>HC). These differences are greatest in medio-lateral sway excursions especially during the dual-task. Our findings have significant implications for fall risk in PD patients.

Disclosures: **M.M. Burke:** None. **B. Taylor:** None. **J. Erram:** None. **J.V. Filoteo:** None. **P.E. Gilbert:** None. **D.J. Goble:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); BTrackS, San Diego, CA. **H.S. Baweja:** None.

Poster

809. Posture: Aging, Injury, and Disease

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 809.14/KK11

Topic: E.06. Posture and Gait

Title: Effects of transcranial direct current stimulation (tDCS) to the dorsolateral prefrontal cortex (DLPFC) on neurocognitive performance and balance in combat military personnel

Authors: K. E. HUPFELD, *C. J. KETCHAM;
Exercise Sci., Elon Univ., Elon, NC

Abstract: Exposure to high-energy blast forces, especially from improvised explosive devices, has become one of the most common causes of casualties of the US military involvement in Iraq and Afghanistan (Trotter et al., 2015). Many military personnel who sustain these injuries experience debilitating neurocognitive impairments when returning to work or civilian life (e.g., memory loss, attention problems, difficulty multi-tasking, and delayed psychomotor/processing speed) (Kang et al., 2012). Transcranial direct current stimulation (tDCS), a cost-efficient and user-friendly form of noninvasive brain stimulation, might provide a promising therapy for treating the deficits that often accompany blast injuries. Anodal tDCS facilitates neuronal activity in a localized cortical area (and the pathways associated with this area) by passing a low-intensity current between two electrode sponges placed on the subject's scalp. This study involved applying tDCS to the dorsolateral prefrontal cortex (DLFPC), which is highly involved in cognitive control, executive functions, and motor planning (Miller & Cummings, 2007). The sample (n=11) included military personnel who self-reported exposure to at least one explosive blast at a distance of less than 100 meters while deployed overseas. Subjects were counterbalanced to complete a neurocognitive task (i.e., the ImPACT test) and a dynamic balance task (Biodex Limits of Stability Test) while receiving 1.0 mA of anodal tDCS to the left DLPFC (F3) or sham stimulation. Preliminary results indicate a trend towards improvements in verbal memory during DLPFC stimulation vs. sham. Those who received DLPFC stimulation first showed significantly faster reaction time and a trend towards becoming faster at the balance task over the two testing sessions. Subjects who had been diagnosed with at least one concussion in the past showed a trend towards greater improvement in verbal memory after tDCS to the DLPFC compared to those who had no history of concussion. Thus, although further testing is warranted, these results indicate that tDCS might serve as an effective therapeutic modality for addressing both neurocognitive and motor deficits in military personnel with blast injuries.

Disclosures: K.E. Hupfeld: None. **C.J. Ketcham:** None.

Poster

809. Posture: Aging, Injury, and Disease

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 809.15/KK12

Topic: E.06. Posture and Gait

Support: VA grant I01BX007080

VA grant E1075-R

NIH grant R01 AG006457 29

Title: Anticipatory postural adjustments after perturbations in people with Parkinson's disease who do and do not freeze

Authors: *D. S. PETERSON[1], C. SCHLENSTEDT[2], F. HORAK[3];
[1]Oregon Hlth. and Sci. Univ., Portland, OR; [2]Univ. of Kiel, Kiel, Germany; [3]Neurol., Oregon Hlth. & Sci. Univ., Portland, OR

Abstract: Introduction: Anticipatory postural adjustments (APAs) prior to voluntary stepping are important to facilitate large and effective steps. However, APAs prior to protective stepping, which occurs after an external perturbation such as a slip or a trip, may be detrimental, delaying step initiation. Indeed, delays in stepping after large external perturbations are closely related to falls. Previous investigations suggest that people with PD who freeze (FR) exhibit APAs prior to protective steps that are larger than healthy adults (HC), and may contribute to delayed stepping. However, it is unknown whether people with PD who do not experience freezing (NF) also exhibit abnormally large APAs prior to protective stepping. Given the relationship between APAs, step latency, and falls, characterizing the APAs prior to protective stepping in people with PD may inform fall prevention interventions. Methods: Thirteen FR, 15 NF, and 12 healthy adults participated. FR and NF groups were matched for age and disease severity. Participants completed cued normal stepping, in response to a small proprioceptive cue, and protective stepping, in response to a quick movement of the support surface (15cm, 56cm/s). Force-plates captured center of pressure (COP) movements and step latency prior to cued and protective stepping. Results: During cued stepping, no differences in APAs were observed across groups. However, during reactive stepping, FR exhibited larger APAs than both NF ($p=0.036$) and healthy adults ($p=0.010$). APAs in NF were similar to HC ($p=0.150$). Further, APA size was directly correlated to step latency in FR ($p=0.01$), but not NF ($p=0.259$) groups. Conclusions: Despite similar disease severity, and similar APAs during cued stepping, FR exhibited larger APAs prior to protective stepping than NF, and these APAs were directly related to worse outcomes (delayed step onset). These results suggest that FR, but not NF, exhibit large APAs

prior to protective stepping which may contribute to worse stepping outcomes. Future work should investigate ways to improve APAs prior to protective stepping in this population.

Disclosures: D.S. Peterson: None. **C. Schlenstedt:** None. **F. Horak:** None.

Poster

810. Central Pattern Generating Circuits: Models

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 810.01/KK13

Topic: E.07. Rhythmic Motor Pattern Generation

Support: NIH Grant MH46742

NIGMS 5T32GM008396

Title: Deep sequencing and single-cell qPCR approaches to identify and characterize genes important for function of the crab stomatogastric ganglion

Authors: *A. J. NORTHCUTT[1], A. G. OTOPALIK[2], V. B. GARCIA[1], E. MARDER[2], D. J. SCHULZ[1];
[1]Univ. of Missouri-Columbia, Columbia, MO; [2]Brandeis Univ., Waltham, MA

Abstract: The crustacean stomatogastric nervous system has a long history as a valuable model for investigating basic neuroscience principles, from motor pattern generation and network dynamics to neuromodulation and behavior. The full potential of this system has, however, been limited by a lack of molecular sequence information necessary for thorough investigations of the molecular underpinnings of network function. To bridge this gap, we have generated a mixed-nervous system transcriptome for *Cancer borealis*, from which we have identified 34 distinct ion channel types, 17 biogenic amine and 5 GABA receptors, 28 major transmitter receptor subtypes including glutamate and acetylcholine receptors, and 6 gap junction proteins - the innexins. Following this mixed-nervous system transcriptome, we then generated a stomatogastric ganglion (STG) specific transcriptome through RNA-seq to determine transcript expression patterns distinct to the STG. To extend the expression patterns seen in the STG to the single-cell level, we performed qPCR on identified neuron cell types within the STG to generate absolute copy number values and cell-specific expression patterns of genes of interest in neuronal output and function. Using this RNA-seq based approach with qPCR validation, we identified genes of high abundance in STG cells that likely play important roles in their overall function. The most abundant transcripts were for the gap junction proteins, the innexins. Additionally, we identified mGluR and TRP channel candidates that were previously undescribed that have high expression

levels in the STG, and are potential candidates for synaptic and modulatory currents that as of yet do not have a molecular correlate. Finally, the most abundant channel transcripts present are the voltage-gated sodium channel (Cb-NaV), calcium-activated potassium channels of both the BK- and SK-types, and the high-voltage activated CaV1 calcium channel. These data begin to shed light on the molecular underpinnings of network output in this well-characterized physiological system.

Disclosures: **A.J. Northcutt:** None. **A.G. Otopalik:** None. **V.B. Garcia:** None. **E. Marder:** None. **D.J. Schulz:** None.

Poster

810. Central Pattern Generating Circuits: Models

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 810.02/KK14

Topic: E.07. Rhythmic Motor Pattern Generation

Support: NSF grant 1257923

Title: Imaging reveals variable neuronal participation in rhythmic motor networks on multiple timescales.

Authors: *E. S. HILL, E. MORAVAC, A. BRUNO, J. WANG, W. FROST;
Cell Biol. and Anat., Rosalind Franklin Univ. of Med. and Sci., North Chicago, IL

Abstract: We recently used VSD imaging to demonstrate that some members of the escape swim network of the marine mollusk Tritonia diomedea participate in the motor program in a surprisingly variable manner, joining the rhythm late, leaving early, or skipping/firing on internal cycles. Further, we demonstrated that with memory formation the swim network rapidly expands in part by the transformation of variable participants into reliable participants. In order to begin to examine if such interesting neurons may be a general feature of rhythmic networks, we searched for their presence in the escape locomotion network of a distantly related mollusk Aplysia californica. The A. californica locomotion behavior comprises two parts: a fast “gallop” lasting for ~ 2 minutes, followed by a slower “crawl” lasting for 20 to 30 minutes. To enable this study we improved our technique to allow continuous imaging for more than 30 minutes. First, we observed that in the dorsal pedal ganglion most rhythmically bursting neurons participate in both the gallop and crawl motor programs, with a smaller number being dedicated to one or the other. Next we confirmed that variably participating neurons are present in both the gallop and crawl networks: they joined the rhythm late, left early and skipped or fired on internal cycles only. During the gallop, variable participation occurred on a scale of seconds, with neurons

joining and leaving the network on a cycle-by-cycle basis. During the crawl, variable participation occurred on a ten-fold longer time scale, with some neurons joining the network, firing rhythmically for a few minutes and then leaving, while others joined minutes into the motor program or left minutes before the end of the crawl. Some variably participating neurons were variable with respect to both the gallop and crawl programs, while others where specific to one. Preliminary data tracking neurons over repeated gallop/crawl episodes show that neurons also varied their level of participation from episode to episode. Our finding of variable participation in multiple species, behaviors and timescales supports the view that variable participation may be a general feature of networks underlying rhythmic motor behaviors, possibly endowing networks with the flexibility to modify themselves as circumstances dictate.

Disclosures: **E.S. Hill:** None. **E. Moravac:** None. **A. Bruno:** None. **J. Wang:** None. **W. Frost:** None.

Poster

810. Central Pattern Generating Circuits: Models

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 810.03/KK15

Topic: E.07. Rhythmic Motor Pattern Generation

Support: NIH Grant NS081013

Title: Measuring the stability of a neural oscillator using orthogonal perturbations

Authors: *J. M. RATLIFF[1], T. O'LEARY[2], A. RINBERG[3], E. MARDER[1];
[1]Brandeis Univ., Waltham, MA; [2]Dept. of Engin., Univ. of Cambridge, Cambridge, United Kingdom; [3]Harvard Sch. of Engin. and Applied Sci., Harvard Univ., Cambridge, MA

Abstract: The crab Cancer borealis lives in environments with disparate temperatures (from 8°C to 24°C) and therefore the animal's nervous system must retain function across these temperature ranges. In particular, central pattern generating circuits, including those in the stomatogastric ganglion (STG) can maintain rhythmic output over surprisingly wide temperature ranges, yet the source of this stability is unknown. Extremes of temperature disrupt STG function leading to 'crashes' in rhythmic activity, thus providing a means to understand temperature robustness by studying mechanisms underlying crashes. We subjected the isolated STG to large, acute temperature perturbations from 11°C to 32°C to assess the stability of the pyloric rhythm. In many preparations, the pyloric rhythm became unstable near 30°C but recovered when cooled. We then pharmacologically isolated the pyloric pacemaker cells (AB and PD) and increased the temperature to the observed crash point of the intact circuit while recording intracellularly from

PD. We probed pacemaker stability by orthogonally perturbing PD with current pulses up to the onset of a crash. This allowed us to probe for evidence of a phenomenon known as 'critical slowing down' whereby recovery from perturbations becomes slower as a system approaches an abrupt change in dynamics, providing a means to predict crashes and identify the underlying mechanisms.

Disclosures: J.M. Ratliff: None. **T. O'Leary:** None. **A. Rinberg:** None. **E. Marder:** None.

Poster

810. Central Pattern Generating Circuits: Models

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 810.04/KK16

Topic: E.07. Rhythmic Motor Pattern Generation

Support: NIH MH060605

NSF DMS1122291

Title: Synaptic factors that determine activity phase in an oscillatory network

Authors: *F. NADIM[1], D. MARTINEZ[2], H. ANWAR[2], A. BOSE[3];
[1]Federated Dept Biol. Sci., [2]Biol. Sci., [3]Mathematical Sci., New Jersey Inst. of Technol., Newark, NJ

Abstract: In oscillatory motor networks, activity in distinct phases of each cycle translate to muscle movements and remains constant despite variations in cycle frequency. The mechanisms of phase maintenance remain unclear. Previous theoretical work proposed that short-term synaptic dynamics (depression and facilitation; peak time; duration; rise and decay rates) could promote phase maintenance (Manor et al, J Neurophys, 2003).
We experimentally quantify how synaptic dynamics influence the activity phase of a neuron. In the crab pyloric network, the burst onset phase of neurons remains constant despite a wide variation in cycle periods (**P** = 0.5-2 s). The lateral pyloric (LP) neuron receives periodic inhibition from the pyloric pacemakers (phase 0) and rebounds to burst at a phase of ~0.32-0.4. We characterized synaptic conductance inputs with amplitude (G_{syn}) and peak time (TP), and used dynamic clamp to introduce synaptic inhibition (E_{syn}=-80 mV) into isolated LP neurons at 5 **P** values. We applied the synaptic input either with a constant duration of 300 ms or a constant duty cycle (duration/ **P**) of 0.3 and measured the burst onset phase (φ_{LP}) of LP with respect to the synaptic activation. Each dynamic clamp trial was done for 30 cycles with fixed G_{syn} and TP which, for different trials, were varied on a grid: G_{syn} = 0.1, 0.2, 0.4 μS and TP = 0, 0.25, 0.5,

0.75, 1.
Our hypothesis was that increasing either G_{syn} or TP as a function of **P** would promote phase maintenance. For fixed values of G_{syn} and TP, φ_{LP} decreased in proportion to 1/**P**. With constant duty cycle input, φ_{LP} could remain constant over a relatively wide range of **P**, if either G_{syn} or TP increased as a function of **P**, and an even larger range if both increased. In contrast, with constant duration inputs, φ_{LP} could only remain constant over a very narrow range of **P**. Interestingly, for a given range of **P**, maintaining φ_{LP} near its natural values was easier than at extreme values (e.g., 0.2 or 0.6).
We also recorded the IPSC waveform of LP during ongoing activity and repeated these experiments using this realistic waveform. We found that, for each **P**, φ_{LP} increased as a function of G_{syn}. This would allow for maintaining φ_{LP} constant over the full range of **P**=0.5-2 s. Using mathematical analysis, we found that the observed value of φ_{LP} could be predicted as
$\varphi_{LP} = DC + \tau_{syn} \ln(G_{syn}/G_{max})/\mathbf{P} - \exp(-c\ G_{syn})$
where DC is the duty cycle, τ_{syn} is the synaptic decay time constant, G_{max} is the maximum possible synaptic strength and the constant c is a threshold for the intrinsic rebound properties of the cell. These results confirm our hypothesis that short-term synaptic dynamics can have an essential role in phase maintenance within oscillatory networks.

Disclosures: **F. Nadim:** None. **D. Martinez:** None. **H. Anwar:** None. **A. Bose:** None.

Poster

810. Central Pattern Generating Circuits: Models

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 810.05/KK17

Topic: E.07. Rhythmic Motor Pattern Generation

Support: NIH MH060605

Title: Single-neuron phase maintenance in an oscillatory network

Authors: ***H. ANWAR**[1], D. MARTINEZ[1], F. NADIM[1,2];
[1]Biol. Sci., NJIT, Newark, NJ; [2]Biol. Sci., Rutgers-Newark, Newark, NJ

Abstract: Many oscillatory activities require precise firing of neurons. In particular, neurons generating rhythmic motor activity often maintain a constant activity phase, despite large changes in frequency, to produce meaningful behavior. Several studies document phase maintenance, yet the underlying mechanisms are unknown. We aim to understand how intrinsic mechanisms and synaptic inputs interact to produce phase stability in a single neuron embedded in an oscillatory network.

The levels of voltage-gated ionic conductances and synaptic currents of neurons in the crab pyloric oscillatory network vary widely across preparations, yet the activity phases of these neurons are maintained across different frequencies. We therefore tested the hypothesis that the synaptic input to a neuron is precisely matched to its intrinsic properties to produce a constant activity phase. To test our hypothesis, we investigated whether 1) the shape or amplitude of the synaptic input is correlated with voltage-gated ionic conductances, 2) the synaptic amplitude influences the activity phase, and 3) the synaptic shape affects the activity phase.
We used the identified lateral pyloric (LP) bursting neuron and measured the IPSC in this neuron during ongoing activity. This IPSC has two components: the input from the pacemakers ($IPSC_{AB}$) and that from the follower PY neurons ($IPSC_{PY}$). In the same neuron we measured the high-thresh. K current (I_{HTK}), I_A and I_h. We found no linear correlations between any of these ionic conductances and IPSC parameters (rise and fall slope, total IPSC or $IPSC_{AB}$ amplitude). We also found that inhibition strength only weakly influenced the time to first spike, which suggested that the IPSC amplitude plays little role in determining activity phase.
Finally, we examined the effect of shape of the synaptic conductance waveform on the activity phase by isolating the LP neuron and driving it with 80 different IPSC waveform shapes, using dynamic clamp. This allowed us to separate the effects of $IPSC_{AB}$ and $IPSC_{PY}$. We found that only $IPSC_{PY}$ affects the LP burst end. Remarkably, LP burst onset phase was most significantly affected by the peak phase of the total IPSC (same as the peak of $IPSC_{AB}$) suggesting that the temporal features of the synaptic input are tuned to interact with a combination of ionic currents in the LP neuron.
Our results show that phase maintenance emerges from mechanisms which do not simply rely on linear correlations between synaptic input and intrinsic properties. Moreover, the temporal dynamics of synaptic input, rather than its strength, are most effective in determining the activity phase of a neuron.

Disclosures: **H. Anwar:** None. **D. Martinez:** None. **F. Nadim:** None.

Poster

810. Central Pattern Generating Circuits: Models

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 810.06/KK18

Topic: E.07. Rhythmic Motor Pattern Generation

Support: NIH NINDS 1 R01 NS085006

Title: Separation of the heartbeat CPG and switch CPG by targeted application of myomodulin in the medicinal leech

Authors: *B. J. NORRIS[1,2], A. WENNING-ERXLEBEN[2], R. L. CALABRESE[2];
[1]California State Univ., San Marcos, CA; [2]Biol., Emory Univ., Atlanta, GA

Abstract: The Leech hearts are two constrictive tubes whose contractions are controlled by a well-defined heartbeat CPG. One heart beats in a rear-to-frontward progression (Peristaltic) and the other beats nearly synchronously. Approximately every 25 to 50 beats, the sides switch. The neural network that controls this switch we will refer to as the switch CPG. When an isolated leech nerve cord is exposed to 10^{-5}M myomodulin, both the heartbeat CPG and the switch CPG decrease their period. If Myomdulin is applied only to Ganglia 3 and 4 (site of the main pacemakers for the heartbeat rhythm) the heartbeat CPG decreases its period, but the switch CPG does not. Conversely, myomodulin applied only to ganglion 5 strongly decreases the switch CPG period but only has a weak effect on the heartbeat CPG period. Even in an isolated ganglion 5, myomodulin decreases the period of the switch CPG. These results suggest that the switch CPG is separate from the heartbeat CPG and probably resides in ganglion 5.

Disclosures: B.J. Norris: None. **A. Wenning-Erxleben:** None. **R.L. Calabrese:** None.

Poster

810. Central Pattern Generating Circuits: Models

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 810.07/LL1

Topic: E.07. Rhythmic Motor Pattern Generation

Support: National Institute of Neurological Disorders and Stroke grant (R01NS085006-01)

National Science Foundation grant (PHY-0750456)

Title: Interaction of the Na^+/K^+ pump current with the h-current regulates bursting activity in CPG neurons

Authors: *D. KUEH[1], W. H. BARNETT[2], G. S. CYMBALYUK[2], R. L. CALABRESE[1];
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Abstract: We were interested in determining the contribution of the Na^+/K^+ pump current to the bursting activity of central pattern generator (CPG) neurons. To determine the pump's contribution, we used monensin, a Na^+-H^+ antiporter, to stimulate the pump current in leech oscillator heart interneurons that form half-center oscillators in the heartbeat CPG. Based on voltage-clamp recordings, we established that monensin stimulates the pump current in these neurons, and this effect can be blocked by strophanthidin. Thus, we used both monensin and strophanthidin as tools to probe the influence of the pump current on the bursting activity of

these neurons. When we performed simultaneous bilateral recordings from paired heart interneurons in normal saline, we found that monensin decreased significantly the burst period of both heart interneurons without significantly affecting their membrane potential. However, the monensin-induced decrease in burst period could be reversed by blocking the *h*-current of these neurons with external Cs^+. Thus, the pump-mediated decrease in burst period requires the *h*-current. We were also able to decrease the burst period of heart interneurons by inhibiting their pump activity with strophanthidin or with K^+-free saline. To determine if the decreased burst period in K^+-free saline was due, in large part, to the change in the K^+ equilibrium potential and not to pump inhibition, we recorded the burst period of the heart interneurons in different saline solutions that contained various low concentrations of K^+. We found that the burst period either increased or remained the same in low concentrations of K^+, leading us to conclude that the decreased burst period in K^+-free saline is mainly due to pump inhibition and not to changes in the K^+ equilibrium potential. We reproduced our results with a Hodgkin-Huxley based model of a half-center oscillator. With this model, we showed that the dynamics of the pump current, which is driven by internal Na^+ concentration dynamics, is essential to normal bursting activity and the effect of monensin on burst period. Taken together, our results show that the interaction of the pump current and the *h*-current plays a significant role in the dynamics of bursting in the leech heartbeat CPG. Given the ubiquity of the pump current in all cells, it is likely that this interaction could be observed in other rhythmically bursting neuronal networks.

Disclosures: D. Kueh: None. **W.H. Barnett:** None. **G.S. Cymbalyuk:** None. **R.L. Calabrese:** None.

Poster

810. Central Pattern Generating Circuits: Models

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 810.08/LL2

Topic: E.07. Rhythmic Motor Pattern Generation

Support: NIH Grant NS081013-4

Title: Robustness of a rhythmic motor pattern to changes in pH

Authors: *J. HALEY, E. MARDER;
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Abstract: Most neural circuits found in marine animal species must maintain function despite significant environmental changes such as temperature, dissolved oxygen concentration, and pH fluctuations in sea water. In the stomatogastric ganglion of the crab, *Cancer borealis*, central

pattern generating circuits produce rhythmic motor patterns. Here, we examine the effect of acute pH changes on the pyloric rhythm, a triphasic motor pattern composed of the Pyloric Dilator (PD), Lateral Pyloric (LP), and Pyloric (PY) neurons, which fire in a repeating sequence. The pH of the haemolymph of *C. borealis* is around 7.9 while that of seawater ranges from 7.5 to 8.4 and averages 8.1. This is a 25 percent increase in acidity compared to 200 years ago, a result of ocean acidification. In this experiment, we recorded the pyloric rhythm while varying the pH of the bath from 5.5 to 10.0. From pH 6.3 to 9.4, a greater than 1000-fold change in hydrogen ion concentration, there was little effect on the triphasic rhythm. In more extreme acid conditions (pH less than 6.0), the network lost the triphasic rhythm, or "crashed", when LP stopped firing. Shortly after the rhythm crashed, all three units went silent. In strongly basic solutions (pH greater than 9.5), the network crashed when LP went silent, while PD continued to fire at a frequency similar to that in control saline (pH 7.5). These results suggest that some neural circuits are extremely robust in response to external perturbations, even in extreme conditions.

Disclosures: J. Haley: None. **E. Marder:** None.

Poster

810. Central Pattern Generating Circuits: Models

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 810.09/LL3

Topic: E.07. Rhythmic Motor Pattern Generation

Support: USAMRAH #SC140038

Title: Dustribution of respiratory-related neurons in C3-C5 cervical segments and their responses to blockade of GABAa and Glycine receptors in decerebrate rats

Authors: T. G. BEZDUDNAYA, M. A. LANE, *V. MARCHENKO;
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Abstract: It is well known that respiratory interneurons play an important role in formation of respiratory motor output for intercostal nerves. However, the detailed distribution and role of respiratory interneurons at the level of phrenic nucleus is still underinvestigated. In 29 experiments using decerebrate, vagotomized and paralyzed (vecuronium Br) rats with bilateral pneumothorax 122 respiratory-related neurons were extracellular recorded from C3-C5 cervical segments corresponded to location of phrenic motoneurons. Motor-(n=35) and interneurons (n=87) were identified by the presence or absence of antidromic response to phrenic nerve stimulation. These units were categorized as follows: Inspiratory (Insp) (n=35) (27 units were identified as motoneurons), Full expiratory (Exp) interneurons (n=17), Pre-inspiratory or

'expiratory type 2' (E2) interneurons (n=15), Inspiratory interneurons with tonic background activity (Insp+BG) (n=27), Inspiratory-expiratory phase-spanning interneurons (Insp-Exp) (n=9), Late-inspiratory (late-Insp) (n=13) (8 units were identified as motoneurons), Exp-Insp (wide phase-spanning) (n=6). Topographical analyses of the phrenic motoneurons reveal two distinct groups of inspiratory motoneurons located at C4-cervical level: ventro-medial and ventrolateral, accordingly. This bimodal distribution of phrenic motoneurons was confirmed by retrograde labeling using different tracers (Fast blue, Texas Red, Cholera Toxin subunit B, Cascade blue). Also, it was found, that Insp+BG interneurons located mostly dorso-medial to motoneuron pools. However, some of them were found in vicinity of the phrenic motoneurons population. GABAzine (high selective antagonist of postsynaptic GABAa receptors) and Strychnine (STR, antagonist of glycine postsynaptic receptors) were applied to 61 cells with microiontophoresis (+20 nA, 2 min) using multibarrel (Carbostar-3) electrode with following labeling by (Neurobiotin 2% , +10 nA, 30 min). In response to application of GABAzine, high-frequency Insp+BG cells did not show significant changes in firing rate while STR elicited increasing of background activity. In response to STR or GABAzine, middle- and low-frequency (late-Insp, e.g.) units showed an altered firing pattern to become early-inspiratory with increasing of tonic background activity. These data evidence that spinal respiratory neurons represent high-heterogeneity network with firing patterns described for ponto-medullary level. The functional significant of fast inhibitory mechanisms in respiratory pattern formation is discussed.

Disclosures: T.G. Bezdudnaya: None. **M.A. Lane:** None. **V. Marchenko:** None.

Poster

810. Central Pattern Generating Circuits: Models

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 810.10/LL4

Topic: E.07. Rhythmic Motor Pattern Generation

Support: NIH Grant F31NS092126

NIH Grant R37NS017813

Title: When complex structures may not matter

Authors: *A. G. OTOPALIK[1,2], A. SUTTON[1,2], E. MARDER[1,2];
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Abstract: Many theoretical and experimental studies have described how neuronal geometry influences propagation of voltage signals and integration of synaptic inputs. Complex and

expansive dendritic trees often execute distributed computations. We present a case wherein geometrical complexity does not constrain neuronal computation. Identified neurons of the crustacean stomatogastric ganglion (STG) exhibit highly stereotyped physiological waveforms, despite complex morphologies. We quantify the morphological and distributed electrical properties of one STG neuron type, the gastric mill (GM) neuron. Using focal glutamate photo-uncaging in tandem with two-electrode current clamp, we measured glutamate reversal potentials at numerous positions across the neuronal structure, varying in their distance from the somatic recording site (100-900 μm). Precise distance, diameter, and taper measurements between the stimulation sites (7-15) and somatic recording sites were generated from 3-dimensional reconstructions of dye-fills of these same neurons. Although response amplitudes varied, glutamate reversal potentials were almost invariant. These data suggest cable properties that minimize electrotonic decrement of voltage signals across the dendritic tree. We explain this result by considering STG circuit function and architecture. This central pattern-generating circuit mediates robust, life-long muscle contractions. This ongoing rhythmic circuit output is driven by graded transmission between reciprocally inhibitory neurons. Electrotonically compact structures allow presynaptic partners to impinge on postsynaptic neuronal activity in a stereotyped manner, regardless of synaptic site location, slow time course of synaptic conductances, and receptor density.

Disclosures: **A.G. Otopalik:** None. **A. Sutton:** None. **E. Marder:** None.

Poster

810. Central Pattern Generating Circuits: Models

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 810.11/LL5

Topic: E.07. Rhythmic Motor Pattern Generation

Support: NSF IOS 1354932

Title: Coordinated increase of conduction velocities allows for phase maintenance of a rhythmic motor pattern

Authors: ***M. DEMAEGD**, M. CRUZ, B. KNOTT, C. BAINBRIDGE, W. STEIN;
Biol. Sci., Illinois State Univ., Normal, IL

Abstract: Rhythmic behaviors, such as breathing and chewing, are reliant on central pattern generators (CPGs) maintaining their phase relationships even when faced with environmental perturbations. In many organisms, long distance axons create a spatial separation between the CPG and the neuromuscular junction. Unique intrinsic and extrinsic factors such as ion channel

complement, membrane capacitance, impedance, and temperature causes axons of different cells to possess distinct conduction velocities and propagation dynamics (Debanne, 2011 Physrev). While phase relationships in CPGs are largely governed by intrinsic and synaptic interactions in neurites and cell bodies, the functional output at the muscle may vary depending on perturbations along the axon. Thus, axonal properties may support phase relationship maintenance, independent of somatic activity.

Here, we use the pyloric CPG in the stomatogastric nervous system of the crab (*Cancer borealis*) to evaluate phasing of rhythmic neurons under fluctuating axonal temperature conditions. The three main CPG neurons (PD, LP, PY) are active at distinct phases of the rhythm and are maintained across a wide temperature range (Tang, 2010 PLoS Biol.). Their axons are several centimeters long with different diameters and propagation velocities. It is unknown if temperature perturbations affect these pyloric axons equally. We hypothesize that axons will respond to temperature changes similarly to maintain phase relationships and functional rhythmicity.

We tested this hypothesis by applying a range of different temperatures to the pyloric axon trunks, while maintaining temperature at the CPG and axon terminals. We measured the conduction velocities of the individual axons and compared phase relationships via extracellular recordings at the CPG and the terminals. Preliminary results show a clear velocity difference between the three neurons at control temperature (LP > PD > PY), but show similar increases in conduction velocity with increasing temperature between 4-23°C (n=3); i.e. axons had similar Q_{10} values (PD, 1.21; LP, 1.36; PY, 1.18). For example, when temperature was increased from 4°C to 13°C conduction velocity increased by 23.8% for PD, 36.0% for LP, and 18.3% for PY. When temperature was increased from 13°C to 23°C conduction velocity increased by 18.6% for PD, 28.3% for LP, and 20.1% for PY. Due to the similar responses, the phase relationship of the pyloric neurons was maintained. We are currently testing the condition in which axons of distinct identity and diameter can generate similar temperature responses utilizing computer modeling.

Disclosures: **M. Demaegd:** None. **M. Cruz:** None. **B. Knott:** None. **C. Bainbridge:** None. **W. Stein:** None.

Poster

810. Central Pattern Generating Circuits: Models

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 810.12/LL6

Topic: E.07. Rhythmic Motor Pattern Generation

Support: ONR Grant N000141210160

GAAN Grant P200A150077

Title: Development of fin function and sensory innervation in zebrafish

Authors: *H. R. KATZ[1], J. LU[2], M. E. HALE[3];
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Abstract: Many animals undergo dramatic developmental changes in body structure that are coupled with changes in behavior, but little work has been done to investigate these transitions at different life stages. Previous work in our lab has shown that pectoral fins serve a respiratory function in larval zebrafish but appear to take on locomotor roles in adults. Ontogenetic changes have been described in fin muscle structure and motor innervation, but it is still unknown how fin behavior and sensation are altered through the transition from larva to adult. To more fully understand how fins develop to serve different functions through life history, we investigated how pectoral fin behavior and sensory innervation change through ontogeny. To conduct behavioral studies, we used a high-speed video camera to record bouts of slow swimming. We found that fin behaviors during these swimming bouts changed significantly throughout development. For example, larvae demonstrated rhythmic, alternating fin beats during forward swimming, initiated by a full synchronous abduction and subsequent, asynchronous adduction. There were, on average, three fin beats per fin for each bout at this stage. In adults, we observed that fin movements generally consisted of a single, synchronized fin adduction at the initiation of swimming. Fin beat frequency decreased significantly ($p<0.0005$) between late larval and juvenile stages, suggesting a possible shift in fin function. We observed increasing diversity in characteristics of pectoral fin movements from the late larval to adult stages. Our results are consistent with the proposal that the development of gills and loss of cutaneous respiration are related to subsequent changes in pectoral fin behavior. To identify how fin sensory innervation reflects these behavioral changes, we used lightsheet microscopy to visualize the sensory nerves in the fin. Our preliminary results show that in larvae, the fin is highly innervated at the surface, but does not display the variety of sensory nerve endings that we observe in adult pectoral fins. This change in sensory endings could reflect the more specific feedback that an animal requires to distinguish between different types of sensory information, such as proprioception and touch, as pectoral fins take on a more locomotor role later in ontogeny.

Disclosures: H.R. Katz: None. **J. Lu:** None. **M.E. Hale:** None.

Poster

810. Central Pattern Generating Circuits: Models

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 810.13/LL7

Topic: E.07. Rhythmic Motor Pattern Generation

Support: ONR Grant N000141210160

Title: The mechanics and sensory feedback of pectoral fins in a model of complex locomotion in adult zebrafish.

Authors: N. N. SAWYER, K. W. HENDERSON, *M. E. HALE;
Univ. of Chicago, Chicago, IL

Abstract: Natural locomotion, such as maneuvering through complex environments, requires arrhythmic and asynchronous behaviors that cannot be fully explained through current models. Here, we characterize the kinematics, mechanics, and sensory feedback relating to the routine turns of zebrafish as a model for such movement. We examined routine turning in both adult wild type (WT) and FGF24$^{-/-}$ finless zebrafish. We used high−speed imaging to film adult fish from dorsal and lateral views as they turned around a 90° corner in a filming tank and quantified aspects of movement before, during, and after the turn. We characterized movements of the body, including pitch, and of the pectoral fins. We recorded two distinct patterns of fin kinematics during the turn. During two-phase turns, the outside fin abducted and then adducted with a sustained downward motion throughout the turn. During one-phase turns, the outside fin adducted with no abduction while maintaining a neutral posture. Post-turn, both pectoral fins returned to a neutral lateral position before once again abducting away from the body. Axially, the body curved into a C-shape during the turn and straightened along the axis of its new heading post-turn. Notably, fish that exhibited one-phase turns had a significantly more negative pitch than fish exhibiting two-phase turns. To examine the role of the pectoral fins in stabilizing routine turns, we examined the differences in pitch and turn duration in FGF24$^{-/-}$ finless mutants. In comparison to WTs that exhibited two-phase turns, mutant fish maintained a significantly more negative pitch through the turn, but there was not a statistically significant difference between the WTs that exhibited one-phase turns and the FGF24$^{-/-}$ mutants. This indicates that the fins play a role in generating body kinematics of the two-phase turns. Using this behavior as a model we examined the role of sensory feedback in generating effective turns. To investigate this, we examined mechanosensation in adult zebrafish pectoral fins and body. We demonstrated physiologically and morphologically that the fins of adult zebrafish have mechanosensory capabilities. With this confirmation of sensory structure and function of the fin, we used temporary ablations in both WT and FGF24$^{-/-}$ mutants to investigate the role of sensory feedback from the lateral line and mechanosensors in the pectoral fin. Our work suggests that the kinematics of the pectoral fins are linked to two distinct behavioral groups: the two-phase and one-phase turn. Additionally, this work provides a baseline for a novel neuromechanical model for natural locomotor behaviors.

Disclosures: **N.N. Sawyer:** None. **K.W. Henderson:** None. **M.E. Hale:** None.

Poster

810. Central Pattern Generating Circuits: Models

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 810.14/LL8

Topic: E.07. Rhythmic Motor Pattern Generation

Support: NIH R01 NS081713

NIH R01 NS090919

NIH R01 NS095366

NSF DMS 1312508

NSF DMS 1516288

Title: Computational modeling and analysis of half-center CPGs

Authors: *J. AUSBORN[1], A. C. SNYDER[2], B. J. BACAK[1], N. A. SHEVTSOVA[1], J. E. RUBIN[2], I. A. RYBAK[1];
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Abstract: The spinal locomotor central pattern generator (CPG) can autonomously generate rhythmic activity with alternating flexion and extension phases over a wide range of frequencies. The organization of this CPG and the neural mechanisms involved in rhythmogenesis remain largely unknown. It is commonly accepted that the rhythmic pattern results from, or at least involves, inhibitory interactions between two neural populations representing flexor and extensor half-centers. The classical half-center concept assumes a symmetrical organization in regard to cellular properties, operational regimes and synaptic interactions between the half-centers (Graham Brown, 1914; McCrea & Rybak, 2008). Another approach suggests an asymmetric, flexor-dominated CPG organization in which only the flexor half-center has intrinsic rhythmic capabilities (Pearson & Duysens, 1976; Zhong et al. 2012; Shevtsova et al. 2015). There is also a possibility that both half-centers can autonomously generate rhythmic activity (Hägglund et al. 2013). In this theoretical study, we have suggested that each of the three mechanisms can operate in the same CPG depending on conditions, such as preparation type or methods used to produce the rhythm. Two distinct models were considered: (i) a large-scale model with flexor and extensor populations (each consisting of 200 neurons modeled in the Hodgkin-Huxley style with sparse excitatory interactions) mutually inhibiting each other via two inhibitory populations and (ii) a reduced model, in which both half-centers were represented by single non-spiking neurons coupled with mutual inhibition. The second model was used for qualitative analysis of the system dynamics. In both cases, neuronal oscillations were based on the slowly inactivating

persistent sodium current. Due to this intrinsic rhythmogenic mechanism, an increase of excitatory drive to each isolated half-center caused a transition from silence to rhythmic bursting and then to tonic activity. Therefore, by manipulating drives to each half-center we could induce systematic transitions between all three half-center mechanisms and analyze the bifurcations involved in transitions between them, the emergence of bistability, and the control of oscillation frequency in each regime. Stable rhythmic activity occurred in both symmetric and asymmetric network structures. However, frequency modulation with changing drive to one or both half-centers was dependent on the underlying rhythm-generating mechanisms and flexor-extensor symmetry. Our study suggests different regimes in locomotor CPG operation and proposes explanations for some seemingly contradictory experimental data.

Disclosures: J. Ausborn: None. **A.C. Snyder:** None. **B.J. Bacak:** None. **N.A. Shevtsova:** None. **J.E. Rubin:** None. **I.A. Rybak:** None.

Poster

810. Central Pattern Generating Circuits: Models

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 810.15/MM1

Topic: E.07. Rhythmic Motor Pattern Generation

Support: BMBF-NSF 01GQ1412

GR 3690/4-1

GR 3690/2-1

Title: Phase reduction of an inter-segmental network model of stick insect locomotion

Authors: *A. YELDESBAY[1,2], P. HOLMES[3], T. TOTH[1], S. DAUN[1,2];
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Abstract: Detailed neuronal network models of animal locomotion are important means to understand the underlying mechanisms that control the coordinated movement of individual limbs. However, the analysis of such systems is a formidable task if they have a large number of variables and parameters. Thus, the complex behavior of the neural network in question can much better be explained by means of a reduced simplified model.
In a previous work [Daun-Gruhn & Tóth, J Comp Neuroscience 2011], an inter-segmental

network model of stick insect locomotion was constructed based on experimental results. It consists of three segments that correspond to the front, middle and hind leg. This model could reproduce the basic locomotion coordination patterns, such as tri- and tetrapod, and the transitions between them.
In this study, we employ phase reduction and averaging theory to this large network model, to reduce the local networks that include the central pattern generators (CPG) and are associated with the protractor-retractor muscle activity of the stick insect. This enables us to analyze of the behavior of the system in a reduced parameters space (3D compared to 60 dimensional).
We show that the reduced model reproduces the results of the original model including the transitions between the coordination patterns. By analyzing the interaction of just two coupled phase oscillators, we found that the neighboring segmental CPGs can operate within two distinct regimes - synchronously and asynchronously, depending on the phase shift between the sensory inputs from the extremities and the phases of the individual CPGs. We demonstrate that this is essential to produce different coordination patterns and the transition between them in the reduced model. Additionally, applying averaging theory to the system of phase oscillators we calculated stable fix points - that correspond to stable coordination patterns. We are now going to use these results to build a model based on the same principles for the investigation of 6-legged walking in different animals. We will then be able to compare stick insect and cockroach locomotion.

Disclosures: **A. Yeldesbay:** None. **P. Holmes:** None. **T. Toth:** None. **S. Daun:** None.

Poster

810. Central Pattern Generating Circuits: Models

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 810.16/MM2

Topic: E.07. Rhythmic Motor Pattern Generation

Support: NIH P01 HD32571

NIH R01 EB-012855

Title: Temporal characteristics of paw shake response in the cat.

Authors: J. GREEN[1], A. KLISHKO[2], B. PRILUTSKY[2], *G. S. CYMBALYUK[1];
[1]The Neurosci. Inst., Georgia State Univ., Atlanta, GA; [2]Georgia Inst. of Technol., Atlanta, GA

Abstract: The structure and functions of the mammalian central pattern generator (CPG) controlling rhythmic behaviors are not fully understood. It is also unclear if the same CPG can

generate rhythmic activity and coordinate multiple motoneuron pools in distinct behaviors, e.g. walking and the paw-shake response. These two behaviors differ not only in the rhythm (1 vs 10 Hz) but also in muscle synergies, groups of muscle acting together. Recently, we have demonstrated that a multifunctional CPG controlling a neuromechanical model of a cat hindlimb can reproduce essential features of rhythm, kinematics and muscle synergies of cat walking and paw-shake (Bondy et al. 2016). Here, we developed a model of a half-center oscillator consisted of two inhibitory interneurons, which acts as a multistable CPG and can generate the rhythms associated with both walking and paw-shaking. In this model, using a pulse of current, a paw-shake response rhythm can be elicited as a transient activity either in a multi-stable regime or in a mono-stable regime. We also developed a population model of the half-center oscillator, consisting of two mutually inhibitory populations of 20 neurons that can also generate the rhythms associated with walking and paw-shaking. Both the two-neuron model and the population model provide a number of testable predictions. One prediction is that the interburst interval increases in each consecutive cycle of a paw-shake response.
We tested this prediction by eliciting paw-shake responses in cats by attaching an adhesive tape to the hind paw and letting the cat walk on a walkway. We recorded EMG activity of multiple hindlimb muscles and hindlimb kinematics. Each paw-shake response consisted of 4 to 10 cycles. In accordance with previous studies (Koshland and Smith 1989), we found a progressive increase of burst period in consecutive paw-shake cycles. Furthermore, we found a progressive increase in EMG interburst interval in consecutive paw-shake cycles, which was consistent with the model prediction. On the other hand, there was no significant trend in EMG burst duration throughout each paw-shake episode. Thus, experimental results are consistent with the predictions of the model.

Disclosures: J. Green: None. **A. Klishko:** None. **B. Prilutsky:** None. **G.S. Cymbalyuk:** None.

Poster

810. Central Pattern Generating Circuits: Models

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 810.17/MM3

Topic: E.07. Rhythmic Motor Pattern Generation

Support: NIH Grant GM103449

Title: Phase analysis in a reduced model of the leech heartbeat system.

Authors: *A. L. WEAVER, B. M. EVOY;
Biol., St. Michael's Col., Colchester, VT

Abstract: Many rhythmic motor behaviors (e.g., walking, breathing) are driven by central pattern generator (CPG) networks and rely on precision in the neuronal activity phasing or relative timing (Marder et al., 2005). The leech heartbeat CPG directs the flow of the leech's own blood in its body and consists of a network of heart interneurons (HN) that coordinate heart excitor (HE) motor neuron activity via inhibitory chemical synapses. Each segmental pair of HE's is connected to one another via electrical coupling. Depending on the segment, the pair of motor neurons in the living system is active across a wide range of phase differences from nearly in-phase to anti-phase (Norris et al., 2007). Prior efforts to model this complete network have not quantitatively matched all contralateral phase values observed (Garcia et al., 2008). We have created a reduced network mathematical model of a single segmental ganglion in Simulink to explore network and intrinsic parameters that contribute to these phase differences.
In the network model, we simulated known neuronal properties and synaptic connections. The pair of HN's were modeled as endogenous bursters with a half-center oscillator network cycle period of 9.45 sec; the HE's were initially modeled as neurons that fire tonically. We varied three network parameters in this study over several orders of magnitude: the maximum conductances of the inhibitory synapse [g_{Syn}] and electrical coupling strength [g_{Coup}]. We also varied the phased delay of the right HN synaptic input [Φ_{Syn}] to better match timing of inhibition found in the living system. Tonic firing HE's did not significantly shift their phasing in response to changing network parameters.
Thus, we varied the set of maximum conductances for the HE neurons in a linear fashion from classical HE (tonic firing) to HN (endogenous bursting) values to ascertain the role of intrinsic properties on phase-shifts. Endogenous bursting HE's shifted their phase over a wide-range (> 0.35) when inhibition and coupling were covaried and we were able to match phasing with several HE pairs from the living system. Duty cycle (burst duration / cycle period) was consistently smaller than observed in the living system.
Our search of network parameter space contributes to an understanding of the mechanisms underlying variable phase differences in neuronal networks and reinforces the importance of interactions between endogenous properties and synaptic connections for producing functional motor patterns.

Disclosures: **A.L. Weaver:** None. **B.M. Evoy:** None.

Poster

810. Central Pattern Generating Circuits: Models

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 810.18/MM4

Topic: E.07. Rhythmic Motor Pattern Generation

Support: DARPA HAPTIX

Title: Topographical organization of peripheral nerve axons following complete nerve transection and regeneration

Authors: *E. ZELLMER, M. MACEWAN, D. MORAN;
Washington Univ. In St. Louis, Saint Louis, MO

Abstract: Peripheral nerve interfaces (PNI) are medical devices used to manipulate and monitor the bioelectric state of peripheral nerve axons. Regenerative nerve interfaces represents a unique group of peripheral interfaces. Unlike other PNIs, their implantation requires a complete or partial transection of the interfaced nerve. Following transection, fibers from the proximal stump reconnect to distant target by regenerating through the interface. This approach allows nerve fibers to be steered into geometries appropriate for electrical interfacing, offering this class of interfaces unique properties. A novel type of regenerative nerve interface called the macro-sieve electrode (MSE) has been developed by our group. The MSE does not impede on nerve regeneration, is robust *in-vivo*, and may be a suitable tool for long term selective interfacing of peripheral nerves.

Regenerative peripheral interfaces such as the MSE targets regenerative nervous tissue which is different in terms of fiber morphology, fiber caliber distribution and overall nerve microarchitecture compared to non-disrupted tissue. In healthy, non-disrupted peripheral nervous tissue, axons innervating the same motor target or related sensory organs are located in close proximity, often electrically insulated from unrelated fibers through fascicular subunits. Without this topographical organization, it would be challenging to achieve selective activation of distal or proximal targets using peripheral nerve interfaces. Studies have shown that following complete nerve transection and subsequent regeneration, the topography of the nerve distal to the disruption changes dramatically including a substantial spatial redistribution of fibers within the trunk.

The degree of spatial clustering between functionally related fibers within this regenerated microarchitecture is of key importance to the performance of regenerative PNIs but is yet to be determined. In this work, this issue is addressed by using computational modeling to analyze *in-vivo* recruitment data generated using chronically implanted MSEs. Specifically, recruitment curves quantifying the force output of skeletal muscles innervated by the rat sciatic nerve were generated *in-silico* using a combined bioelectric/neuron model together with a model representing the output of regenerated musculature and compared with recruitment curves generated *in-vivo*. The model was used to quantify the degree of spatial clustering between functionally related fibers within regenerated peripheral nerve trunks *in-vivo*.

Disclosures: **E. Zellmer:** None. **M. MacEwan:** None. **D. Moran:** None.

Poster

810. Central Pattern Generating Circuits: Models

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 810.19/MM5

Topic: E.07. Rhythmic Motor Pattern Generation

Title: Parameter tuning for stable bipedal walking of a neuromusculoskeletal model by genetic algorithms

Authors: *D. ICHIMURA[1,2], Y. TAKAGI[2], T. YAMAZAKI[1];
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Abstract: Rehabilitation is repetition of trial and error. For each patient,therapists test different rehabilitation methods until they find an effective one for the specific patient. This process could take very long time and be painful. If we can eliminate the trial-and-error process, this will be beneficial for the patients. A potential way to do this is to use computer simulation. It is possible to build a neuromusculoskeletal model that takes conditions of a specific patient into account, and test various rehabilitation using the model. Thus, a personalized neuromusculoskeletal model will provide a means to reduce the cost and pain in rehabilitation, which would realize taylor-made rehabilitation for individual patients.A technical challenge is parameter tuning for the model. We must first tune model parameters so that the model shows normal behavior.
Then, we simulate lesions and examine whether the lesions reproduce symptoms that a patient exhibits. However, there are a number of parameters to be tuned in a realistic neuromusculoskeletal model. For example, our neuromusculoskeletal model for bipedal walking, which consists of a body composed of rigid links and joints for lower extremities, a set of central pattern generators (CPGs), and a cerebellar model, has 48 parameters. It is difficult to tune the parameters for normal bipedal walking by hand.In this study, we employed genetic algorithms (GAs) for the parameter tuning. We implemented a GA algorithm using Message Passing Interface(MPI), a library for parallel computing. At the beginning of the iteration, the model fell down immediately. During the iteration, the model gradually increased the duration of the walk and the walking distance. After 180 generations, the model acquired stable bipedal walking. We also adopted the same method for a small humanoid robot to train the robot walk.
These results suggest that GAs provide an efficient means to train a large-scale neuromusculoskeletal model using multicore computers.

Disclosures: D. Ichimura: None. **Y. Takagi:** None. **T. Yamazaki:** None.

Poster

810. Central Pattern Generating Circuits: Models

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 810.20/MM6

Topic: E.07. Rhythmic Motor Pattern Generation

Support: Lillywhite Endowment to Utah State University

Title: Adult cortical activation patterns during timing of fine movements: an fNIRS study

Authors: *S. ALPHONSA[1], B. E. STUDENKA[1], R. B. GILLAM[2];
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Abstract: The field of time perception and time production proposes that individuals possess a single internal, central clock that behaves as a general-purpose timer. Tasks such as finger tapping are believed to use the internal clock whereas circle drawing does not. There is a large body of behavioral evidence supporting the distinction between event and emergent timing (Ivry et al., 2002; Robertson et al., 1999; Spencer, Zelaznik, Diedrichsen, & Ivry, 2003). Several studies have documented neural activation during temporal control of event timing (tapping) but neural activation during emergently timed tasks (circle drawing) have not been examined. The extent to which tapping and circle drawing tasks share cortical activation may lend insight into the regions associated with the independent or shared timing mechanisms involved in these tasks. In order to elucidate this, 29 (±22.9 years; 14M and 15F) college-age students were tested using Functional Near Infrared Spectroscopy (fNIRS). Subjects performed tapping and circle drawing using the synchronization-continuation paradigm for 30 seconds with rests in between. We hypothesized that tapping and circle drawing tasks would recruit different cortical areas during their performance. From the behavioral measures (Wing and Kristofferson timing model, 1973), we found a subset of individuals who appeared to time both tapping and circle drawing tasks using a clock (clock timers, n=4) and a subset who did not use a clock for circle drawing (non-clock timers, n=20). Contrasts showed an overall greater activation for clock timers compared to non-clock timers. Also, this activation was greater for circle drawing compared to tapping in the same areas. ROI-based time series analyses showed significantly greater activation between 10-20 seconds for circle drawing in Supplementary Motor Area (SMA), Superior Parietal Lobule (SPL) and Inferior Parietal Lobule (IPL) ($p<0.001$) compared to tapping. There was an opposite trend in activation patterns for these tasks in the Temporal Area. This activation was again observed to be greater for clock compared to non-clock timers in the same areas. We conclude that clock timers showed increased recruitment of areas responsible for timing (beat perception, paced movements, synchronization, perception and interpretation of sensory information)

compared to non-clock timers. This is the first study that compared neural activation during event and emergent tasks.

Disclosures: **S. Alphonsa:** None. **B.E. Studenka:** None. **R.B. Gillam:** None.

Poster

810. Central Pattern Generating Circuits: Models

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 810.21/MM7

Topic: E.07. Rhythmic Motor Pattern Generation

Support: National Institutes of Health K12HD073945

James Zumberge Individual Research Awar

USC provost fellowship

Title: An exploration of the capacity of coupled-oscillator CPG models to adapt to dynamic perturbations during simulated bipedal locomotion

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Abstract: Humans exhibit the ability to integrate sensory information with ongoing motor activity to skillfully adapt to walking in different environments. This process is commonly studied during walking by introducing novel perturbations to the environment via dual-belt treadmills or viscoelastic force fields. In both paradigms, spatiotemporal variables associated with gait (e.g. step lengths) are initially perturbed, but gradually return to baseline values. Although there are many studies on adaptation, the question "why do we adapt back to baseline?" remains unanswered. One hypothesis is that adaptation may result from dominant contributions of spinal pattern generating circuits (CPGs) that are not overcome by supra-spinal centers. Because it is difficult to isolate the role of spinal circuits during human locomotion, oscillator-based models of the CPG may provide a unique insight into the role of the spinal cord during locomotor adaptation.
Here, we use locomotor adaptation as a model paradigm to explore the capacity of coupled-oscillator CPG models to explain previously-reported behavioral observations from human experiments. While these models have been used to extend our conceptual understanding of the role of CPGs during locomotion, the extent to which they are capable of explaining human behavior remains to be seen. We simulated two experimental paradigms: split-belt adaptation and adaptation to a unilateral elastic force field. Our simulation included a two-level CPG and a

pendulum-based mechanical model to generate limb angle trajectories and provide measures of step length and foot velocity similar to the variables measured in human studies. The model integrated sensory feedback with ongoing motor activity through a process known as phase resetting. This process allows the CPG to reset its current state in the oscillatory pattern, at the onset of a specific event (e.g. toe off).
The presence of phase resetting had a marked effect on how the model responded to each perturbation. During split-belt walking, convergence to baseline symmetric step lengths was achieved when phase resetting was enabled, but failed in its absence. Although the model was capable of adapting to a simulated split-belt treadmill perturbation, no such adaptation was observed during walking with an elastic force field. Together, our results suggest that spinal circuits and limb afferents may play an important role in facilitating split-belt treadmill adaptation. In contrast, the inability of coupled oscillator models to adapt to a dynamic force fields implies that more complex, perhaps supra-spinal circuits are necessary to compensate for state-dependent perturbations.

Disclosures: **A. Marjaninejad:** None. **F. Valero-Cuevas:** None. **J. Finley:** None.

Poster

811. Rhythmic Motor Patterns: Neuromodulation

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 811.01/MM8

Topic: E.07. Rhythmic Motor Pattern Generation

Support: NSF Grant IOS-1354567

NSF Grant IOS-1353023

NIH grant P20GM0103423 from NIGMS

University of Hawaii Undergraduate Research Opportunity Program

Doherty Award from Bowdoin College

Title: Allatostatin- C signaling systems in the lobster: Identification and characterization of peptides and receptors

Authors: M. E. STANHOPE[1], M. K. ARMSTRONG[1], J. H. CARMICHAEL[1], R. R. FISHER[1], T. J. LAMEYER[1], M. G. PASCUAL[2], P. WALSH[1], A. E. CHRISTIE[2], *P. S. DICKINSON[1]; [1]Bowdoin Coll, Brunswick, ME; [2]Univ. of Hawaii at Manoa, Honolulu, HI

Abstract: C-type allatostatins (AST-Cs) are a group of pleiotropic peptides in the arthropods. In the lobster *Homarus americanus*, two AST-C isoforms, pQIRYHQCYFNPISCF (AST-C I) and SYWKQCAFNAVSCFamide (AST-C II) [disulfide bridging between the two cysteine residues in each peptide], were previously identified; both have been shown to modulate the output of pattern generators in the stomatogastric and cardiac ganglia. Here we present evidence for a third *H. americanus* AST-C isoform, GNGDGRLYWRCYFNAVSCF (AST-C III) [disulfide bridge between the two cysteines], identified via *in silico* transcriptome mining. AST-C III, like AST-Cs I and II, is cardioactive in the lobster. Like the other isoforms, it elicits a decrease in contraction frequency when perfused through the whole heart. Perfusion with AST-C III also results in a decrease in contraction amplitude in hearts that respond to AST-C I and II with contraction amplitude decreases. Like AST-C I and II, AST-C III can also elicit increases in contraction amplitude in some hearts.
Transcriptomic data had previously identified three different AST-C receptors in the lobster nervous system, although the distribution of these receptors was unknown. Using PCR, we confirmed the predicted receptor sequences and examined the distribution of the three receptor-encoding transcripts in several parts of the lobster nervous system, as well as in peripheral tissues. We found that the receptors are differentially distributed in the brain, the eyestalk ganglia, and the cardiac ganglion. Specifically, no more than two of the three receptors were present in any individual cardiac ganglion, with AST-C R1 not identified in any of the cardiac ganglia examined. Searches of publicly available transcriptomes from a number of other decapod species suggest that the presence of three AST-C peptides and three putative AST-C receptors is conserved throughout this taxon. What is not yet known, however, is the interactions between the peptides and receptors, notably whether each receptor is specific for one peptide or whether they bind multiple peptides. Nonetheless, the fact that all three peptides elicit effects in the CG, where no more than two receptors have been seen in a single lobster, suggests that at least one of the receptors is somewhat promiscuous. Additionally, the fact that the three peptides cause a similar range of effects, even though they can have different effects on contraction amplitude in an individual lobster, suggests the possibility that all three peptides activate the same receptor(s) or that the receptors trigger similar intracellular pathways.

Disclosures: **M.E. Stanhope:** None. **M.K. Armstrong:** None. **J.H. Carmichael:** None. **R.R. Fisher:** None. **T.J. Lameyer:** None. **M.G. Pascual:** None. **P. Walsh:** None. **A.E. Christie:** None. **P.S. Dickinson:** None.

Poster

811. Rhythmic Motor Patterns: Neuromodulation

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 811.02/MM9

Topic: E.07. Rhythmic Motor Pattern Generation

Support: NIH grant HL116508.

Title: Enhanced licking and grooming lead to increased c-fos expression in medullary serotonin-containing neurons and increased immunostaining for serotonin 2c receptors in the hypoglossal motor nucleus

Authors: *L. KUBIN, R. K. DAS, A. PARKAR, K. B. HERR;
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Abstract: Activation of motoneurons by serotonin (5-HT)-containing cells helps maintain postural tone and enables movement, especially during stereotyped behaviors. These motor effects of 5-HT are mainly mediated by the excitatory 5-HT_{2A} and 5-HT_{2C} receptors. We are interested in the role of 5-HT in the control of the tongue-innervating hypoglossal (XII) motoneurons for their important role in both ingestive behaviors and preventing upper airway collapse in obstructive sleep apnea patients. We previously found that mRNA and protein for 5-HT_{2A}, but not 5-HT_{2C}, receptors have higher levels in the XII nucleus at active period onset than at rest onset. We have now tested whether expression levels for these receptor proteins vary with experimentally altered intensity of tongue use. Six groups of three Sprague-Dawley rats were subjected from 7pm to 7am to three behavioral conditions resulting in different intensities of tongue use: W-water *ad lib*; S-water with sucrose (100mM) and saccharine (6mM) to increase drinking; S+O-water with sucrose/saccharine+peanut oil applied to fur to increase grooming. Drinking and locomotor activity (LMA) were measured using infrared beam technique, after which rats were perfused and brainstem slices were subjected to immunohistochemistry. Medullary 5-HT-containing cells with and without nuclear c-Fos were counted, and immunostaining for 5-HT_{2A} and 5-HT_{2C} receptors minus background was measured in the XII nucleus. Both S and S+O rats had elevated lick counts during the test night when compared to the previous water night; LMA did not differ among the treatments. The percentage of 5-HT cells with Fos-positive nuclei was higher in S+O rats than in W rats (27%±14 (SD) vs. 14%±5, p=0.03) in the raphé obscurus and tended to be elevated in both S and S+O rats in raphé pallidus and parapyramidal region. Immunostaining for 5-HT_{2C} receptors was significantly higher in S+O, but not S, rats than in W rats when measured in the entire XII nucleus (65±8 vs. 60±8 arbitrary units; p=0.008) and also in its dorsal and ventral compartments measured separately. There was no difference among the treatments for 5-HT_{2A} receptors. Thus, 5-HT_{2C} receptor immunostaining in the XII nucleus increases concurrently with increased behavioral activation of medullary 5-HT cells and enhanced use of the tongue. This may relate to elevated synthesis or turnover of 5-HT_{2C} receptors. The absence of effects on 5-HT_{2A} receptors suggests that their previously reported day-night difference is circadian clock-, rather than use-, dependent.

Disclosures: L. Kubin: None. **R.K. Das:** None. **A. Parkar:** None. **K.B. Herr:** None.

Poster

811. Rhythmic Motor Patterns: Neuromodulation

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 811.03/MM10

Topic: E.07. Rhythmic Motor Pattern Generation

Support: SNSF grant 320030_149561

Title: Modulating brain state using a novel TMS-based neurofeedback approach

Authors: *K. L. RUDDY[1], J. H. BALSTERS[1], D. MANTINI[1,2], N. WENDEROTH[1];
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Abstract: Various transcranial brain stimulation techniques have been used in an attempt to modulate excitability of the human corticomotor system, often with weak or mixed results. To date, there exists no reliable method to robustly upregulate or downregulate the state of the motor system. Our aim was to use neurofeedback of the size of motor evoked potentials (MEPs) in response to transcranial magnetic stimulation (TMS), to train participants to self-modulate their own brain state. The goal was to harness experimental control over the excitability of the motor system, in order to investigate the oscillatory brain activity that mediates these different states, using electroencephalography (EEG).
Separate sessions (300 trials each) were carried out for upregulation (UP) and downregulation (DOWN) of MEP amplitude. In the UP condition subjects were rewarded for larger than average first dorsal interosseous (FDI) MEPs, with visual feedback showing amplitude as a green bar, a positive sound-byte, and a small financial incentive. Smaller than average MEPs were not rewarded, a red bar displayed the amplitude, and a negative sound-byte was heard. The reverse occurred in the DOWN sessions. Background muscle activity was monitored throughout and each trial only commenced when muscles were sufficiently relaxed. The final 60 trials of training occurred during simultaneous EEG recording.
MEP amplitudes in the muscle from which neurofeedback was provided were significantly altered from baseline by the end of 150 DOWN training trials (all $p<0.005$) and 240 UP training trials (all $p<0.01$). No changes in MEP amplitude occurred in a nearby control muscle that was not providing neurofeedback. EEG data collected during upregulation and downregulation suggests that high and low levels of corticomotor excitability are mediated by oscillatory signatures in the alpha and beta bands that are distinct compared to those in the gamma band.
Our approach uses brain stimulation in a non-traditional way to achieve robust neuromodulation. Using this method to harness experimental control over the excitability of the motor system

opens many possibilities for future investigations of how altered brain state influences motor behaviour.

Disclosures: **K.L. Ruddy:** None. **J.H. Balsters:** None. **D. Mantini:** None. **N. Wenderoth:** None.

Poster

811. Rhythmic Motor Patterns: Neuromodulation

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 811.04/MM11

Topic: E.07. Rhythmic Motor Pattern Generation

Support: NIH Grant R37-NS29436 (MPN)

NSF Grant IOS-1153417 (DMB)

Title: Peptidergic (G-SIFamide/MCN5) modulation of a rhythmically-active microcircuit.

Authors: D. M. BLITZ[1], A. P. COOK[2], *M. P. NUSBAUM[2];
[1]Dept. of Biol., Miami Univ., Oxford, OH; [2]Dept of Neurosci., Perelman Sch. of Medicine, Univ. of Pennsylvania, Philadelphia, PA

Abstract: G-SIFamide (SIF) is a peptide cotransmitter of the projection neuron MCN5 in the crab *Cancer borealis* stomatogastric nervous system (Dickinson et al, 2010 SfN Abstr). This previous study showed, qualitatively, that bath-applied SIF excites the pyloric (PR)- and gastric mill (GMR) rhythms in the stomatogastric ganglion (STG), and concluded that many previously described MCN5 actions on the PR (Norris et al, 1996 J Neurophysiol) are likely SIF-mediated. Here, we (a) quantitatively analyze bath-applied SIF actions on the PR and compare them with the MCN5 actions, and (b) compare a GMR-like response elicited by SIF application or MCN5 stimulation.
Bath-applied SIF excited the PR, but subsets of PR parameters exhibited distinct response thresholds (RM-ANOVA, Holm-Sidak post-hoc test; n=4-10). For example, 10 nM SIF decreased PR cycle period ($p<0.01$), increased LP neuron spike rate ($p<0.05$) and IC neuron spikes/burst ($p<0.001$). In contrast, response threshold was 1 μM for increased PD neuron phase off ($p<0.001$), LP spikes/burst ($p<0.02$), LP phase on ($p<0.03$) and LP phase off ($p<0.01$). Comparing the PR response to SIF vs MCN5 stimulation is complicated by MCN5 ionotropic inhibitory and electrical synapse actions, but MCN5 modulation persists post-stimulation (Norris et al, 1996). Similar to applied 1 μM SIF, the post-MCN5 PR exhibited all the above-indicated changes except LP phase on.

Tonic MCN5 stimulation (>20 Hz) also drove a GMR-like pattern (cycle period 12.5 s, n=7) in which the IC, LPG & DG neurons exhibited coordinated rhythmic bursting, with limited or no bursting in the canonical GMR neurons LG and Int1. During this rhythm, the intraburst pattern of IC & LPG was often tonic (i.e. they lost their PR-timed pattern), and several state-dependent synaptic actions appeared (e.g. IC inhibited LPG; LPG inhibited DG) (n=3-5). A similar pattern, or aspects of it (e.g. DG and/or IC bursting) occurred during SIF application (≥1 uM: n=5). Comparable SIF applications in *C. irroratus* similarly excited the PR (n=4/4) and yielded the GMR-like pattern (n=2/3).
It is not surprising that SIF and MCN5 do not have identical actions, as there is another pair of SIF neurons innervating the STG (Dickinson et al, 2010). Also, unlike the continual presence of bath-applied SIF, tonic MCN5 activity did not likely cause continual transmitter release, due to PR-timed inhibitory synapses from PY neurons onto MCN5 STG axon terminals (n=3). The impact of this inhibition on MCN5 actions remains to be determined. We aim to more firmly elucidate the role of SIF in MCN5 actions on the PR and GMR, including its coordinated influence with the MCN5 small molecule cotransmitter and electrical synaptic actions.

Disclosures: D.M. Blitz: None. **A.P. Cook:** None. **M.P. Nusbaum:** None.

Poster

811. Rhythmic Motor Patterns: Neuromodulation

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 811.05/MM12

Topic: E.07. Rhythmic Motor Pattern Generation

Support: JSPS-KAKENHI No. 15H01587

JSPS-KAKENHI No. 26460327

Title: Possible role of glycine-related spontaneous activity in the developmental network.

Authors: *A. ARATA[1], A. NISHIYAMA[2], T. KAKIZAKI[4], H. SHIMOMURA[3], Y. TAKESHIMA[3], Y. YANAGAWA[4];
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Abstract: Neuronal circuits generating fetal movement in mammals are localized in the brainstem and the spinal cord and they are thought to effective neuronal development and mental health. Fetal movement included respiratory related movement, jaw movement, locomotion

related movement. Fetal movements are thought to be involved emotional development because the child who was shown with little fetal movement became autism. However, the neuronal mechanisms of the fetal motor development are not fully understood. We examined the first step of relationship between fetal movement and the network development concerned to respiratory activity and spontaneous fetal motor activity in the perinatal period. The network development is important for excitatory and inhibitory synaptic balance. In our previous study, we could not detect any respiratory activity even substance P application in the VGAT KO mice, and could see strong inhibition of respiratory network in the GAD 67, 65 double KO mice (Fujii et al, Neurosci., 146: 1044-52, 2007). So, we concluded glycine is an important factor of network formation during perinatal period. In this study, we focused on the involvement of the glycine-related activity that showed excitation in fetal period but showed inhibition in neonatal period. We also focus on the NMDA receptors with glycine-binding site utilizing in vitro isolated brainstem-spinal cord preparation taken from fetal and neonatal rats. In prenatal (embryonic day 18-20) preparations, two kinds of spontaneous rhythmic activities were recorded from 4th cervical nerve root (C4). One activity had a regular cycle periodical representing respiratory activity (RA), and the other one presented irregularly, larger in amplitude and not related to respiratory movements (non-respiratory activity, NRA) which was recorded from C4 and C8. In contrast, only RA was observed in neonatal (postnatal day 0-4) preparations recorded from C4 nerve root. NRA were observed in vitro preparations correlated with an upper limb and dorsal part of the ribcage movement. NRA was probably fetal movement. The fetal movement was completely blocked and respiratory activity was slightly blocked by antagonists of glycine-binding-site of the NMDA receptor such as 5,7-Dichlorokynurenic acid (DCKA) or L-689560. GlyT2-KO mice which decrease glycine release from presynaptic terminals showed low frequency of fetal movement and decrease of respiratory phase. These results suggested that 1) glycine played a crucial role in generating fetal movement mediated with glycine-binding-site of the NMDA receptor, 2) glycine must be required to the construction of respiratory network.

Disclosures: **A. Arata:** None. **A. Nishiyama:** None. **T. Kakizaki:** None. **H. Shimomura:** None. **Y. Takeshima:** None. **Y. Yanagawa:** None.

Poster

811. Rhythmic Motor Patterns: Neuromodulation

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 811.06/NN1

Topic: E.07. Rhythmic Motor Pattern Generation

Title: Tonic 5nM dopamine (DA) permits and abolishes activity-dependent regulation of the hyperpolarization-activated (I_h) and transient potassium (I_A) currents, respectively, in the lateral pyloric neuron (LP), a component of the pyloric circuit of the spiny lobster, Panulirus interruptus

Authors: *A. R. PARKER[1], D. J. BARO[2];
[1]Georgia State Univ., Lawrenceville, GA; [2]Georgia State Univ., Atlanta, GA

Abstract: The 14 component neurons of the pyloric pattern generator work in concert to produce a constant rhythmic output. In somatic intracellular recordings, each of the neurons displays ~1Hz, 20mV oscillations in membrane potential with depolarized plateaus (slow wave activity) and passively spreading action potentials from the spike initiation zone are also recorded on top of the plateaus. Maintenance of several neuronal activity features, such as spike timing, is critical for preserving a stereotyped circuit output. Activity features are determined by a balance of conductances, and a given feature can be maintained by preserving its underlying conductance correlations. In LP, spike timing is influenced by two opposing subthreshold conductances, I_A and I_h. We previously recorded LP activity during experiments where I_A was blocked with 4-aminopyridine (4AP) in the presence or absence of 5nM DA. 4AP altered many aspects of LP activity, including spike timing. However, spike timing was restored over minutes in the DA but not saline treatment group, despite continuous 4AP application in both groups. Additional experiments showed that tonic 5nM DA permitted bi-directional activity-dependent regulation of LP I_h so that when 4AP altered LP activity, the change in activity drove a compensatory change in I_h that restored spike timing. We hypothesized that DA-enabled activity-dependent regulation of LP I_h normally compensates for activity-dependent changes in LP I_A to maintain a positive correlation between LP I_A and I_h and thereby, spike timing. One corollary of this hypothesis is that LP I_A is regulated in an activity-dependent manner. To test this idea, LP duty cycle (duration of depolarized plateau ÷ cycle period) was manipulated in the absence of DA. When duty cycle was abolished (TTX) vs. increased by 50%, we observed a mean ~ 15% increase vs. decrease in LP I_A maximal conductance (G_{max}), respectively. Ongoing experiments suggest that spike activity does not regulate LP I_A G_{max}. We next characterized DA's effect on LP I_A. Tonic application of 5nM DA did not alter LP I_A G_{max} in the absence of changes in activity. However, much to our surprise, tonic nM DA prevented activity-dependent regulation of LP I_A! These findings disproved our hypothesis: DA does not enable activity-dependent regulation of I_h to compensate for activity-dependent regulation of I_A. Instead, DA switched the conductance that was regulated by slow wave activity. In the absence of tonic 5nM DA, changes in duty cycle regulated LP I_A (max ~15%) but not I_h; in the presence of tonic 5nM DA, changes in duty cycle regulated LP I_h (max ~10%) but not I_A. Neither conductance was affected by DA in the absence of a change in activity.

Disclosures: **A.R. Parker:** None. **D.J. Baro:** None.

Poster

811. Rhythmic Motor Patterns: Neuromodulation

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 811.07/NN2

Topic: E.07. Rhythmic Motor Pattern Generation

Support: NS 17813

Title: Animal-to-animal variability of circuit components revealed by neuromodulation in the absence of spikes

Authors: *P. ROSENBAUM, E. MARDER;
Biol. Dept., Brandeis Univ., Waltham, MA

Abstract: Nervous systems are under the constant influence of neuromodulators, altering intrinsic neuronal properties and synaptic strengths. Rhythm generating circuits that produce stereotypic motor patterns must have a robust and reliable response to neuromodulators, considering animal-to-animal variability of intrinsic properties and synaptic strengths.
We investigated the effects of the neuromodulator red pigment concentrating hormone (RPCH) on the pyloric rhythm of the stomatogastric ganglion (STG) of the crab *Cancer borealis*. RPCH elicits a robust pyloric rhythm associated with a substantial increase in the number of LP spikes/burst. Synapses between neurons in the STG can be pulse-mediated and graded. When action potentials were blocked by TTX, RPCH elicited rhythms were more highly variable then in the absence of TTX. LP was always strongly depolarized with a long period, ranging from 3.5s to 40s, and still received inhibition on a faster pyloric timescale. PD received large amplitude inhibition from the LP neuron and contributed low amplitude oscillations in a pyloric frequency. While these rhythms were reliably elicited in RPCH and TTX they showed remarkable animal-to-animal variability. These data suggest that in the absence of action potentials and action potential mediated synaptic transmission animal-to-animal variability in the response of pyloric neurons to RPCH and variability in synaptic strengths between pyloric neurons is revealed.
NS 17813

Disclosures: P. Rosenbaum: None. **E. Marder:** None.

Poster

811. Rhythmic Motor Patterns: Neuromodulation

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 811.08/NN3

Topic: E.07. Rhythmic Motor Pattern Generation

Support: NSF DMS 1313861

NIH MH060605

Title: Neuromodulation produces complex changes in resonance profiles of neurons in an oscillatory network

Authors: *D. M. FOX[1], H. G. ROTSTEIN[2], F. NADIM[3];
[1]Biol. Sci., [2]Mat Sci., [3]Biol. Sci. & Math Sci., NJIT, Newark, NJ

Abstract: Membrane potential resonance (MPR), a peak in the amplitude of the membrane impedance profile ($Z(f)$) at a nonzero frequency (f_{res}), has been proposed to be important for the generation of CNS oscillations. We are interested in how neuromodulation modifies MPR properties.

We examined the effects of the neuromodulatory peptide proctolin on the previously reported MPR properties in the pacemaker PD and follower LP neurons in the crab pyloric oscillatory network. In PD, application of proctolin increased the MPR amplitude ($Q_Z = Z_{max} - Z_0$) without changing f_{res}. In contrast, LP displayed a small trough in Z at f~0.25Hz in addition to a peak at f_{res} ~1.4Hz in normal saline. Increased concentrations of proctolin increased the amplitude of the trough, shifted f_{trough} and f_{res} to higher frequencies (f_{trough} ~ 1Hz and f_{res} ~2.5Hz at 1 μM proc) and changed Qz.

Proctolin activates a fast inward current (I_{MI}). Our unpublished data indicates that it also activates a slow frequency-dependent inward current (I_{MI2}) in LP. I_{MI}, which is a fast amplifying current, would explain the increase in MPR amplitude in PD. However, the underlying biophysical mechanisms of a trough in the impedance profile are not well understood. For hippocampal interneurons (Pike et al., 2000) this phenomenon has been proposed to emerge from the interaction between a resonant and a slower amplifying current (Richardson et al., 2003). We similarly hypothesized that f_{trough} was generated by the existence of a slow amplifying current. We tested this using a conductance-based model of pyloric neurons that captures single peak MPR in the presence of a calcium current (I_{Ca}) to which we added a slow current. We found that either a slow inward rectifier potassium current or a slowly-activating I_{MI}-like current produced the observed trough. We examined the effects of changing the maximal conductance (G) and time constant τ_m of this current on Z. Increasing G for low τ_m increased MPR amplitude, whereas increasing G for high τ_m decreased Q_Z and resulted in the appearance of the trough at low frequencies. Fixing G, while changing τ_m showed that the trough appears as an intermediate step

between low-pass filtering and single peak MPR. It remains to be shown whether I_{MI2} could produce the observed impedance profile in LP.
These results indicate that small differences in slow low-threshold currents could result in distinct subthreshold oscillatory properties in the PD and LP neurons. The functional consequences of the presence of a trough in the impedance profile are not known. We speculate that the trough separates the frequency domains in frequency-preference regions dominated by the resonant peak and the non-oscillatory dynamics.

Disclosures: **D.M. Fox:** None. **H.G. Rotstein:** None. **F. Nadim:** None.

Poster

811. Rhythmic Motor Patterns: Neuromodulation

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 811.09/NN4

Topic: E.07. Rhythmic Motor Pattern Generation

Support: CONACYT Grant 59873 (JQ)

CONACYT Grant 219707 (CMV)

NIH grant NS45248 (SH)

Title: Serotonin reduces synaptic efficacy of myelinated afferents and depresses PAD by the activation of 5-HT_{1B} receptors in the *In vitro* mouse spinal cord

Authors: *D. GARCÍA-RAMIREZ[1], J. MILLA-CRUZ[1], J. CALVO[1], C. VILLALÓN[2], S. HOCHMAN[3], J. QUEVEDO[1];
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Abstract: We reported previously that serotonin (5-hydroxytryptamine; 5-HT) markedly depressed low-threshold afferent stimulation-evoked primary afferent depolarization (PAD) as well as monosynaptic transmission by presynaptic mechanisms in the *in vitro* mouse spinal cord (García-Ramírez et al., PLoS One, 2014). We also reported that the non-selective 5-$HT_{1B/1D}$ receptor agonist, zolmitriptan, depressed PAD and monosynaptic transmission evoked by stimulation of myelinated afferents (SFN Abstract 828.11). The aim of the present study was to investigate whether 5-HT_{1B}, 5-HT_{1D} or both receptor subtypes are involved in these actions. Experiments were carried out on the P6-7 sagittally-hemisected mouse lumbar spinal cord with intact nerves for afferent stimulation. Stimulus strength was based on multiples of threshold (xT) of the most excitable fibers recorded from the incoming afferent volley. Peripheral nerves were

stimulated at strengths that preferentially recruited myelinated afferents (2 xT). PAD was inferred from dorsal root potentials (DRPs) recorded at L3-L5 dorsal roots while monosynaptic responses were recorded in the deep dorsal horn as intraspinal extracellular field potentials (EFPs), as intracellular excitatory postsynaptic currents (EPSCs), or as excitatory postsynaptic potentials (EPSPs). A paired-pulse protocol assessed homosynaptic EFP depression with conditioning - test intervals between 25 ms – 10 sec. The effects produced by selective agonists for 5-HT_{1B} and 5-HT_{1D} receptors (1 μM) were analyzed. In this respect, the selective rodent 5-HT_{1B} receptor agonist CP-93,129, significantly depressed DRPs and EFPs (by 42 and 62% of control, respectively) whereas the 5-HT_{1D} agonist PNU142633 did not (13 and 4% of control, respectively). CP-93,129 also depressed EPSCs and EPSPs (by 24 and 62% of control, respectively) and reduced the magnitude of homosynaptic depression (n=5) similar to that seen with serotonin and zolmitriptan. These results lead us to conclude that 5-HT depresses synaptic efficacy of myelinated afferents via activation of 5-HT_{1B} receptors. Depression of DRPs may be due to a decrease in synaptic transmission of afferent fibers giving PAD, but we cannot exclude effects downstream on the interneuronal pathways mediating PAD.

Disclosures: D. García-Ramirez: None. **J. Milla-Cruz:** None. **J. Calvo:** None. **C. Villalón:** None. **S. Hochman:** None. **J. Quevedo:** None.

Poster

811. Rhythmic Motor Patterns: Neuromodulation

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 811.10/NN5

Topic: E.07. Rhythmic Motor Pattern Generation

Support: ISU Cross Disciplinary Grant

Title: Spatial distribution effects on axonal excitability and modulation

Authors: *E. ROSA[1], R. FOLLMANN[2], W. STEIN[2];
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Abstract: Axons do more than just conduct action potentials (APs). They possess complex membrane properties and are endowed with ionotropic and metabotropic receptors for transmitters and neuromodulators that can alter conduction velocity, induce spike failures and initiate ectopic spiking. Axonal modulation and spike propagation dynamics can contribute significantly to the coding and computational capability for neuronal communication (Bucher & Goaillard, Prog Neurobiol 2011). Little is known about the underlying mechanisms leading axonal modulation to affect AP propagation and dynamics. Here we present results of numerical

simulations aimed at developing a better understanding of this matter. Our axonal mathematical model consists of compartments electrically connected in series in a linear chain format, with each compartment being represented by Hodgkin-Huxley equations. Our axon model shows AP propagation delays, clear history dependence and a range of firing rates (Follmann et al, Phys Rev E 2015). Axon modulation is likely to affect the excitability of the axonal membrane, for example by influencing ion conductances. The hyperpolarization-activated current (I_h) has been shown to be affected by dopamine modulation in motor axons (Ballo et al, J Neurosci 2010) and to underlie ectopic spiking in sensory axons (Daur et al, Frontier Comp Neurosci 2012). To examine the effects of excitability changes in the axonal membrane on the spike initiation and propagation, we first implemented I_h in the middle of the axon trunk, extended to a few compartments. As an alternative way to alter axon excitability, we changed the leak conductance in the same compartments. Both manipulations elicited ectopic spiking at low frequency that propagated along the extension of the axon in both directions. To investigate the effects of spatially distributed modulation (see also Scott et al, Nature Comm 2014) we implemented various scenarios using low g_L values in the middle and neighboring compartments. The overall result was lower firing rates in the respective compartments with APs propagating in both directions. To test the effects of changes in axon excitability on AP propagation, we elicited bursts of APs in the first compartment and measured them as they arrived at the last compartment. APs were affected by the middle compartment's ectopic spiking in both cases of ectopic spikes generated by adding I_h and by lowering the value of g_L. Additionally, our preliminary results show that the pattern of the bursts was affected by the firing rate of the ectopic spikes, reinforcing that ectopic spiking may affect not only AP propagation but also information encoding at the axon initial segment.

Disclosures: E. Rosa: None. **R. Follmann:** None. **W. Stein:** None.

Poster

811. Rhythmic Motor Patterns: Neuromodulation

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 811.11/NN6

Topic: E.07. Rhythmic Motor Pattern Generation

Support: MINA project (EU grant)

Title: Sustained block of cannabinoid-1 receptor induced changes in spinal motoneurons

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Abstract: Inverse agonists/antagonists of cannabinoid-1 receptors (CB1Rs) such as rimonabant and its other diarlypyrazole derivatives are proposed for the treatment of drug dependence and obesity. Because of these lengthy health conditions, these pharmacological treatments always require long term dosage. While these drugs are primarily targeted at brain limbic structures, little is known of their effects on locomotor networks that amply express CB1Rs. This issue was investigated in the present report. Previous work in our lab has shown that the sustained (24 h) blockade of CB1R using N-(Piperidin-1-yl)-5-(4-iodophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1H-pyrazole-3-carboxamide, AM251 or rimonabant, severely and irreversibly depresses the rhythmic pattern generated by *in vitro* neonatal rat spinal preparations. However, the exact cellular mechanism that results in inhibition of locomotor network activity is not understood and might comprise damage to vulnerable motoneurons. In the present study, we focused on how lumbar motoneuronal activity changed after sustained application of AM251 using isolated neonatal (age: P0-P2) Wistar rat spinal preparations. AM251 (5 microM) inhibited the action of anandamide (5 microM) on adenylyl cyclase activity of spinal cord preparations, indicating effective block of CB1Rs. By counting nonphosphorylated neurofilament marker SMI-32 stained large neurons in the ventral lumbar region of spinal cord, we found that AM251 applied for 24 h did not affect motoneuronal survival. Likewise, the antidromic field potential of lumbar motoneuronal pools was not changed when compared to sham preparations. In addition, we studied the changes in N-methyl-D-aspartate (NMDA), α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA), glycine and γ-aminobutyric acid (GABA) induced depolarization by recording ventral roots activity in the lumbar region after 24 h of AM251 exposure. When compared to sham preparations, AM251 treatment evoked minimal decline of NMDA induced depolarizations, whereas it significantly (30 %) reduced the AMPA mediated activity. These results suggest that chronic CB1R blockade decreased the excitation of the motoneuronal pool without affecting their survival perhaps via a combination of network and direct motoneuron actions. To further explore the changes in characteristics of individual motoneurons we are currently analyzing their single cell excitability after AM251 application.

Disclosures: **P. Veeraraghavan:** None. **L. Ballerini:** None. **A. Nistri:** None.

Poster

811. Rhythmic Motor Patterns: Neuromodulation

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 811.12/NN7

Topic: E.07. Rhythmic Motor Pattern Generation

Support: NS17813

Title: History dependent effects of repeated neuromodulator application to a small motor circuit

Authors: *D. J. POWELL[1], T. O'LEARY[2], E. MARDER[1];
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Abstract: Nervous systems, including motor circuits, are influenced by a milieu of hormones, modulators, and fast transmitters. Although much is known concerning the acute effects of many different neuromodulators on nervous systems, less is known about the effects of a repeated, long term application of a single modulator. We are attempting to understand how neuromodulators affect nervous systems long after the modulator has been removed from the extracellular environment. We investigate the history dependent effects of a muscarinic agonist, oxotremorine, on the stomatogastric ganglion (STG) of the crab *Cancer borealis*. In this system, muscarinic like acetylcholine receptors (mAChRs) indirectly gate a voltage-dependent ligand-gated current (I_{MI}). The STG motor pattern is driven by an intrinsic bursting neuron which generates a regular pattern of activity, and together with two electrically coupled cells and six follower cells generates the pyloric rhythm. Previous work has shown that mAChRs are present on all of the cell types responsible for producing this rhythmic motor output. Exposure to oxotremorine produces a reliable, acute increase in rhythm cycle frequency. To investigate the history dependence of oxotremorine, we apply the modulator for set periods of time, and then via a fast perfusion of saline, wash out the modulator and record the pyloric rhythm for several hours until the cycle frequency has returned to a pre-modulator rate. The protocol of exposure and washout is repeated. We see a sustained increased in the rhythm's cycle frequency at time points long after the modulator is no longer present. We are analyzing the data to accurately define the time course of recovery as a function of time of application and modulator concentration.

Disclosures: D.J. Powell: None. **T. O'Leary:** None. **E. Marder:** None.

Poster

811. Rhythmic Motor Patterns: Neuromodulation

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 811.13/NN8

Topic: E.07. Rhythmic Motor Pattern Generation

Support: DFG Grant Schm 1084/3-1

Title: Descending modulation of thoracic motor activity in the stick insect

Authors: *T. STOLZ, M. DIESNER, S. NEUPERT, J. SCHMIDT;
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Abstract: Neuromodulators are instrumental in the selection of task-specific motor output in animals. The biogenic amine octopamine (OA) is a key modulator of insect thoracic locomotor networks. In inactive stick insects, for example, OA alters the response properties of a leg-proprioceptive feedback system towards those that characterize the active state of animals (Büschges et al. 1993). Furthermore, OA increases a tonic depolarization, ubiquitous in mesothoracic leg motoneurons during walking (Westmark et al. 2009). Until now, the identity of octopaminergic neurons modulating thoracic motor activity has remained elusive. In insects, OA can be released from dorsal unpaired median (DUM) neurons. Six DUM neurons with somata located in the posterior part of the locust subesophageal ganglion have axons that are bilaterally descending (abbreviated DUM-SD) to thoracic ganglia (Bräunig and Burrows, 2004). We hypothesize that presumably homologous neurons in the stick insect might be candidates for the modulation of thoracic motor activity. Using semi-intact preparations and intracellular recordings, we observed the generation of action potentials in DUM-SD neurons during stance phases, when animals were stepping with a single middle leg (N=33) and during restrained six-legged walking (N=6). Mechanical stimulation by passive movement of legs was excitatory to DUM-SD neurons (N=40). In contrast, pharmacologically evoked activity of central pattern generating neurons (CPGs) had no effect on DUM-SD neuron activity (N=14). Thus, the excitatory input to DUM-SD neurons during walking most likely arises from leg sensory organs rather than from coupling to CPG activity. In order to test a possible role of DUM-SD neurons in the modulation of thoracic motor activity, we studied the effect of DUM-SD neuron activity on reflex responses evoked by stimulation of the mesothoracic femoral chordotonal organ (fCO). We observed two major effects: 1. Stimulation of some DUM-SD neurons decreased resistance reflex responses in middle leg extensor tibiae motoneurons (N=10). 2. Spike activity in other DUM-SD neurons induced an increase in *extensor tibiae* motoneuron activity (N=15). Additionally, it increased the likelihood for the occurrence of assistance reflex responses during fCO stimulation (N=10). Preliminary results of recent experiments using MALDI-TOF MS indicate that the somata of both DUM-SD neurons mediating excitatory as well as inhibitory effects on *extensor tibiae* motoneuron activity contain OA. Thus, individual octopaminergic neurons appear to differentially modulate a specific motor behavior, rather than promoting a general state of arousal.

Disclosures: **T. Stolz:** None. **M. Diesner:** None. **S. Neupert:** None. **J. Schmidt:** None.

Poster

811. Rhythmic Motor Patterns: Neuromodulation

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 811.14/NN9

Topic: E.07. Rhythmic Motor Pattern Generation

Support: NSF IOS 1354932

Title: Spatial preference of cell body location in the crustacean commissural ganglion

Authors: *R. FOLLMANN, C. J. GOLDSMITH, W. STEIN;
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Abstract: Central pattern generators (CPGs) govern many behaviors and the most vital functions of the body such as locomotion, breathing or chewing (Harris-Warrick 2011, Curr Opin Neurobiol). In both vertebrates and invertebrates, CPGs are under continuous modulatory control by descending projection neurons. The release a variety of different neuromodulators from these neurons allows CPGs to generate a wide variety of outputs (Kiehn 2006, Annu Rev Neurosci; Diehl et al. 2013, J Neurosci). Despite their importance in motor control and modulation, a description of the anatomical organization of distinct classes of descending projections is lacking. We study descending motor control on the level of individual neurons using the pyloric (filtering) and gastric mill (chewing) CPGs in the crustacean stomatogastric ganglion. Several distinct and identified descending projection neurons (dPNs) from the paired commissural ganglia (CoGs) innervate these CPGs. We use a combination of retrograde tracing of axonal projections and whole-ganglion stainings with lipophilic fluorescent dyes (Goldsmith et al. 2014, PLoS ONE) to investigate the anatomical organization of dPN cell body location in relation to all other neurons in the CoG. On average, the ganglion dimensions (in μm) were 606.0±54.5, 487.8±49.1, and 105.8±27.8 for the anteroposterior, mediolateral, and dorsoventral axes, respectively (N=51). We obtained up to 220 somata in a single ganglion (151.63±32.39 somata; N=51), covering a wide diameter range (2.5-137 μm, 16.9±11.7 μm). To examine somata location across preparations we used a proportionality relationship to map cell bodies of all preparations onto an average. We characterized the 3D spatial distribution of clusters of somata projecting to different targets (stomatogastric ganglion, labrum, thoracic ganglion and brain) by selectively backfilling their respective axonal projections. Our results show that somata associated with different pathways overlapped spatially, but had distinct preferences within the ganglion: the center of mass of each cluster was found proximal to the origin of the pathway through which its neurons project. Identified dPNs were restricted to the most medial and anterior 25% of the ganglion, with diameters larger than 70% of all other CoG somata. Further, we determined the location of identified modulatory projection neurons in relation to neuronal

landmarks, providing an anatomical guide which will facilitate future experimentation involving descending modulatory pathways.

Disclosures: R. Follmann: None. **C.J. Goldsmith:** None. **W. Stein:** None.

Poster

811. Rhythmic Motor Patterns: Neuromodulation

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 811.15/NN10

Topic: E.07. Rhythmic Motor Pattern Generation

Support: NIH Grant 41878-00 02

NIH Grant 41660-03 07

NIH Grant 41872-00 02

CNPq Grant 470904

Title: Understanding the skin response to transcranial Direct Current Stimulation (tDCS)

Authors: *N. KHADKA[1], F. EZQUERRO[2], A. H. MOFFA[2,3], A. L. ZANNOU[1], F. ZUNURA[1], D. Q. TRUONG[1], F. FREGNI[4], J. DMOCHOWSKI[1], A. R. BRUNONI[2,3], M. BIKSON[1]; [1]Dept. of Biomed. Engin., The City Col. of New York, New York, NY; [2]Interdisciplinary Ctr. for Applied Neuromodulation (CINA), Univ. Hospital, Univ. of Sao Paulo, Sao Paulo, Brazil; [3]Service of Interdisciplinary Neuromodulation, Univ. of São Paulo, São Paulo, Brazil; [4]Spaulding Neuromodulation Center, Spaulding Rehabil. Hosptial, Harvard Med. Sch., Boston, MA

Abstract: Given that transient cutaneous sensation (e.g. itching, tingling, warmth) and skin erythema (so called “flare”) are the primary reported side effects of tDCS, it is crucial to address the mechanism of current passage and the corresponding skin response. Small non-injurious changes in skin temperature during tDCS may influence cutaneous sensation and even influence head current flow pattern and hence induce skin flare. Such changes may also confound blinding of subjects (e.g. sensation of warmth that is based on real temperature changes) or operators (e.g. in the active stimulation case, sponges are warmer or more erythema is seen compared to sham). Temperature was measured during pre, post, and stimulation phases for both phantom and subject forearms. Temperature elevations were predicted using Finite Element Method multi-physics (current flow and bioheat) models of skin comprising three tissue layers (epidermis, dermis, and subcutaneous layer with blood perfusion) or of the phantom. In addition, we

investigated how rater blinding is influenced by tDCS-induced erythema. A semi-automated image processing also determined redness and simulated a probability skin heatmap, and surface area coverage of redness. Finally, we examined adverse effects and subjects' blinding. In the phantom, the temperature difference (ΔT) under both anode and cathode, compared to control, was not significantly different and less than 0.1^0C. Stimulation of subjects resulted in a gradual increase in temperature under active electrode compared to control. The FEM phantom model predicted comparable maximum ΔT of ~0.27^0C (at t=20 min) for the control and anode/cathode cases. The FEM skin model predicted a maximum ΔT of 0.98^0C (t=20 min) for control and ΔT of 1.36 ^{0}C under anode/cathode electrodes. Erythema was present, but less intense in sham compared to active groups. Erythema intensity was inversely and directly associated to correct sham and active guessing. Image analyses showed that erythema also occurs after sham and its distribution is homogenous below electrodes. Tingling frequency was higher using thin compared to thick sponges, whereas erythema was more intense under thick sponges. Our results indicate a moderate and non-hazardous increase in temperature at the skin surface during tDCS that is independent of polarity, and results from stimulation induced blood flow rather than joule heat. Optimal investigator blinding is achieved when erythema after tDCS is mild. Erythema distribution under the electrode is patchy, occurs after sham tDCS and varies according to sponge thickness. We discuss methods to address skin erythema related tDCS unblinding.

Disclosures: **N. Khadka:** None. **F. Ezquerro:** None. **A.H. Moffa:** None. **A.L. Zannou:** None. **F. Zunura:** None. **D.Q. Truong:** None. **F. Fregni:** None. **J. Dmochowski:** None. **A.R. Brunoni:** None. **M. Bikson:** None.

Poster

811. Rhythmic Motor Patterns: Neuromodulation

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 811.16/NN11

Topic: E.07. Rhythmic Motor Pattern Generation

Support: Swedish Research Council VR-M-K2013-62X-03026

Swedish Research Council VR-NT-621-2013-4613

European Union Seventh Framework Programme (FP7/2007-2013) under grant agreement no 604102 (HBP)

Karolinska Institutet's Research Funds

StratNeuro Karolinska Institutet

Centre National de la Recherche Scientifique and the Muséum National d'Histoire Naturelle

Title: The pH-sensing feedback system of the CNS

Authors: *B. ROBERTSON[1], E. JALALVAND[1], H. TOSTIVINT[2], P. WALLÉN[1], S. GRILLNER[1];
[1]Dept. of Neuroscience, Karolinska Institutet, Stockholm, Sweden; [2]Muséum Natl. d'Histoire Naturelle, Paris, France

Abstract: For survival of the organism, acid-base homeostasis is vital. Here, we describe a novel mechanism, intrinsic to the spinal cord and brain, with sensors that detect pH changes and that in the spinal cord act to restore pH to physiological levels by reducing motor activity (lamprey). This pH-sensor consists of ciliated somatostatin-expressing cerebrospinal fluid-contacting (CSF-c) neurons, which in the spinal cord target the locomotor network. They have a low level of activity at pH 7.4. However, at both alkaline and acidic pH the activity of the individual CSF-c neuron is markedly enhanced through the action of two separate channel subtypes (Jalalvand et al., 2016a,b). The alkaline response depends on PKD2L1 channels that have a large conductance and an equilibrium potential around 0 mV, both characteristics of mouse PKD2L1 channels. The acidic response is due to an activation of ASIC3, since APETx2, a specific antagonist of ASIC3 blocks the activation. The discharge pattern of the CSF-c neurons is U-shaped with a minimum frequency around pH 7.4 and a marked increase already at slightly lower and higher pH. During ongoing locomotor activity in the isolated spinal cord, an increase, as well as a decrease of pH, will reduce the locomotor burst rate. These effects are mediated by CSF-c neurons via somatostatin release (Jalalvand et al., 2016a,b).
Somatostain-expressing CSF-c neurons are also present in a specific region of hypothalamus with bulb-like protrusions into the third ventricle. These CSF-c neurons have the same properties as those in the spinal cord, i.e. they are activated by small deviations from physiological pH 7.4. The acidic response is mediated via ASIC3 and the alkaline most likely through PKD2L1 channels as in the CSF-c cells lining the central canal. Their axons ramify in the hypothalamus and surrounding areas.
CSF-c neurons thus represent a novel innate homeostatic mechanism, designed to sense any deviation from physiological pH within the CNS and it will reduce ongoing motor activity. Since CSF-c neurons are found in all vertebrates, their pH-sensing function is most likely conserved.
References:
Jalalvand et al. (2016a) Ciliated neurons lining the central canal sense both fluid movement and pH through ASIC3. Nat Commun 7:10002. doi: 10.1038/ncomms10002.
Jalalvand et al.. (2016b) The spinal cord has an intrinsic system for the control of pH. Curr Biol http://dx.doi.org/10.1016/j.cub.2016.03.048.

Disclosures: B. Robertson: None. **E. Jalalvand:** None. **H. Tostivint:** None. **P. Wallén:** None. **S. Grillner:** None.

Poster

811. Rhythmic Motor Patterns: Neuromodulation

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 811.17/NN12

Topic: E.07. Rhythmic Motor Pattern Generation

Support: NSF grant IOS-1121973

NIH grant P20GM103423 from NIGMS

NSF grant IOS-1354567

Doherty Fellowship from Bowdoin College

Title: Characterization and mechanism of stretch feedback in the heart of the American lobster, Homarus americanus

Authors: *X. QU, E. S. DICKINSON, K. HARMON, P. S. DICKINSON;
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Abstract: The neurogenic heart of the American lobster, *Homarus americanus* is controlled by the cardiac ganglion (CG), a simple central pattern generator. The CG consists of four posterior premotor neurons and five anterior motor neurons, all of which can generate intrinsically repeated and rhythmic driver potentials that in turn trigger action potentials. To produce flexible outputs, the heart is modulated by many neuromodulators, and the CG receives feedback from intrinsic sensory pathways. The nitric oxide negative feedback pathway decreases the heartbeat frequency, while stretch is thought to exert a positive effect and increase the heart rate. Previous studies have identified several stretch-activated channels in a variety of species. Specifically, these channels open and cause changes in membrane potential while the cell is subjected to mechanical stress. We characterized the stretch feedback response of the CG in the American lobster and aim to investigate the underlying mechanism. During the experiment, the CG and the muscles surrounding and underlying the main trunk of the CG were isolated from the whole heart. To characterize the response to stretch, one of the motor neurons was recorded intracellularly while the entire muscle bundle was stretched transversally. Subsequently, the stretch was limited to the motor neurons, and then the premotor input was removed. The response of the CG to the stretch stimulation consists of three complex stretch-phase dependent components. During the stretch extension phase, driver potentials exhibit a phase delay, which is positively correlated with the rate of change in force of stretch. During the stretch hold phase, driver potential burst duration decreases and burst frequency increases. During the stretch return phase, driver potential burst duration tends to increase back to or beyond the baseline burst duration. When stretch was removed from the premotor cells, or when the input from the

premotor cells was isolated from the motor neurons, the phase delay response disappeared, whereas the decrease in burst duration during the hold phase remained. When simple depolarizing current or hyperpolarizing current was injected into the neurons, not all of the complex characteristics of stretch responses could be reproduced, suggesting a mechanism that involves more than just a simple opening of ion channels. The differential response at each stretch phase possibly indicates a mechanism involving both a depolarizing cation channel and a hyperpolarizing potassium channel. Differential activations and time courses of these two channels may contribute to this complicated response pattern of the CG.

Disclosures: X. Qu: None. **E.S. Dickinson:** None. **K. Harmon:** None. **P.S. Dickinson:** None.

Poster

811. Rhythmic Motor Patterns: Neuromodulation

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 811.18/NN13

Topic: E.07. Rhythmic Motor Pattern Generation

Support: NIH grant NIGMS 5T32GM008396

NIH grant MH46742

Title: Effects of neuromodulation on synchronized activity of electrically coupled motor neurons with variable intrinsic properties

Authors: *B. J. LANE, D. K. WILSON, D. J. SCHULZ;
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Abstract: Neuromodulation is a ubiquitous mechanism providing short-term adaptability of network excitability, but networks must be able to maintain appropriate timing of their outputs during such shifts in output. The precisely synchronized motor neurons in the cardiac ganglion of the crab *C. borealis* can be highly variable in their underlying conductances. This potentially leaves synchrony vulnerable to perturbation when a subset of cellular conductances is pharmacologically blocked. This study extends this principle to ask whether altering a subset of cellular conductances with neuromodulation should also be expected to desynchronize network activity, or if networks are prepared to maintain stable synchrony during neuromodulation. We found that serotonin desynchronizes burst waveforms, whereas dopamine did not. Both significantly increased network burst frequency, number of spikes per burst, and spike frequency. Only dopamine targeted electrical coupling, causing a mean coupling conductance increase of ~240%. We then asked whether this modulation of electrical coupling might exert a

protective effect, and thus prevent the desynchronization induced by serotonin. Serial application of dopamine followed by serotonin, or simultaneous co-application of both modulators showed little to no change in synchrony, and often induced a “doublet” bursting phenotype characteristic of serotonin. These data indicate that networks might not be prepared to maintain synchrony in the face of neuromodulation, but that targeting electrical synapses can help to ensure synchrony is maintained during modulation.

Disclosures: **B.J. Lane:** None. **D.K. Wilson:** None. **D.J. Schulz:** None.

Poster

812. ALS: Genetic Models

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 812.01/NN14

Topic: C.05. Neuromuscular Diseases

Support: NIH MARC Training Grant T34 GM08718

NIH Grant NS078429

Himelic Family Foundation

Title: A novel *Drosophila* model of ALS based on profilin 1

Authors: ***E. N. MUNOZ**, A. COYNE, B. ZAEPFEL, S. YAO, D. ZARNESCU;
Univ. of Arizona, Tucson, AZ

Abstract: Amyotrophic lateral sclerosis (ALS) is a fatal neurodegenerative disorder that leads to death of patients usually within 2 to 5 years of diagnosis. Rare mutations in the profilin 1 gene PFN1 cause 1-2% of familial ALS, however the mechanism of pathology remains unknown. Profilin 1, a well-studied actin binding protein, is involved in multiple cellular processes, such as actin polymerization, membrane trafficking, and GTPase signaling. Efforts towards developing animal models of ALS based on profilin 1 have been made using yeast and *Drosophila*. Here we describe a novel *Drosophila* ALS model based on the expression of human wild type profilin 1, ALS-linked C71G mutant profilin 1, and synthetic mutant H120E profilin 1, in motor neurons. We utilized the Gal4/UAS system to express the proteins of interest specifically in motor neurons. A larval turning behavioral assay showed a decrease in locomotor function caused by expression of wild type, C71G and H120E profilin 1 variants compared to controls. Expression of profilin 1 variants in motor neurons altered bouton and branch number at the neuromuscular junction in a variant dependent manner. In addition wild type and mutant profilin 1 altered the localization of Futsch protein at the *Drosophila* neuromuscular suggesting defects in microtubule

stability. Ultimately, this novel *Drosophila* model affords the tools to study the mechanisms behind ALS pathogenesis caused by profilin 1 mutations and their link to other factors of disease.

Disclosures: **E.N. Munoz:** None. **A. Coyne:** None. **B. Zaepfel:** None. **S. Yao:** None. **D. Zarnescu:** None.

Poster

812. ALS: Genetic Models

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 812.02/OO1

Topic: C.05. Neuromuscular Diseases

Title: Uncovering cellular energetics at the neuromuscular junction in a *Drosophila* model of ALS

Authors: *E. MANZO[1], I. LORENZINI[4], A. G. O'CONNER[1], J. BARROWS[2], A. JOARDAR[1], R. SATTLER[4], D. C. ZARNESCU[3];
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Abstract: Amyotrophic Lateral Sclerosis (ALS), also known as Lou Gehrig's Disease, is a fatal neurodegenerative disorder affecting upper and lower motor neurons. TAR DNA-binding protein 43 (TDP-43) is found in cytoplasmic inclusions in almost all non-SOD1 mediated ALS cases and is thought to play a major role in pathogenesis of the disease. Our lab has previously shown that overexpression of either wild type or mutant human TDP-43 in motor neurons of *Drosophila* melanogaster induces motor deficits and reduces lifespan. Using this model we have performed global metabolomics profiling and identified several significant changes consistent with alterations in glucose and lipid metabolism. Specifically, increased pyruvate in both TDP^{WT} and disease associated TDP^{G298S} models is suggestive of altered glucose metabolism. We also found increased tricarboxylic (TCA) cycle intermediates and pyruvate, which are also upregulated in plasma from ALS patients. Based on these preliminary results we hypothesize that improving glucose and lipid metabolism through genetic and dietary intervention can provide protection against neurodegeneration. We employed molecular and genetic techniques to determine the basis of altered glucose metabolism. Our preliminary data indicate that a high sugar diet, or the genetic expression of either the human glucose transporters 3 or 4 (Glut3 or Glut4) in motor neurons, suppresses toxic effects caused by of TDP-43. Additionally, Glut3 expression is altered in both fly and human iPSC motor neurons (MNs). To further test whether the expression of TDP-43 affects glucose transporter dynamics, we have used total internal reflection fluorescence

(TIRF) microscopy, and found that in primary MNs expressing TDP^{WT}, there are comparable levels of Glut4-GFP at the plasma membrane immediately after insulin stimulation. In contrast, 14 min after stimulation, Glut4-GFP persists at the surface in TDP-43 expressing cells but not in controls. These data suggest Glut3/Glut4 alterations in expression and dynamics, in both both fly and C9 iPSC MNs, and are consistent with defects in glycolysis identified through metabolomics. Indeed, pfk mRNA, a key indicator of glycolytic activity is significantly upregulated in TDP-43 expressing flies and C9 iPSC MNs with TDP-43 pathology. Taken together, our findings indicate specific metabolic alterations in ALS and highlight the predictive power of *Drosophila* as a model organism for human disease.

Disclosures: E. Manzo: None. **I. Lorenzini:** None. **A.G. O'Conner:** None. **J. Barrows:** None. **A. Joardar:** None. **R. Sattler:** None. **D.C. Zarnescu:** None.

Poster

812. ALS: Genetic Models

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 812.03/OO2

Topic: C.05. Neuromuscular Diseases

Support: MDA Grant 255293 to DCZ

UBRP

Title: Altered metabolism in a tdp-43 model of als in *Drosophila*

Authors: *A. O'CONNER, E. MANZO, S. ZARNESCU, M.-B. ROBERTS, D. ZARNESCU; Univ. of Arizona, Tucson, AZ

Abstract: ALS, or amyotrophic lateral sclerosis, is a fatal progressive neurodegenerative disease for which there is currently no cure. Several genes have been linked to ALS, including TDP-43, which encodes an RNA binding protein and has been associated with the vast majority of ALS cases. While only 2-3% of ALS cases harbor mutations in TDP-43, more than 95% of patients exhibit TDP-43 positive cytoplasmic inclusions. A *Drosophila* model of ALS using both wild-type and mutant TDP-43 expression has been shown to recapitulate several pathogenic hallmarks of the disease, including motor dysfunction and decreased survival.
Because metabolic changes have been seen in ALS patients, we have investigated whether similar defects are also present in our fly model. Indeed, metabolomics studies show that, as in ALS patients, flies expressing TDP-43 in motor neurons exhibit a significant increase in pyruvate, the end product of glycolysis, and alterations in the TCA cycle. Using a larval

locomotion assay that quantifies differences in locomotor function, we have tested the effects of dietary changes on larvae expressing TDP-43 in motor neurons or glia. Increased dietary glucose appears to alleviate motor dysfunction in wild-type and mutant larvae (both in motor neuronal and glial expression), while also increasing survival time in adult flies. Consistent with these findings, expression of the glucose transporter GLUT4 in diseased larvae shows a similar improvement in motor function. Additionally, the introduction of different fats into the diet of larvae expressing TDP-43 in motor neurons appears to improve motor function at specific dosages. Taken together, these data suggest that the TDP-43 based fly model of ALS experiences specific alterations in metabolism that parallel the changes seen in patients and offer novel strategies for therapeutic and dietary intervention for ALS.

Disclosures: **A. O'Conner:** A. Employment/Salary (full or part-time): University of Arizona. **E. Manzo:** A. Employment/Salary (full or part-time): University of Arizona. **S. Zarnescu:** None. **M. Roberts:** A. Employment/Salary (full or part-time): University of Arizona. **D. Zarnescu:** A. Employment/Salary (full or part-time): University of Arizona.

Poster

812. ALS: Genetic Models

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 812.04/OO3

Topic: C.05. Neuromuscular Diseases

Support: ALS Finding A Cure

Biogen Idec

Judith and Jean Pape Adams Charitable Foundation

DEARS Foundation

Title: Knock-in dsod1 mutations cause als-like phenotypes in *Drosophila*

Authors: *A. H. HELD, P. MAJOR, D. LIPSCOMBE, K. A. WHARTON;
Brown Univ., Providence, RI

Abstract: Amyotrophic Lateral Sclerosis (ALS) is the most common adult onset motor neuron disease and results in lethality for 80% of patients within 5 years due to the lack of treatment options. ALS manifests itself in patients as a progressive loss of both upper and lower motor neurons, and thus, as a loss in mobility. In addition to motor neuron death, ALS pathologies can include the formation of protein aggregates, alterations in RNA metabolism, evidence of

oxidative stress and mitochondrial abnormalities, and defects in neurotransmission. While motor neuron death is apparent post-diagnosis, the cellular and molecular mechanisms associated with the initial stages of disease are poorly understood. We have made use of a new Drosophila ALS model produced by knocking in synonymous ALS causing mutations in the *Drosophila superoxide dismutase 1* (*dSod1*) gene (Sahin et al 2016). $dSod1^{G85R}$ mutant adults die prematurely while eclosing from their pupal case, with a disruption in abdominal neuromuscular junctions (NMJs), defective in bouton number, muscle capacitance, and mini excitatory post-synaptic potential frequency. These defects are reminiscent of late stage ALS patients that show signs of muscle atrophy and denervation, and likely contribute to the inability of these flies to eclose from the pupal case. Interestingly, earlier behavioral deficits are seen in mutant larvae as a reduction in locomotion, yet, we found no major changes in NMJ function or structure compared to controls. However, when motor neuron projections were left intact in a preparation that maintains the peristaltic muscle contractions characteristic of larval locomotion, our recordings showed that nerve activity tightly correlates with muscle contraction. In these recordings, $dSod1^{G85R}$ mutant larvae demonstrated a decrease in the frequency of nerve activity in this fictive crawling preparation. The lack of an NMJ phenotype and the decrease in peristaltic activity strongly suggests that defects outside the NMJ cause the earlier behavioral defects in this *dSod1* knock-in model of ALS. We are continuing to investigate these early phenotypes and their relation to the later neurodegenerative phenotype. We expect these studies to offer important insights into mechanisms responsible for the progression of ALS and provide possible targets for therapeutic intervention.

Disclosures: **A.H. Held:** None. **P. Major:** None. **D. Lipscombe:** None. **K.A. Wharton:** None.

Poster

812. ALS: Genetic Models

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 812.05/OO4

Topic: C.05. Neuromuscular Diseases

Support: NIH Grant NS071186

ALS Association

Title: Generation of a model for pre-symptomatic ALS in *Drosophila* by substitution of TBPH with wild type and mutant hTDP-43

Authors: *D. B. MORTON, J.-C. CHANG;
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Abstract: Amyotrophic lateral sclerosis (ALS) is a devastating neurodegenerative disease characterized by progressive paralysis caused by the loss of motor neurons. In most cases, death occurs 3-5 years after initial diagnosis. There are no current treatments available that halt or significantly slow symptoms. It is critical to the understanding of the etiology and progression of ALS to be able to diagnose the disease before there are any overt symptoms resulting from motor neuron loss. Post-mortem examination of ALS patients reveals that in most cases motor neurons are characterized by cytoplasmic inclusions that contain the RNA-binding protein, TDP-43 and a loss of nuclear localization of TDP-43. The presence of mutant forms of TDP-43 in both familial and sporadic ALS strongly suggests these mutations are causative of the disease.
Current animal models for TDP-43 dysfunction consist of either over-expression of wild type or mutant TDP-43 in a background of normal expression of endogenous TDP-43 or loss of function. Although these models have revealed the essential role of TDP-43 and the deleterious effects of its mis-regulation, they do not fully recapitulate the physiological and pathological characteristics of ALS. In an effort to generate an improved animal model for ALS and other TDP-43 proteinopathies, we used the CRISPR/cas9 targeted genome editing system to replace the endogenous TDP-43 orthologue in *Drosophila*, named TBPH, with wild type and mutant human TDP-43 (hTDP-43) keeping the endogenous regulatory domains and 3' & 5' UTRs of the TBPH gene intact. We have successfully generated flies in which the coding region of TBPH was replaced with a cDNA for wild type hTDP-43 and two ALS associated mutants hTDP-43 G294A and hTDP-43 M337V.
Real time RT-PCR using a probe to the 5' UTR of TBPH showed that the levels of wild type hTDP-43 transcript was similar to that of TBPH in control flies suggesting that the regulation of expression of hTDP-43 in flies was normal. Similarly, these flies showed unchanged survival, development times, fecundity and longevity compared to control flies. Surprisingly, flies in which TBPH was substituted for hTDP-43 G294A or hTDP-43 M337V also had no significant behavioral or developmental phenotypes. Immunoblots however, revealed the presence of high molecular weight forms of hTDP-43 in these two mutant lines and immunofluorescence of the CNS revealed non-nuclear localization of hTDP-43 that are not seen in flies expressing wild type hTDP-43. These phenotypes are characteristic of ALS post mortem tissues and as these flies do not exhibit behavioral phenotypes could be a good model for pre-symptomatic ALS.

Disclosures: D.B. Morton: None. **J. Chang:** None.

Poster

812. ALS: Genetic Models

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 812.06/OO5

Topic: C.05. Neuromuscular Diseases

Support: MIUR (SIR project RBSI14B1Z1)

Title: Effects of mGlu5 receptor genetic ablation in the SOD^{1G93A} mouse model of amyotrophic lateral sclerosis

Authors: *C. USAI[1], L. CATTANEO[2], M. MILANESE[2], T. BONIFACINO[2], M. MELONE[3], E. GALLIA[2], I. MUSANTE[4], F. CONTI[3], A. PULITI[4], G. BONANNO[2];
[1]Natl. Rese Council, Genova, Italy; [2]Dept. of Pharm. and Ctr. Excel. Biomed. Res., Univ. of Genoa, Genoa, Italy; [3]Dept. Exper. and Clin. Med., Unit Neurosci. Cell Biol., Univ. Politecnica delle Marche and Ctr. Neurobiol. of Aging, INRCA IRCCS, Ancona, Italy; [4]Dept. Neurosci., Rehabil., Ophthalm., Genet. and Maternal and Child Hlth., Univ. of Genoa and Gaslini Inst., Genoa, Italy

Abstract: Amyotrophic lateral sclerosis (ALS) is an adult-onset disease characterized by degeneration of upper and lower motor neurons (MNs). The etiology of ALS remains unknown. The mechanism of MN damage and death has been ascribed to several cellular and molecular alterations and glutamate(Glu)-mediated excitotoxicity is considered one major factor of neurodegeneration. Moreover, several studies demonstrate that damage of MNs is sustained also by pathologic changes in non-neuronal cells. Group I metabotropic glutamate receptors (mGluR1, mGluR5) are actively involved in the regulation of important cellular processes and their expression and function have been found to be altered in different experimental model of ALS. We have shown the presence of excessive Glu exocytosis in the spinal cord of SOD1^{G93A} mice, the most popular model for human ALS. This abnormal Glu release was induced by different mechanisms, including the activation of presynaptic Group I metabotropic Glu receptors. As a matter of fact, in a very recent study we demonstrated that genetic knock-down of mGluR1 in SOD1^{G93A} mice has a positive impact on disease onset and progression and on life span. In the present work we investigated the role of mGluR5 in ALS by a similar approach. With this aim we generated SOD1^{G93A} mice with half expression of mGluR5 (SOD1^{G93A}mGluR5$^{+/-}$). Kaplan Meyer analysis and behavioral tests as well as light microscopy, western blot, Glu release and fluorometric assays were executed to assess survival, clinical symptoms and biochemical and functional parameters. The down regulation of mGluR5 in SOD1^{G93A} mice induced the delay of pathology onset and a significant prolongation of life span. Surprisingly, these results were not accompanied by improved motor performances in behavioral tests. However we registered a significant preservation of spinal motor neurons, reduced astroglia and microglia activation, modification in the autophagic pathway and a normalization of the altered Glu-induced Glu release triggered by the activation of Group I mGluRs. Overall, our findings demonstrate that mGluR5 down-regulation has a significant impact *in-vivo* on ALS clinical outcome and provide a rationale for pharmacological approaches based on the selective block of Group I mGluRs.

Disclosures: **C. Usai:** None. **L. Cattaneo:** None. **M. Milanese:** None. **T. Bonifacino:** None. **M. Melone:** None. **E. Gallia:** None. **I. Musante:** None. **F. Conti:** None. **A. Puliti:** None. **G. Bonanno:** None.

Poster

812. ALS: Genetic Models

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 812.07/OO6

Topic: C.05. Neuromuscular Diseases

Support: NIH Grant NS081426

NIH Grant NS069616

Title: Meta-analysis of treatment efficacy in relation to disease progression in the G93A SOD1 mouse model of amyotrophic lateral sclerosis

Authors: *T. E. KITTEL, R. KIM, T. ZHANG, G. COAN, C. S. MITCHELL;
Biomed. Engin., Georgia Inst. of Technol., Atlanta, GA

Abstract: Amyotrophic lateral sclerosis (ALS), also known as Lou Gehrig's Disease, is a debilitating motor neuron disease with no cure; the only approved treatment, Riluzole, typically extends survival by only several months. The G93A transgenic mouse, genetically engineered to express the copper/zinc superoxide dismutase-1 (SOD1) glycine 93 to alanine mutation, is the most common ALS mouse model. The various treatments for the SOD1 G93A mouse model can be categorized as pertaining to apoptosis, axonal transport, chemistry, energetics, excitability, inflammation, oxidative stress, proteomics, or systemic approaches. A meta-analysis was performed in an effort to determine if certain treatment categories may be more effective than others at specific points during disease duration. Quantifiable results were extracted from published studies testing various treatments on the B6SJL-Tg mouse model compared to a nontransgenic control. The treatment results of over 200 peer-reviewed articles were normalized to their controls to yield over 11,000 normalized values. Prior to analysis, these values were divided into 7 different disease stages. ANOVA, in combination with the post-hoc Tukey's test, was performed for each stage across the treatment categories. Our findings demonstrate that those treatments targeting inflammation are significantly more effective than all other approaches in the very early stages of life (1-64 days). No statistically significant differences, with respect to outcome, were identified between treatments for the period preceding ALS onset (65-87 and 88-100 days). Treatments targeting excitability demonstrate superior performance at onset (101-112 days). No treatments were determined to perform significantly better than others immediately following onset (113-122, 123-140 days), but systemic approaches did yield significantly worse results during the later stages of disease progression (123-140 days). Finally, only anti-apoptotic treatments perform significantly better as the mice begin to die (140+ days). Our findings support the notion that ALS is a complicated neurodegenerative disease requiring an equally complex treatment procedure. Such a regimen would combine multiple treatments targeting different molecular mechanisms, selected on the basis of disease stage. Further research

pursuing this stage-oriented treatment approach will be necessary to refine the results of this analysis.

Disclosures: **T.E. Kittel:** None. **R. Kim:** None. **T. Zhang:** None. **G. Coan:** None. **C.S. Mitchell:** None.

Poster

812. ALS: Genetic Models

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 812.08/OO7

Topic: C.05. Neuromuscular Diseases

Support: ALS Association 15-IIP-203

Title: SOD-1 loss of function and gain of function contribute to neurodegeneration in patient allele knock-in models of familial ALS in C. elegant

Authors: ***S. N. BASKOYLU**, J. YERSAK, P. O'HERN, A. C. HART;
Neurosci., Brown Univ., Providence, RI

Abstract: Amyotrophic lateral sclerosis (ALS) is an adult-onset, progressive disease of the nervous system marked by loss of cortical glutamatergic and spinal cholinergic motor neurons. The second most common cause of familial ALS (fALS) is mutation of Cu/Zn superoxide dismutase 1 (SOD1). These mutations likely confer toxic properties: overexpression of fALS SOD1 leads to synaptic dysfunction and dramatic SOD1 aggregation (PMID:19165329), reminiscent of the final stages of motor neuron decline. However, overexpression models may obscure the potential impact of diminished fALS-SOD1 activity in neuronal dysfunction. It is therefore unclear how altered fALS-SOD1 activity affects neuronal function in early stages of disease.

Here, we examine the impact of fALS SOD1 mutations in single-copy fALS SOD1 knock in models in *C. elegans.* We introduced the equivalent ALS mutations for A4V, H71Y, L84V, G85R and G93A into the *C. elegans* SOD1 ortholog *sod-1* using MosSCI or CRISPR. We found that fALS *sod-1* alleles accelerated the aggregation of human wild-type SOD1 protein in motor neurons and that oxidative stress was sufficient to increase the aggregation of human wild-type SOD1 protein. Furthermore, oxidative stress lead to degeneration of glutamatergic neurons in both fALS *sod-1* and *sod-1* loss-of-function animals, suggesting that *sod-1* function is required for neuronal survival under oxidative stress. Intriguingly, oxidative stress lead to degeneration of cholinergic motor neurons only in fALS *sod-1* mutants but had no effect on neuronal survival in *sod-1* loss-of-function animals. Thus, exogenous stressors unmask or aggravate defects observed

in fALS *sod-1* animals and can cause neurodegeneration. Our findings further suggest that single-copy fALS SOD-1 knock in models greatly differ from models over-expressing human fALS SOD1. We conclude that both loss and gain of toxic SOD-1 function may be involved in disease pathogenesis.

Disclosures: **S.N. Baskoylu:** None. **J. Yersak:** None. **P. O'Hern:** None. **A.C. Hart:** None.

Poster

812. ALS: Genetic Models

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 812.09/OO8

Topic: C.05. Neuromuscular Diseases

Support: NIH NINDS F32 Grant F32NS089290

Target ALS

Title: Comparative analysis of the effects of genetically-altered UPR on disease pathogenesis in different mtSOD1 ALS mouse models

Authors: *Y. DZHASHIASHVILI[1], C. P. MONCKTON[2], R. B. KUNJAMMA[1], B. POPKO[1]; [1]Neurol., Univ. of Chicago, Chicago, IL; [2]Univ. of Illinois at Chicago, Chicago, IL

Abstract: Amyotrophic lateral sclerosis (ALS) is a progressive neurodegenerative disease, characterized by premature death of upper and lower motor neurons in the brain and spinal cord. The disease is ultimately fatal with no cure. Thus, there is an urgent need for a better understanding of ALS pathogenesis in order to develop effective remedies for this devastating disorder. Mutations in the Cu/Zn superoxide dismutase (SOD1) gene account for ~20% of all the familial ALS forms, corresponding to 1%-2% of all ALS cases. One of the suggested mechanisms by which mtSOD1 exerts its toxic effects involves the intracellular accumulation of abnormal mtSOD1 aggregates that trigger endoplasmic reticulum (ER) stress and activate its adaptive signal transduction pathways, including the unfolded protein response (UPR). PERK (the eIF2a kinase) is central to the UPR and is the most rapidly activated pathway in response to mis- or unfolded proteins in the ER. Our recent findings suggested that different SOD1 mutants are not equivalent in terms of their response to a genetically-altered UPR. Therefore, here we compare and contrast the response to PERK haploinsufficiency, as well as GADD34 and CHOP deficiency, in several lines of mtSOD1 transgenic mice that express known ALS mutant forms of SOD1: G93A high-copy (transgenic strain with an early disease onset that is widely used in pre-clinical ALS research), G93A low-copy (mice exhibit a delayed disease course compared to that

of G93A high-copy mice), G85R, and G37R. These studies provide a more complete understanding of how the ER stress response is involved in the survival of oligodendrocytes and motor neurons, the two key cell types that die in ALS.

Disclosures: Y. Dzhashiashvili: None. **C.P. Monckton:** None. **R.B. Kunjamma:** None. **B. Popko:** None.

Poster

812. ALS: Genetic Models

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 812.10/OO9

Topic: C.05. Neuromuscular Diseases

Support: NIH Grant NS087351

Title: Combining the hexanucleotide repeat expansion and loss of function of c9orf72 to model Amyotrophic Lateral Sclerosis in the mouse.

Authors: *L. P. BOGDANIK, L. CANTOR, A. KIEFFER, C. LUTZ;
The Jackson Lab., Bar Harbor, ME

Abstract: An abnormal (GGGGCC)n repeat expansion in the human gene C9ORF72 is the major cause of both sporadic and familial Amyotrophic Lateral Sclerosis, This discovery launched considerable efforts to create preclinical models that would recapitulate the genetic alteration and neurodegeneration observed in patient. In humans, the repeat expansion is associated with both a toxic gain-of-function originating in the repeat itself, and a partial loss-of-function of the C9ORF72 gene. Independent transgenic mouse models have been created that carry the repeat-expansion in an otherwise wild-type genetic background. They present with RNA foci and accumulation of di-peptides in the nervous system - hallmarks of the disease, but do not develop any of the clinical signs. Another set of mouse mutants with a loss of the C9ORF72 ortholog develop a complex, overt autoimmune disease but only a subtle neurodegeneration that does not result in locomotor impairment.
Here, we present a mouse mutant combining a C9ORF72 BAC transgene with repeat expansion (Jax Stock No 23099) and a loss-of-function of the murine C9ORF72 (Jax Stock No 27068), developed to better model the complex genetic mechanisms at play in ALS. The mouse originates from a transgenic carrying more than 1,000 hexanucleotide repeats expansion in the context of the complete human gene, and from a deletion of the translation start codon of the murine C9ORF72. Mice were aged up to six months, an age at which neither the transgenic nor the loss-of-function show locomotor impairments. The phenotypic assessment included nervous

system histology, in-situ hybridization for RNA foci, peripheral axon counts, electrophysiology, immune cells flow cytometry, and behavioral and locomotor testing.
This new model does not develop the sudden and fast-progressing locomotor impairment observed in more aggressive models. However, it allows to tease out the drivers from the bystanders among the molecular and cellular manifestations of the disease, and therefore to identify appropriate preclinical read-outs for the search of therapies. It also expand our understanding of C9ORF72's function in the nervous system in coping with various cellular stresses.

Disclosures: **L.P. Bogdanik:** None. **L. Cantor:** None. **A. Kieffer:** None. **C. Lutz:** None.

Poster

812. ALS: Genetic Models

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 812.11/OO10

Topic: C.05. Neuromuscular Diseases

Support: ARC DECRA DE130101591

Title: Progressive motor deficits and neuropathology in a TDP43 transgenic mouse of Amytrophic lateral sclerosis

Authors: ***Y. D. KE**, A. VAN HUMMEL, S. IPPATI, L. M. ITTNER;
Sch. of medical sciences, The Univ. of New South Wales, Unsw sydney, Australia

Abstract: Amytrophic lateral sclerosis (ALS) also known as Lou Gehrig's disease is a rapidly progressive, invariably fatal neurological disease that results from the gradual death of motor neurons. Mutations in several genes including TARDBP encoding TDP43, have been identified to make up over two thirds of all familial ALS. This nuclear transactive response DNA-binding protein 43 (TDP-43) undergoes relocalization to the cytoplasm with formation of cytoplasmic deposits in neurons in ALS and frontotemporal dementia (FTD). Pathogenic mutations in the TDP-43-encoding *TARDBP* gene in familial ALS as well as non-mutant human TDP-43 have been utilized to model FTD/ALS in cell culture and animals, including mice. We have recently reported in Acta Neuropathologica (2015) a novel A315T mutant TDP-43 transgenic mouse, iTDP-43 ^{A315T}, with controlled neuronal over-expression. In the present follow-up study of 8 month old mice, we focused on the neuropathology of spinal cord alpha-motor neurons and the progression of motor deficits. We found that constitutive expression of human TDP-43 ^{A315T} resulted in a progressive deterioration of gait, initially affecting hind limbs, before progressing to front limbs These changes in gait were captured using a digital gait analysis system (DigiGait)

which provides a comprehensive analysis of dynamic gait traits. In addition to gait anomalies, iTDP-43 ^{A315T} mice showed progressive decline in a range of motor tests, including Rotarod, challenging pole test and hanging wire test. Finally, we performed a stereological analysis of spinal cord alpha-motor neurons in aged iTDP-43 ^{A315T} mice. Immunohistological analysis of serial spinal cord sections showed cytoplasmic TDP-43 deposition together with a concomitant reduction in motor neuron numbers. In addition, we found p62-positive inclusions in a subset of neurons. Taken together, iTDP-43 ^{A315T} mice present with progressive motor deficits, associated with TDP-43 pathology in spinal cord alpha motor neurons, resembling both clinical and neuropathological features of ALS.

Disclosures: **Y.D. Ke:** None. **A. van Hummel:** None. **S. Ippati:** None. **L.M. Ittner:** None.

Poster

812. ALS: Genetic Models

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 812.12/OO11

Topic: C.05. Neuromuscular Diseases

Support: Alzheimer's Association NIRG-12-241456

NIH-NIA-K01 1K01AG042500-01A1

NIH-NIGMS INBRE 5P20GM103446

NIH-NIGMS 5P20GM103653

Delaware Economic Development Office Grant

Title: A frontotemporal dementia and motor neuron disease mouse model of TDP-43 proteinopathy

Authors: A. HARMON[1], S. DAVIS[1], K. GAN[1], *M. A. GITCHO[1,2];
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Abstract: Motor neuron disease (MND) or amyotrophic lateral sclerosis (ALS) is a neurological disorder that involves the progressive loss of motor neurons. The death of these motor neurons leads to a loss of voluntary muscle control that can affect speaking, walking, breathing, and swallowing leading eventually to death. There is currently no cure for ALS therefore understanding mechanisms associated with the progression of this disease is crucial to developing a treatment. Transactive response DNA binding protein of 43kda (TDP-43) functions

as a heterogeneous nuclear ribonucleoprotein (hnRNP) and is the major pathological protein in frontotemporal dementia (FTD, 50%) and sporadic ALS (95%). Mutations in TDP-43 account for ~5% of familial ALS cases. In a subset of cases with TDP-43 proteinopathy, patients clinically display both frontotemporal temporal dementia and motor deficits (FTD-MND). We have characterized an age-dependent decrease in motor function associated with pathological changes in mice selectively driving expression of the TDP-43 A315T familial mutation and TDP-43 nuclear localization defective (αNLS) in spinal cord and brain. In addition, TDP-43 αNLS mice show signs of anxiety similar to those with frontotemporal dementia. These models may provide a better understanding of TDP-43 proteinopathies leading to the development of therapeutics to target these devastating diseases.

Disclosures: **A. Harmon:** None. **S. Davis:** None. **K. Gan:** None. **M.A. Gitcho:** None.

Poster

812. ALS: Genetic Models

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 812.13/OO12

Topic: C.05. Neuromuscular Diseases

Support: Weston Brain Institute RR130306

ALS Canada Graduate Scholarship

Title: Knockin of point mutations using the CRISPR/Cas9 system and HDR to generate ALS missense mutations in zebrafish tardbp and fus.

Authors: *G. A. ARMSTRONG[1], A. LISSOUBA[2], P. DRAPEAU[3];
[1]Dept. of Pathology and Cell biology, ?CRCHUM, Montreal, QC, Canada; [2]CRCHUM, Montreal, QC, Canada; [3]Département de Neurosciences, CRCHUM, Montreal, QC, Canada

Abstract: The methodology for site-directed editing of single nucleotides in the vertebrate genome is of considerable interest for research in biology and medicine. The clustered regularly interspaced short palindromic repeats (CRISPR)/CRISPR-associated protein 9 type II (Cas9) system has emerged as a simple and inexpensive tool for editing genomic loci of interest in a variety of animal models. In zebrafish, error-prone non-homologous end joining (NHEJ) has been used as a simple method to disrupt gene function, however DNA repair by NHEJ has limited value for generating specific single nucleotide polymorphisms (SNPs). We sought to develop a method to easily create site-specific SNPs in the zebrafish genome. Here, we report simple methodologies for using CRISPR/Cas9-mediated homology directed repair (HDR) using

single-stranded oligodeoxynucleotide donor templates (ssODN) for site-directed single nucleotide editing in zebrafish *tardbp* and *fus*. Mutations in *TARDBP* and *FUS* are associated with amyotrophic lateral sclerosis (ALS). Using CRISPR/Cas9-mediate HDR we generated the analogous missense mutations *tardbp*^{A379T} (*TARDBP*^{A382T}), *tardbp*^{G347C} (*TARDBP*^{G348C}), and *fus*^{R536H} (*FUS*^{R526H}) mutations.

Disclosures: **G.A. Armstrong:** None. **A. Lissouba:** None. **P. Drapeau:** None.

Poster

812. ALS: Genetic Models

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 812.14/OO13

Topic: C.05. Neuromuscular Diseases

Title: Novel targets for modulation of plasticity in a mouse model of motoneuron degeneration

Authors: R. GULINO[1], S. FORTE[2], R. PARENTI[1], *M. GULISANO[1];
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Abstract: A successful spinal cord repairing strategy should involve the activation of neural precursor cells. Unfortunately, their ability to generate neurons after injury appears limited. Another process promoting functional recovery is synaptic plasticity. We have previously studied some mechanisms of spinal plasticity by using a mouse model of motoneuron depletion induced by cholera toxin-B saporin. TDP-43 is a nuclear RNA/DNA binding protein involved in amyotrophic lateral sclerosis. Although considerable attention has been devoted to the toxic effects of the TDP-43 cytoplasmic aggregates, the functional role of this factor remains poorly investigated. Notably, TDP-43 is present in the dendrites where it behaves as a modulator of local RNA translation. Moreover, it is crucial for synaptic plasticity and locomotion in Drosophila. Here, we would like to deepen the investigation of this model of spinal plasticity. After lesion, we observed a glial reaction and an activity-dependent modification of Synapsin-I, Shh, Noggin, Numb and TDP-43 proteins. Multivariate regression was used to model the possible association between these proteins, as well as with the motor performance. We found that Shh and Noggin could affect motor performance and that these proteins could be associated with both TDP-43 and Numb, thus suggesting that TDP-43 is likely an important regulator of synaptic plasticity. Given the well-known role of morphogens such as Shh, Noggin and Numb in neurogenesis and the above described functions of TDP-43, we believe that an in vivo manipulation of their signaling pathways after lesion could represent a putative method of improving regeneration and recovery by affecting synaptic plasticity and/or neurogenesis.

Disclosures: **R. Gulino:** None. **S. Forte:** None. **R. Parenti:** None. **M. Gulisano:** None.

Poster

812. ALS: Genetic Models

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 812.15/OO14

Topic: C.05. Neuromuscular Diseases

Title: Mice lacking Death Receptor 6 (Tnfrsf21) develop spontaneous, progressive motor neuron degeneration

Authors: B. IKIZ, M. SCHANER, S. D. CROLL, Y. BAI, W. FURY, M. G. DOMINGUEZ, B. ZAMBROWICZ, N. STAHL, A. J. MURPHY, L. E. MACDONALD, *M. L. LACROIX-FRALISH;
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Abstract: Amyotrophic lateral sclerosis (ALS) is the one of the most frequent adult-onset paralytic disorders, characterized by the loss of upper and/or lower motor neurons. A number of transgenic rodent models carrying mutations that cause familial ALS have been created and have been shown to mimic the disease to various extents. Here we report a novel finding that deletion of the Death Receptor 6 (DR6, Tnfrsf21) gene in mice produces a spontaneous disease in mice that shares many hallmarks of ALS.
Death Receptor 6 is a type 1 transmembrane protein member of the tumor necrosis factor receptor superfamily and is highly expressed in lymphoid organs, brain, heart, kidney and pancreas. The Death Receptor family members are well described for their role in mediating ligand-dependent apoptosis in various cell types, although much less is known about DR6 in this regard. Our thorough behavioral assessment of *Tnfsf21*$^{-/-}$ mice unexpectedly showed severe upper and lower motor neuron dysfunction characterized by tremor, significant hind limb paresis, gait impairment and motor incoordination starting at around 13 weeks of age. Most of the mice progressed to complete paralysis and a significant number of mice died at around 21 weeks of age. Spinal cord histology from these mice at 20 weeks showed significant loss of ventral horn alpha motor neurons. In order to begin to understand the pathological mechanisms involved we performed RNASeq analysis on brain and spinal cord tissues from pre-symptomatic mice and end-stage disease *Tnfsf21*$^{+/-}$ or *Tnfsf21*$^{-/-}$ mice compared to *Tnfsf21*$^{+/+}$ mice. We further investigated the mechanisms involved in the observed motor neuron degeneration in a series of studies using mouse embryonic stem cell-derived motor neurons lacking *Tnfsf21*. Using this system we observed cell autonomous motor neuron death, involving oxidative stress, mitochondrial dysfunction and enhanced glutamate excitotoxicity. All of these findings taken

together suggest that *Tnfsf21*$^{-/-}$ mice may be a promising new model to study and understand the pathological mechanisms of motor neuron diseases.

Disclosures: **B. Ikiz:** None. **M. Schaner:** A. Employment/Salary (full or part-time): Regeneron Pharmaceuticals, Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Regeneron Pharmaceuticals, Inc. **S.D. Croll:** A. Employment/Salary (full or part-time): Regeneron Pharmaceuticals, Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Regeneron Pharmaceuticals, Inc. **Y. Bai:** A. Employment/Salary (full or part-time): Regeneron Pharmaceuticals, Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Regeneron Pharmaceuticals, Inc. **W. Fury:** A. Employment/Salary (full or part-time): Regeneron Pharmaceuticals, Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Regeneron Pharmaceuticals, Inc. **M.G. Dominguez:** A. Employment/Salary (full or part-time): Regeneron Pharmaceuticals, Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Regeneron Pharmaceuticals, Inc. **B. Zambrowicz:** A. Employment/Salary (full or part-time): Regeneron Pharmaceuticals, Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Regeneron Pharmaceuticals, Inc. **N. Stahl:** A. Employment/Salary (full or part-time): Regeneron Pharmaceuticals, Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Regeneron Pharmaceuticals, Inc. **A.J. Murphy:** A. Employment/Salary (full or part-time): Regeneron Pharmaceuticals, Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Regeneron Pharmaceuticals, Inc. **L.E. Macdonald:** A. Employment/Salary (full or part-time): Regeneron Pharmaceuticals, Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Regeneron Pharmaceuticals, Inc. **M.L. LaCroix-Fralish:** A. Employment/Salary (full or part-time): Regeneron Pharmaceuticals, Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Regeneron Pharmaceuticals, Inc..

Poster

812. ALS: Genetic Models

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 812.16/PP1

Topic: C.05. Neuromuscular Diseases

Title: CRISPR/Cas9 genome editing in the zebrafish Danio rerio as a tool to examine ALS-associated gene function in motor neurons.

Authors: *C. SMITH[1], L. LABOISSONNIERE[2], R. CHOWDURY[2], M. LYNCH[3], M. SIERRA[1], J. TRIMARCHI[2];
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Abstract: Amyotrophic lateral sclerosis (ALS) is a progressive neurodegenerative disease characterized by the deterioration of motor neurons. The pathogenesis of ALS is largely undefined; however, recent exome-sequencing projects have uncovered new genes with mutations that are linked to familial or sporadic cases. The identification of these genes provides an opportunity to better understand the underlying mechanisms of the disease. The current challenge is to understand the *in vivo* function of these genes, with the hope that this insight will shed light on their connection to ALS pathology. To determine the functional roles of ALS-associated genes, we have chosen to employ the zebrafish as our model. A number of our candidate genes have multiple isoforms remaining in the zebrafish as a result of a genome duplication millions of years ago. We first examined the expression of a cohort of ALS-linked genes using *in situ* hybridization. This allowed us to identify which genes are localized to motor neuron populations, as well as to establish those isoforms with significant differences in their expression locations. Upon identifying those genes with selective expression in the nervous system, we chose to utilize genome editing technology to engineer mutations in the zebrafish. To begin our investigation of ALS-associated gene function, we have designed clustered regulatory interspaced short palindromic repeats (CRISPRs) and engineered targeted mutations in a number of these ALS-linked genes in zebrafish. In these ongoing studies, we are characterizing fish homozygous for the different CRISPR-induced mutations. Additionally, to more easily visualize any motor neuron defects, we are also crossing these mutants into an *mnx1*:GFP transgenic background. The presence of the GFP will enable us to clearly observe the effects of protein loss on motor neuron development and degeneration. These experiments will provide insights into the function of these genes in motor neuron development and, we hope, ultimately reveal how their dysfunction leads to motor neuron death.

Disclosures: C. Smith: None. **L. Laboissonniere:** None. **R. Chowdury:** None. **M. Lynch:** None. **M. Sierra:** None. **J. Trimarchi:** None.

Poster

812. ALS: Genetic Models

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 812.17/PP2

Topic: E.10. Motor Neurons and Muscle

Support: UAMS startup funds

UAMS College of Medicine Research Council

NIGMS IDeA awards P30 GM110702

P20GM109005

NINDS R21NS088653

Title: Transcriptome analysis of mutant hPFN1 mouse model of ALS

Authors: *D. FIL, A. DELOACH, D. ALKAM, M. KIAEI;
Neurobio. and Developmental Sci., Univ. of Arkansas For Med. Sci., Little Rock, AR

Abstract: Amyotrophic lateral sclerosis (ALS) is a progressive motor neuron disorder resulting in paralysis of voluntary muscles and eventually leading to death. The mechanism of neuronal degeneration and muscle atrophy in ALS is poorly understood. Familial ALS (fALS) cases have been associated with a set of gene mutations (e.g., SOD1, TARDBP, FUS/TLS, OPTN, UBQLN2, VCP, hnRNPA2B1, hnRNPA1, TBK1, TUBA4A and C9ORF72). Identification of these genes points toward specific pathogenic processes and hints at specific mechanism of motor neuron death. Recent association of mutated cytoskeletal regulating protein, profiln1 (PFN1)[1-3], in 25 families with fALS cases implicate actin dynamics as a factor in the disease onset and progression. To investigate the pathogenicity of mutant hPFN1 *in vivo* and explore the role of cytoskeletal disruption in ALS, we generated mutant hPNF1^{G118V} transgenic mice. As previously reported these animals recapitulate key clinical and pathological features of ALS. We have employed the NextGen sequencing and analyzed spinal cords for changes in transcriptome as a result of mutant hPFN1^{G118V} expression. We have identified gene candidates affected at the onset and throughout progression of ALS. Our preliminary findings with Gene Set Enrichment (GSE) analysis from RNAseq data generated from total spinal cord RNA from mutant PFN1 and controls indicate an array of genes as possible players in cytoskeletal disruption and motor neuron dysfunction (i.e. Immune response, antigen processing and presentation, regulation of TNF production, apoptosis). We will present data to validate key genes that can sheds the light on the mechanism and overall changes associated with the pathology and identify potential targets for investigation.
References: ADDIN EN.REFLIST 1 Wu, C. H. *et al.*. *Nature* **488**, 499-503 (2012). 2 Ingre, C. *et al. Neurobiology of aging* **34**, 1708 e1701-1706 (2013). 3 Smith, B. N. *et al. Neurobiology of Aging* (2015) **36**(3). 1602e17-27.

Disclosures: D. Fil: None. **A. DeLoach:** None. **D. Alkam:** None. **M. Kiaei:** None.

Poster

813. Neuroendocrine Anatomy and Physiology

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 813.01/PP3

Topic: F.03. Neuroendocrine Processes

Support: R01-NS38809

R01-NS43330

R01-DK68098

F32 DK104366

Title: Sex differences in glutamatergic output from arcuate kisspeptin neurons to POMC and AgRP neurons

Authors: *J. QIU[1], M. A. BOSCH[1], C. C. NESTOR[1], S. L. PADILLA[2], R. D. PALMITER[2], M. J. KELLY[1,3], O. K. RØNNEKLEIV[1,3];
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Abstract: Kisspeptin (Kiss1) neurons in the hypothalamic arcuate nucleus ($Kiss1^{ARH}$) co-express Kiss1, neurokinin B and dynorphin all of which are down regulated in females in the presence of elevated physiological levels of circulating 17β-estradiol (E2). $Kiss1^{ARH}$ neurons also co-express vesicular glutamate transporter 2 (vGluT2), which was recently found to be reduced in gonad-intact compared to castrated male mice (Nestor *et al., Molecular Endocrinology* 2016). To explore a potential E2 regulation of vGluT2 expression in females, we dispersed and harvested pools of $Kiss1^{ARH}$ neurons from ovariectomized (OVX) and OVX + E2-treated mice and used real-time PCR for quantitative analysis of changes in gene expression. In contrast to the peptide neurotransmitters, mRNA that encodes for vGluT2 was increased in $Kiss1^{ARH}$ neurons in E2-treated females by 2-fold ($p<0.01$). We then explored the effects of E2 treatment on $Kiss1^{ARH}$ -mediated glutamate release onto POMC and AgRP neurons using optogenetics and whole-cell recording in hypothalamic slices. Light stimulation of $Kiss1^{ARH:ChR2}$ neurons evoked a fast glutamatergic response in both POMC and AgRP neurons in slices from OVX and E2-treated females. Using a paired-pulse protocol (two 5 ms light stimulations separated by 50 ms) we found that E2 treatment increased the probability of glutamate release from $Kiss1^{ARH}$ neurons by ~ 2-fold onto both POMC and AgRP neurons. Together, these studies illustrate a clear sex difference in the glutamatergic output from $Kiss1^{ARH}$ neurons to POMC and AgRP neurons,

which may, in part, underlie the differential effect of gonadal steroids on feeding behavior between males and females.

Disclosures: **J. Qiu:** None. **M.A. Bosch:** None. **C.C. Nestor:** None. **S.L. Padilla:** None. **R.D. Palmiter:** None. **M.J. Kelly:** None. **O.K. Rønnekleiv:** None.

Poster

813. Neuroendocrine Anatomy and Physiology

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 813.02/PP4

Topic: F.03. Neuroendocrine Processes

Support: CIHR Grant 394324

Title: Influence of sex and sexual maturity on prolactin receptor expression in the rat subfornical organ

Authors: ***A. KAMESH**, A. V. FERGUSON;
Queen's Univ., Kingston, ON, Canada

Abstract: Prolactin is a peptide hormone with over 300 biological functions including those that require binding to prolactin receptor (PRL-R) in neurons within the brain (Bole-Feysot et al., 1998). In order to enter the brain, circulating prolactin must overcome the lipophilic blood-brain barrier. As such, areas of the brain that do not possess a blood-brain barrier, such as the subfornical organ (SFO), may be especially sensitive to systemic prolactin levels. Circulating prolactin is different across sexes, before and after sexual maturity is reached; and in females, across the estrous cycle (Dohler and Wuttke, 1975; Nequin et al. 1979; Silveyra et al., 2007). The goal of this study is to characterize PRL-R expression at the SFO in Sprague Dawley rats and compare expression between males and females, juveniles and adults, and across the estrous cycle. Real-time quantitative PCR (RT-qPCR) was used to determine expression levels of PRL-R mRNA by initial reverse transcription of the mRNA into cDNA for RT-qPCR analysis. The data were then normalized to the housekeeping gene glyceraldehyde 3-phosphate dehydrogenase and compared. Average PRL-R mRNA expression levels are not found to be significantly different between males and females, in both the juvenile and adult comparison groups ($p>0.79$). PRL-R mRNA expression in females at the SFO is 7.4-fold higher in adults as compared to juvenile female rats ($p<0.01$) and in males, trends towards 3-fold higher expression in adulthood ($p=0.17$). Differences in PRL-R mRNA expression at the SFO may also occur over the estrous cycle in females; while values trend towards high PRL-R mRNA expression during proestrous and reduced levels during diestrous, these differences are not significant ($p>0.40$). Thus, PRL-R

binding at the SFO likely share similar features in males and females, may be dependent on the sexual maturity of the animal and may be influenced by estrous cyclicity.

Disclosures: **A. Kamesh:** None. **A.V. Ferguson:** None.

Poster

813. Neuroendocrine Anatomy and Physiology

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 813.03/PP5

Topic: F.03. Neuroendocrine Processes

Support: CONACYT 45680

Title: The TRPV1 receptors are modulated by estradiol and progesterone in the ovary of guinea pig

Authors: ***V. ALATRISTE**[1,2], I. MARTÍNEZ[1], D. I. LIMÓN[1], L. MARTÍNEZ[1], I. HERRERA-CAMACHO[1], F. LUNA[1], O. GONZÁLEZ-FLORES[2];
[1]BUAP, Puebla, Mexico; [2]CIRA, CINVESTAV-UAT, Tlaxcala, Mexico

Abstract: We have reported that TRPV1 receptors modulate the ovarian follicular development and the onset of puberty in guinea pig. However, it is litter known if modulation of that receptor is dependent on the effects of estradiol or/and progesterone. The goal of the present study was to determine whether the estradiol, progesterone or a combination of both steroids (estradiol+progesterone) can modulate the expression of the TRPV1 in the ovarian follicles cells. Twenty four infantile guinea pigs (10 days old) divided in 4 groups (n=6) were used in this study. Group 1: vehicle (sesame oil); Group 2: 5 µg/kg of estradiol (E); Group 3: 2 mg/kg progesterone (P,); Group 4: 5 µg/kg E+2mg/kg P, all compound were administered subcutaneously. At 16 days old, the guinea pigs were sacrificed with CO_2 and the ovaries were collected. Later, histological slides were made and stained with H&E for counting ovarian follicles. Others histological slides were used for immunohistochemistry and to quantity the TRV1-positive ovarian follicular cells. We found that the number of secondary and tertiary follicles increased with E and E+P treatment, but not the animals that received only P. In addition, the numbers of TRPV1-positive cells increased in both theca and interstitial cells of the ovaries but not in the atretic follicles. Our results showed that only the treatment with E or with E+P stimulate the TRPV1 receptors expression and increase the ovarian follicular development.

Disclosures: **V. Alatriste:** None. **I. Martínez:** None. **D.I. Limón:** None. **L. Martínez:** None. **I. Herrera-Camacho:** None. **F. Luna:** None. **O. González-Flores:** None.

Poster

813. Neuroendocrine Anatomy and Physiology

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 813.04/PP6

Topic: F.03. Neuroendocrine Processes

Support: DGAPA-UNAM (PAPIIT IN206712)

DGAPA-UNAM (PAPIIT IN206416)

CONACYT (CB 154931)

Title: A switch in RNA transcript levels down-regulates the activity of the thyrotropin-releasing hormone-degrading ectoenzyme in primary cultures of tanycytes

Authors: A. RODRÍGUEZ-RODRÍGUEZ, A. COTE-VÉLEZ, B. URRIETA-CHÁVEZ, P. JOSEPH-BRAVO, *J.-L. CHARLI;
Inst. de Biotecnología, Univ. Nacional Autonoma de Mexico (UNAM), Cuernavaca, Mexico

Abstract: The activity of the hypothalamus-pituitary-thyroid (HPT) axis sets systemic thyroid hormones (TH) levels. In this axis, neurons of the paraventricular nucleus of the hypothalamus release thyrotropin-releasing hormone (TRH) into the extracellular space of the median eminence, from where it reaches, through portal vessels, the anterior pituitary. Tanycytes, a population of specialized glial cells implicated in barrier functions lining the ventral part of the third ventricle, express *in vivo* high levels of pyroglutamyl peptidase II (PPII), the TRH-degrading ectoenzyme. These cells include β2-tanycytes, which send, through the median eminence, cytoplasmic projections that end in the vicinity of TRH nerve terminals and portal capillaries. Although PPII is broadly distributed in the brain, signals that decrease HPT axis activity, as systemic administration of thyroid hormones or fasting, increase the activity of PPII specifically in the median eminence, suggesting that tanycyte PPII limits the amount of TRH released to the anterior pituitary, providing an additional mechanism to control HPT axis activity. This suggestion has been substantiated experimentally, since PPII inhibition can increase serum thyrotropin concentration. β-tanycytes are in contact with a large repertoire of signals, since median eminence is a blood brain barrier-free area. Apart from TH, signals that regulate expression and activity of PPII, and hence HPT axis activity are unknown. To identify new regulators of PPII, we established primary cultures of tanycytes from median eminences of 10 days old Wistar rats, in serum supplemented medium. Primary cultures showed the tanycyte markers nestin, vimentin and DARPP-32 by immunofluorescence. Although cultures expressed PPII mRNA, we couldn't detect PPII activity in basal conditions, nor in cultures treated with TH, or with a low-glucose medium exposure. We found that tanycyte cultures expressed less of the complete PPII isoform than of the truncated isoform of PPII, which exerts a dominant negative

effect over the complete isoform. This result differs from the *in vivo* status since median eminence of 10 or more days old rats showed substantial PPII activity, and a lower expression of the truncated isoform than of the complete isoform. Therefore, *in vitro* conditions switch the balance between both PPII isoforms, favoring the expression of the truncated isoform. These data suggest caution is required to interpret results with tanycytes in primary culture, since they may show altered expression of key regulators of HPT axis.

Disclosures: A. Rodríguez-Rodríguez: None. **A. Cote-Vélez:** None. **B. Urrieta-Chávez:** None. **P. Joseph-Bravo:** None. **J. Charli:** None.

Poster

813. Neuroendocrine Anatomy and Physiology

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 813.05/PP7

Topic: F.03. Neuroendocrine Processes

Title: The neural regulation of thyroid and parathyroid glands

Authors: *H. HOTTA[1], A. ONDA[1], H. SUZUKI[1], A. SRIDHAR[2], K. FAMM[2];
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Abstract: Thyroid and parathyroid glands receive dual innervation by sympathetic (cervical sympathetic nerve: CST) and parasympathetic (superior laryngeal nerve: SLN) nerve fibers. Blood flow of the glands is reciprocally regulated by these dual innervation. Hormones secreted from the glands are known to be regulated by humoral factors, and possibility of neuronal regulation by the autonomic nerves has been suggested by pharmacological and denervation experiments. We aimed to examine effects of electrical stimulation of efferent or afferent nerve fibers innervating thyroid and parathyroid glands on secretion of 3, 3', 5-triiodothyronine (T3), thyroxine (T4), calcitonin (CT) and parathormone (PTH) from thyroid and parathyroid glands in rats, to identify the optimal parameters of electrical stimulation for selective hormone release. Adult male rats were anesthetized and artificially ventilated. Animal's respiration and core body temperature was maintained at physiological levels. The thyroid venous blood and systemic arterial blood was collected. Concentration of hormones in these blood plasma was measured by ELISA. Secretion rates of hormones from the glands were calculated from the plasma concentrations and flow rates of thyroid venous plasma. SLNs or CSTs were stimulated bilaterally with a rectangular pulses of 0.5 ms pulse width. Firstly, to define role of efferent nerve fibers, stimulation was applied to cut peripheral segments using bipolar hook electrodes with a supramaximal intensity to excite all nerve fibers, at various frequencies (upto 40 Hz).

Secretion rates of CT and T4 were increased or decreased, respectively, during stimulating SLNs or CSTs. Secretion rate of PTH was increased during CST stimulation, but was not consistently affected during SLN stimulation. T3 secretion was not affected during either stimuli. Secondly, we examined effects of selective stimulation of afferent nerve fibers in the SLN. Using cuff electrodes, stimulation was applied to intact SLNs with a subthreshold intensity for efferent nerve fibers. Secretion rates of CT and T4 increased during stimulation of intact SLNs at 40 Hz. The results suggest that excitation of myelinated afferents induced by low-intensity and high frequency stimulation of intact SLNs promote secretion of both CT and T4 from thyroid gland, probably via reflex activation of parasympathetic efferent nerve fibers in SLN.

Disclosures: **H. Hotta:** B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution; GSK Bioelectronics Exploratory Funding. **A. Onda:** None. **H. Suzuki:** None. **A. Sridhar:** None. **K. Famm:** None.

Poster

813. Neuroendocrine Anatomy and Physiology

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 813.06/PP8

Topic: F.03. Neuroendocrine Processes

Support: Hungarian National Brain Research Program (NAPA1/3)

Hungarian Science Foundation (OTKA K109710)

Title: Investigation of the glycinergic innervation of TRH neurons in the hypothalamic paraventricular nucleus

Authors: E. VARGA[1], E. FARKAS[1], G. ZSÉLI[1], M. WATANABE[2], H. U. ZEILHOFER[3], R. M. LECHAN[4,5], *C. FEKETE[1,4];
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Abstract: Glycine (Gly) is a classical neurotransmitter that has role in both inhibitory and excitatory synapses. Glycinergic neurons are primarily located in the brainstem and spinal cord,

but ascending glycinergic projections are also involved in the regulation of forebrain neurons. To understand whether glycinergic inputs are involved in the regulation of the hypophysiotropic thyrotropin-releasing hormone (TRH) neurons, the glycinergic innervation of the TRH-synthesizing neurons in the paraventricular nucleus (PVN) and the effect of Gly on the electrophysiological properties of these cells were studied.
Double-labeling immunocytochemistry for TRH and Gly transporter 2 (GlyT2), a marker of glycinergic neurons, demonstrated that GlyT2-immunoreactive (IR) axons established contacts with 53±2% of TRH neurons in the PVN. Symmetric type synaptic associations were observed between the GlyT2-IR varicosities and the TRH neurons. Presence of glycine receptor-immunoreactivity were also observed in the TRH neurons.
Using retrograde tract tracing in GlyT2-GFP mice, we have shown that the glycinergic input of the PVN originates exclusively from two brain regions, the raphe magnus (RMg) and the ventrolateral periaqueductal gray (VLPAG). By virus mediated expression of reporter protein in the glycinergic neurons of the RMg and VLPAG of GlyT2-Cre mice, we have demonstrated that both of these nuclei are involved in the glycinergic innervation of the TRH neurons within the PVN.
Next, we used patch clamp electrophysiology to investigate the effect of Gly on TRH neurons in TRH-GFP mice. Application of Gly (2 mM) markedly decreased the membrane potential and completely blocked the firing of the TRH neurons. To understand whether this effect of Gly is exerted directly on the TRH neurons, the effect of Gly was also studied in the presence of TTX. Application of Gly decreased resting membrane potentials of TRH neurons from -49.6±2% to -63.0±3% even in the presence of TTX. Effect of Gly was prevented by strychnine (2 μM) in all cases.
Our data demonstrate that the TRH neurons in the PVN receive glycinergic inputs from the RMg and the VLPAG. The symmetric type synaptic connection and the results of electrophysiological experiments demonstrate the inhibitory nature of these inputs.

Disclosures: **E. Varga:** None. **E. Farkas:** None. **G. Zséli:** None. **M. Watanabe:** None. **H.U. Zeilhofer:** None. **R.M. Lechan:** None. **C. Fekete:** None.

Poster

813. Neuroendocrine Anatomy and Physiology

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 813.07/PP9

Topic: F.03. Neuroendocrine Processes

Support: DGAPA-UNAM (PAPITT IN208515)

Title: Thyrotropin-releasing hormone neurons of the dorsomedial nucleus of the hypothalamus and energy balance

Authors: K. VARGAS ORIHUELA[1], L. JAIMES-HOY[1], H. URBINA[1], E. SÁNCHEZ-JARAMILLO[2], *P. I. JOSEPH-BRAVO[1], J.-L. CHARLI[1];
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Abstract: In mammals, multiple brain circuits contribute to the maintenance of energy balance. Central administration of thyrotropin-releasing hormone (TRH) or TRH agonists reduces food intake in normal rodents and hungry rats. These effects may involve hypothalamic targets, since local injection of TRH into medial and lateral hypothalamus (LH) reduces feeding behavior in rats. Apart from the hypophysiotropic TRH neurons of the paraventricular nucleus of the hypothalamus, various additional groups of TRH neurons are present in the hypothalamus, and TRH receptors are expressed in multiple hypothalamic nuclei. However, the circuits in which these TRH neurons are involved are poorly understood. The dorsomedial nucleus of the hypothalamus (DMH) has an important role in energy homeostasis. In this region, a significant population of TRH neurons receives afferents from the subparaventricular zone, an output region of the suprachiasmatic nucleus. The DMH sends glutamate-TRH projections to the LH, which expresses both TRH receptors, predominantly TRH-R1. TRH exerts an indirect inhibition of the firing rate of melanin-concentrating hormone (MCH) neurons of LH through the activation of GABA neurons. This result is consistent with the detection of TRH axons terminating on or near LH GABA neurons. Since MCH neurons send orexigenic projections, the TRHergic DMH-LH projection may transmit anorexic signals through these GABAergic neurons. The purpose of this project was to determine whether the TRHergic DMH-LH projection senses energy balance changes. We used RT-PCR, immunocytochemistry and *in situ* hybridization to analyze the functional state of the projection. Fasting decreased TRH expression in the DMH of In female rats. In male rats, fasting enhanced TRH-R1 expression in the LH. In adult mice, fasting for 24 h reduced, while refeeding strongly enhanced, the number cFOS positive cells in all areas of the DMH. These data suggest that the TRHergic DMH-LH projection senses energy balance.

Disclosures: K. Vargas Orihuela: None. **L. Jaimes-Hoy:** None. **H. Urbina:** None. **E. Sánchez-Jaramillo:** None. **P.I. Joseph-Bravo:** None. **J. Charli:** None.

Poster

813. Neuroendocrine Anatomy and Physiology

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 813.08/PP10

Topic: F.03. Neuroendocrine Processes

Support: CONICET PIP 0863/12

Title: Hyperthyroidsm modulates hypotalamic Tyrosine Hydroxilase activity and PRL signaling during late pregnancy and early lactacion in rats.

Authors: *G. E. PENNACCHIO[1,2,3], C. ACOSTA[4,5], A. SELTZER[4], M. SOAJE[2,5], G. A. JAHN[2], S. R. VALDEZ[2,3];
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Abstract: Thyroid disorders compromise fertility in women of reproductive age and cause pregnancy disorders and lactation failure. Prolactin (PRL) is essential for female reproduction. The main regulator of PRL secretion is dopamine, produced by the dopaminergic neurons located in the medial basal hypothalamus (MBH). To explore if hyperthyroidism affects PRL secretion through alterations of the hypothalamic dopaminergic systems, we studied the effect of T4 treatment on hypothalamic expression of Tyrosine hydroxylase (TOH, the rate-limiting enzyme for dopamine synthesis), PRL receptor (PRLR), members of the PRL signaling pathway (STAT, SOCS, CIS), in MBH during late pregnancy and early lactation. We also studied this neurons express thyroid receptors by immunofluorescence (IF). Wistar control (Co: vehicle-treated) and hyperthyroid (HyperT: T_4 sc, 250 µg/kg/day) rats were mated 8 days after the start of treatment and sacrificed at days 19 (G19), 20 (G20), 21 (G21) of pregnancy and day 2 of lactation. Total RNAs were extracted from MBH and the mRNA expression was measured using real time PCR. In control rats, the mRNA expression of PRLR long, STAT5b, SOCS3, SOCS1 and CIS showed similar patterns of variations between late pregnancy and early lactation. HyperT rats showed a similar pattern but PRLR and SOCS3 mRNAs. STAT5 protein varied in parallel with changes in PRLR mRNA in both groups; the protein level decreased from G19 to G20 and remained low thereafter in controls while in the HyperT group values were significantly higher than controls in G19 and L2. CIS protein levels increased in controls at G20 and fell afterwards to levels similar to G19, while in the HyperT group CIS was significantly higher at G19 compared with controls and declined afterwards to values similar to controls. In controls,TOH mRNA and protein values diminished from G19 to G21 and remained low on L2. In HyperT rats TOH mRNA was similaar to controls on G19 and G20 but significantly higher on G21 and L2. HyperT decreased significantly TOH protein at G19 and G20. In control rats, p-TOH declined slowly from G20 to L2. HyperT increased significantly p-TOH on G19 and L2 compared with the controls. IF showed that TOH+ neurons also express TRβ, suggesting a possible direct action of THs on these neurons. Conclusion: the activity of hypothalamic neurons that regulate PRL secretion is affected by the HyperT, resulting in increased PRL signaling and TOH activation on G19 and L2. This pattern can be correlated with the advancement in the antepartum PRL peak followed by impaired PRL secretion during lactation previously observed in HyperT rats, that compromises the hyperprolactinemia necessary for a successful lactation.

Disclosures: **G.E. Pennacchio:** None. **C. Acosta:** None. **A. Seltzer:** None. **M. Soaje:** None. **G.A. Jahn:** None. **S.R. Valdez:** None.

Poster

813. Neuroendocrine Anatomy and Physiology

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 813.09/PP11

Topic: F.03. Neuroendocrine Processes

Support: Starting Investigator Grant from the ERC (ENDOSWITCH 261286)

Swedish Research Council (2014-3906)

Novo Nordisk Fonden

the Strategic Research Programme in Diabetes at Karolinska Institutet.

Hjärnfonden

Title: Adaptive resetting of tuberoinfundibular dopamine (TIDA) neuronal network activity in lactation and other reproductive states

Authors: ***C. T. PEREZ**, A. HELLYSAZ, J. VAN LUNTEREN, C. BROBERGER; Karolinska Inst., Stockholm, Sweden

Abstract: Reproduction requires a series of appropriately timed adaptive physiological changes. A key mediator of such changes is the pituitary hormone, prolactin. Blood prolactin levels increase dramatically in the mother in late pregnancy and during the postnatal period to stimulate lactation and promote maternal behavior. A brief, but pronounced, peak of prolactin also occurs in the estrus phase of the estrous cycle, but under most other conditions hormone levels are low. The blood prolactin profile is shaped by tuberoinfundibular dopamine (TIDA) neurons in the hypothalamus, which exert tonic inhibition on prolactin secretion. While high prolactin states are typically associated with removal of this powerful inhibition, little is known about the network changes within the TIDA population that are associated with adaptation to reproductive needs. Here, we performed *in vitro* Ca^{2+} imaging using transgenic mice expressing the calcium-sensitive fluorescent protein GCaMP3 under control of the dopamine transporter promoter to visualize TIDA neurons in the arcuate nucleus. Earlier work has demonstrated that TIDA neurons display rhythmic oscillations of membrane potential and action potential firing (DJ Lyons et al., 2010). Here, peaks in Ca^{2+} signaling correlated with great fidelity to TIDA UP states as revealed by simultaneous whole-cell recordings. Next, we compared different oscillation parameters *i.e.*

frequency, network correlation and rhythmicity between males, and females in different estrous cycle stages and during lactation. Oscillation frequency was similar in adult males (0.25 ± 0.06 Hz) and across the estrous cycle (diestrus/metestrus = 0.32 ± 0.06 Hz; proestrus/estrus = 0.36 ± 0.06 Hz), as was rhythmicity. In lactation, however, frequency was significantly faster (0.53 ± 0.04 Hz), and rhythmicity was attenuated. These changes reversed with weaning. The degree of synchronization between neurons remained the same in all conditions. Ongoing experiments are examining potential changes in membrane properties that may explain the switch in network activity.
Our findings suggest a reconfiguration of the TIDA network– reflected as changes in oscillation frequency - that occurs during long-term changes in the physiological need for prolactin (*i.e.* lactation) but not for briefer peaks in circulating prolactin (*i.e.* the estrus phase). Such alterations of hypothalamic ensemble activity may form part of the adaptation to reproductive needs, and indicate ability for reversible plasticity.

Disclosures: C.T. Perez: None. **A. Hellysaz:** None. **J. van Lunteren:** None. **C. Broberger:** None.

Poster

813. Neuroendocrine Anatomy and Physiology

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 813.10/PP12

Topic: F.03. Neuroendocrine Processes

Support: CONACyT Grant 181334

CONACyT Fellowship 45270

Title: Artificial rearing modifies the negative feedback in the gh/igf-1 axis in neonatal rats

Authors: *C. G. TORIZ[1], A. MARTÍNEZ-MUÑOZ[2], C. SOLANO-AGAMA[1], I. JIMÉNEZ-ESTRADA[1], M. GONZÁLEZ DEL PLIEGO[3], M. E. MENDOZA-GARRIDO[1], A. I. MELO-SALAZAR[2];
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Abstract: Pituitary gland development continues during the postnatal period. During this time the dominant pituitary cell phenotype are the somatotropes, which release Growth Hormone (GH). This hormone together with the Insulin-like growth factor 1 (IGF-1; most of it become

from the liver and is stimulated by GH) promotes the growth of the long bones. Recently we found that the plasmatic levels of GH as well the basal secretion levels (by primary culture) was higher on postnatal day (pnd) 7, but not on pnd 14 and 21 in pups rats that suffered artificial rearing (AR rats) than the levels founded in pups that were reared by their mother (MR rats). However, the proportions of positive GH and positive prolactin (PRL) cells were similar between groups in all evaluated ages. Interestingly the proportion of cells that released both hormones was decreased in AR rats of pnd 14. To assess whether the above data are due to hormonal differences, we measured the concentration of GH and PRL in homogenates of anterior pituitary (Milliplex RPTMAG-86K, Millipore) from MR and AR rats of pnd 7, 14 and 21. In addition, we measured serum IGF-1, total and free (IGF-1 Mouse ELISA Kit ab100695, Abcam), as well the morphometric parameters of the tibial bone. The results show that, in comparison to MR rats, the circulating levels of IGF-1 total and free ($p < 0.01$), as well the linear density of the tibial bone ($p < 0.01$) was lower in AR rats of pnd 7 and 14, respectively. However, we did not find difference in the total content of PRL or GH at any evaluated age. Taken together, this data suggests that the AR alters the negative feedback of pituitary hormone secretion during the first two weeks of life.

Disclosures: **C.G. Toriz:** None. **A. Martínez-Muñoz:** None. **C. Solano-Agama:** None. **I. Jiménez-Estrada:** None. **M. González del Pliego:** None. **M.E. Mendoza-Garrido:** None. **A.I. Melo-Salazar:** None.

Poster

813. Neuroendocrine Anatomy and Physiology

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 813.11/PP13

Topic: F.03. Neuroendocrine Processes

Support: Starting Investigator Grant from the ERC (ENDOSWITCH 261286)

Swedish Research Council (2014-3906)

Novo Nordisk Fonden

The Strategic Research Programme in Diabetes at Karolinska Institutet.

Title: GABAergic modulation of tuberoinfundibular dopamine (TIDA) neuron network activity.

Authors: ***R. AMMARI**, C. BROBERGER;
Neurosciences, Karolinska Institutet, STOCKHOLM, Sweden

Abstract: The role of GABA in neuroendocrine control remains poorly understood, despite the ubiquity of this inhibitory transmitter in the hypothalamus. This question is particularly relevant in tuberoinfundibular dopamine (TIDA) neurons, which have been proposed to use GABA as a co-transmitter. TIDA neurons control the pituitary secretion of prolactin through tonic inhibition, and thus play a central role in reproduction as prolactin is required for successful pregnancy and nursing. The role of GABA within the lactotrophic axis has primarily been studied in terms of its actions in the pituitary, but the possibility that it is involved in setting TIDA network properties is largely unexplored. This issue is especially intriguing given recent evidence that TIDA neurons *in vitro* form a gap junction-linked network that discharges in highly rhythmic, synchronized oscillations (Lyons et al., 2010). Here, whole-cell recordings were performed on slice preparations of TIDA neurons from P21-P35 male rats. Bath application of GABA at 10 μM reconfigured the oscillation such that overall frequency remained unchanged, but the phases within the duty cycle shifted temporal relationships. At 100 μM GABA, the oscillation was replaced by a flat baseline. This effect could partly be explained by a $GABA_B$ receptor-mediated hyperpolarization (likely via GIRK channels). A parallel modulation by $GABA_A$ was also seen, however, as the selective agonist, muscimol (10 μM) also abolished the oscillation, but at a highly depolarized membrane potential (Vm= -51 ± 2mV, n=5). Furthermore, blockade of the $GABA_A$ receptor by Gabazine attenuated firing by shortening UP states, indicating endogenous release. Surprisingly, paired recordings (n=75) failed to reveal evidence of inhibitory synaptic TIDA-TIDA connectivity. Yet, we did find evidence of a tonic $GABA_A$ mediated current in voltage clamp recordings, using Gabazine. When THIP (2μM), an agonist selective for δ subunit-containing extrasynaptic $GABA_A$ -R, was applied, membrane potential was modulated such that relatively hyperpolarized TIDA neurons depolarized, and relatively depolarized neurons hyperpolarized towards a membrane potential of -70 ± 2 mV. These data suggest that GABA provides a stabilizing influence on TIDA network activity, possibly providing feedback autoinhibition. This homeostatic control, rather than relying on hard-wired inhibitory recurrent axon collaterals appears to be encoded as fluctuations in ambient, extrasynaptic GABA, analogous to what has recently been found for dopamine autoreceptor control in this system (Stagkourakis et al., 2016).

Disclosures: **R. Ammari:** None. **C. Broberger:** None.

Poster

813. Neuroendocrine Anatomy and Physiology

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 813.12/PP14

Topic: F.03. Neuroendocrine Processes

Support: NIH/NINDS NS029728

Title: A comparative high spatial resolution analysis of genetic markers for neuronal GABA and glutamate in the rat hypothalamus

Authors: *A. G. WATTS[1], N. T. CARLOS[2], F. J. ABU-JABER[2], G. SANCHEZ-WATTS[2], J. D. HAHN[2];
[1]Biol. Sci., USC, Los Angeles, CA; [2]Biol. Sci., Univ. of Southern California Dept. of Biol. Sci., Los Angeles, CA

Abstract: Fast synaptic neurotransmission in the brain predominantly involves the amino acid neurotransmitters glutamate (GLU) and gamma-Aminobutyric acid (GABA). Both play a critical and pervasive role in normal brain function. Dysfunction of GABA and GLU neural circuits is implicated in numerous brain diseases. While much is known about the actions and brain expression of GLU and GABA in the cerebral cortex, cerebral nuclei, and thalamus, substantially less is known at the level of the hypothalamus. To increase understanding of GABAergic and glutamatergic hypothalamic neural circuits, we have performed a systematic high spatial resolution comparative analysis of genetic markers for both using in situ hybridization (ISH). For GABA, we applied 35S-labeled riboprobes to detect the presence of mRNA for two isoforms of the GABA synthetic enzyme glutamate decarboxylase (GAD-65, GAD-67); for GLU we applied a 35S-labeled riboprobe to detect a vesicular glutamate transporter (VGLUT2) mRNA, which shows abundant hypothalamic expression. Series of sequential brain sections were subjected to ISH for each riboprobe; an adjacent series was processed for Nissl cytoarchitecture. RESULTS: Analysis of 83 cytoarchitecturally defined hypothalamic regions (following the rat brain atlas of Swanson, 2004) revealed the percentage of regions with detectable signal: GAD-65 (88%), GAD-67 (82%), VGLUT2 (94%). Using a 4-rank approach, regions with high or very high ranked signal included, for GAD-65: subfornical organ (SFO), lateral preoptic area (LPO), lateral hypothalamic area perifornical region, and the following hypothalamic nuclei: anterodorsal- and ventrolateral preoptic, suprachiasmatic (SCH), medial preoptic (MPN), anterior (AHN), arcuate (ARH), dorsomedial, periventricular posterior part (PVp), and tuberal; for GAD-67: SFO, SCH, AHN, ARH, PVp, tuberomammillary nucleus, and LHA posterior region; for VGLUT2: LHA anterior region, median preoptic- and anteroventral periventricular nuclei, SFO, MPN, AHN, and the following hypothalamic nuclei: supraoptic, ventromedial, posterior, medial mammillary, and subthalamic. Differences in inter- and intraregional reporter signal level and distribution were most apparent between VGLUT2 and the GAD isoforms; however, substantial differences were also noted between GAD-65 and GAD-67. These data inform a developing model of hypothalamic neural circuitry and support a continuing effort to obtain a comprehensive network model for the mammalian brain.

Disclosures: A.G. Watts: None. **N.T. Carlos:** None. **F.J. Abu-Jaber:** None. **G. Sanchez-Watts:** None. **J.D. Hahn:** None.

Poster

813. Neuroendocrine Anatomy and Physiology

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 813.13/PP15

Topic: F.03. Neuroendocrine Processes

Title: RFRP-3 actions on corticotropin-releasing hormone neurons

Authors: *J. KIM, G. M. ANDERSON, K. J. IREMONGER;
Univ. of Otago, Dunedin, New Zealand

Abstract: RFamide-related peptide-3 (RFRP-3) has recently been shown to stimulate corticotropin-releasing hormone (CRH) neurons which drive the neuroendocrine stress axis. Although the receptor for RFRP-3 is densely expressed in the paraventricular nucleus (PVN), relatively few (~30%) co-express CRH. Therefore the stimulatory effect of RFRP-3 on CRH neuron may involve both direct and indirect actions. To address this, we used loose on-cell and whole cell patch clamp electrophysiology on CRH neurons using acute brain slices from mice that express Cre-dependent tdTomato specifically in CRH neurons. RFRP-3 (100 nM) increased CRH neuron action potential firing in 4 of the 13 cells tested (>50% of initial firing rate) however it had no effect on the remaining cells. Overall, there was no significant increase in RFRP-3 induced firing rate. Next we used whole cell electrophysiology in the presence of 6-cyano-7-nitroquinoxaline-2,3-dione (CNQX) or picrotoxin to determine whether RFRP-3 affects GABA or glutamate synaptic transmission, respectively, on CRH neurons. Changes in spontaneous and evoked inhibitory and excitatory post synaptic currents (IPSC and EPSC) were measured using the paired pulse protocol. RFRP-3 did not affect eIPSC or eEPSC current amplitudes and paired pulse ratios. RFRP-3 did however reduce sIPSC current frequency (>20% reduction) in 9 of the 17 cells tested. RFRP-3 had no effect on sEPSC frequency. In comparison to the observations *in vivo*, RFRP-3 has a rather modest effect on CRH neuron excitability in brain slices. This suggests that RFRP-3 may have actions elsewhere in the brain to stimulate the stress axis. Our data so far indicates that RFRP-3 actions in the PVN may involve either direct stimulation of CRH neurons and/or disinhibition of GABA transmission. We are currently testing this further using transgenic mice that express genetically encoded calcium indicator GCaMP6f in CRH neurons.

Disclosures: J. Kim: None. **G.M. Anderson:** None. **K.J. Iremonger:** None.

Poster

813. Neuroendocrine Anatomy and Physiology

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 813.14/PP16

Topic: F.03. Neuroendocrine Processes

Support: NIA Grant AG032325

Title: Localization and levels of luteinizing hormone in the mouse brain during estrous cycle stages

Authors: *P. BIDINOTTO[1], K. SRACIC[1], J. A. BLAIR[2], S. BHATTA[2], G. CASADESUS[1,2]; [1]Dept. of Biol. Sci., [2]Sch. of Biomed. Sci., Kent State Univ., Kent, OH

Abstract: Previous work in our laboratory demonstrates the importance of luteinizing hormone (LH) signaling in learning and memory and AD. Though we have also previously demonstrated that LH is present in the brain, the neuroanatomical and cellular localization of LH has not been determined. Additionally, we have identified differences in brain levels of LH depending on reproductive status, however whether brain LH levels change during the estrous cycle and whether these are associated with fluctuations in neuroplasticity and cognition observed during this cycle is also not known. To address this, we carried out immunofluorescence to determine the brain regions and cellular types LH is localized to and measured brain LH levels by sandwich ELISA at different stages of the estrous cycle. High expression of LH is visualized in the retrosplenial cingulate cortex, hippocampal regions including the subiculum, the sensory motor cortex, and subcortical regions associated with processing spatial learning and memory information. Furthermore, we have also identified the expression of LH and GAD67 to be co-localize indicating that LH is expressed in GABAergic neurons. Preliminary data also suggests that, similarly to estrogen levels, expression levels of brain LH may be estrous-cycle stage dependent. Together, the regional and cellular expression of LH, the encouraging estrous cycle dependency preliminary results support the role of LH as a cognitive and emotional circuit regulatory hormone.

Disclosures: P. Bidinotto: None. **K. Sracic:** None. **J.A. Blair:** None. **S. Bhatta:** None. **G. Casadesus:** None.

Poster

813. Neuroendocrine Anatomy and Physiology

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 813.15/QQ1

Topic: F.03. Neuroendocrine Processes

Support: NIH Grant R21HD076430 (CKW)

Title: Evidence for progesterone receptor expression within Cajal-Retzius cells of the neonatal dentate gyrus

Authors: *A. J. NEWELL, C. K. WAGNER;
Psychology, Univ. At Albany, Albany, NY

Abstract: Steroid hormones activate nuclear receptors, which as transcription factors, alter fundamental mechanisms of neural development. Progesterone receptors (PR) are transiently expressed in many regions of the perinatal rodent brain, including regions typically associated with cognitive function. Nuclear PR is expressed in cells of the molecular layer of the dentate gyrus within the hippocampus beginning late in gestation and continuing through at least P14. Ultrastructural morphology and neurochemical phenotype suggest that PR is expressed in immature neurons of the molecular layer in the neonatal brain. To determine the birthdate of these PR expressing neurons, BrdU (50 mg/kg i.p.) was administered to pregnant females or to neonates on E19-20, E21-22, P1-2, P3-4, or P5-6. Tissue was collected on P7 and dual label fluorescent immunocytochemistry for BrdU-ir and PRir was performed. Confocal microscopy revealed that the vast majority of PR cells are born between P3 and P6, suggesting that immature PRir neurons are derived from postnatal neurogenesis. The ontogeny and anatomical distribution of these PRir neurons suggest that they may be Cajal-Retzius neurons, a developmental cell type integral in cortical and hippocampal lamination. Indeed, PRir and Reelin-ir, a marker for Cajal-Retzius cells, were almost 100% co-localized in the molecular layer on P7. Taken together, these results suggest that PR activity within recently generated Cajal-Retzius cells may influence dentate gyrus organization and the development of hippocampal circuitry.

Disclosures: **A.J. Newell:** None. **C.K. Wagner:** None.

Poster

813. Neuroendocrine Anatomy and Physiology

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 813.16/QQ2

Topic: F.03. Neuroendocrine Processes

Support: NIH Grant R21HD076430 (CKW)

Title: Dopaminergic innervation patterns within medial prefrontal cortex are altered by developmental exposure to a synthetic progestin used to prevent preterm birth.

Authors: *M. LOLIER, C. K. WAGNER;
Univ. At Albany, Albany, NY

Abstract: The use of the synthetic progesterone, 17α-hydroxyprogesterone caproate (17-OHPC), for the prevention of recurrent preterm birth in women, has become common practice despite little understanding of its potential effect on the developing fetus. 17-OHPC is typically administered from about week 16 to week 36 of gestation, which corresponds to a critical period of development for the mesocortical dopamine pathway. Given that perturbations in this pathway are often implicated in behavioral disorders such as attention deficit hyperactivity disorder (ADHD), investigating the effects of 17-OHPC exposure on neural development is critical. Previous research in rodent models indicates that nuclear progesterone receptors are transiently expressed during development in dopaminergic cells of the ventral tegmental area that project to the medial prefrontal cortex (mPFC) and within target cells of the mPFC itself. Exposure to 17-OHPC during development increased tyrosine hydroxylase immunoreactive (THir) fiber density in the mPFC and impaired cognitive flexibility and increased perseveration in adolescence. In the present study, 17-OHPC (0.5mg/kg in sesame oil, s.c.) was administered to male and female rats from the day of birth (P1) through P7 and THir fiber distribution within the prelimbic mPFC was analyzed. There was a significant main effect of sex ($p<0.008$) with THir fibers covering a wider area in lamina 5 of females compared to males. There was a significant interaction ($p<0.021$) between sex and 17-OHPC treatment in which 17-OHPC significantly reduced the width of THir fibers in females to the level of males, but 17-OHPC had no effect in males. These findings reveal a potential novel sex difference in dopaminergic innervation patterns of the mPFC during development and suggest that 17-OHPC may exert differential effects on the development of the mesocortical dopamine pathway in males and females.

Disclosures: **M. Lolier:** None. **C.K. Wagner:** None.

Poster

813. Neuroendocrine Anatomy and Physiology

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 813.17/QQ3

Topic: F.03. Neuroendocrine Processes

Support: CNPq

FAPESP

CAPES

Title: Effects of estrogen therapy on neurochemistry of female rats in animal model of perimenopause

Authors: *N. PESTANA[1], C. M LEITE[2], R. CAROLINO[2], P. RIVAS[3], L. L K ELIAS[4], J. ANTUNES RODRIGUES[4], J. ANSELMO-FRANCI[5];
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Abstract: Perimenopause is a period transition from reproductive to non-reproductive life characterized by neuroendocrine, metabolic and behavioral changes. A well-established experimental model for perimenopause studies refers to exposure of animals to diepoxide 4-vinylcyclohexene (VCD), which leads to gradual failure of ovarian function by progressive depletion of primordial and primary follicles. Ovarian steroids influence brain regions involved in the control of mood through specific receptors: estrogens receptors α and β (ERα and ERβ) and progesterone receptor (PR). Both ER and PR are widely expressed in brain regions controlling reproduction as well as in other brain areas associated with mood. The aim of this study was to investigate whether gradual follicular depletion induced by VCD results in changes in the neurochemistry of female rats in brain nuclei that control mood and the role of estradiol on these changes. Female rats (28 days) were daily injected with VCD (160mg/Kg) or corn oil (O) for 15 days. Approximately 55 days after the first VCD or O injection, pellets of 17β-estradiol or O were inserted s.c in the dorso-lateral region (Groups O+O; VCD+O; VCD+E). 21 days after, rats were decapitated in the morning of diestrus. The brains were removed to punch out hippocampus and amygdala to assess NA and 5-HT content by HPLC/ED as well as LC and DRN to analyze the expression of mRNA for ERβ and PR by PCR/RT. Plasma levels of estradiol and progesterone were also evaluated. Levels of estradiol were similar in the O+O and VCD+O groups, and significantly higher in the VCD+E group. Progesterone levels were lower in the

VCD+O and E therapy restored the control levels. In the DRN VCD+O rats exhibited a lower expression of PR mRNA, and E did not change it. No difference was observed in the expression of ERβ mRNA among all groups. In the LC, PR mRNA expression in the VCD+O did not differ from O+O, but E decreased it. On the other hand the expression of ERβ mRNA was lower in the VCD+O rats while E did not modify it. In the amygdala, 5-HT content was significantly reduced in VCD+E rats compared to the other groups. NA content showed a similar pattern. In the hippocampus, 5-HT content was significantly reduced in the VCD+O rats compared to the O+O group and E therapy restored the content to the control values. The NA content was similar in the O+O and VCD+O groups and lower in the VCD+E animals. Data of VCD+O rats suggest that the decrease in progesterone levels, as well as in the ERβ and PR expression and content of 5-HT in brain areas related to mood might be responsible for some of the mood disturbances that occur during perimenopause. The effects of estradiol in modifying the altered parameters are area-dependent.

Disclosures: **N. Pestana:** None. **C. M Leite:** None. **R. Carolino:** None. **P. Rivas:** None. **L. L K Elias:** None. **J. Antunes Rodrigues:** None. **J. Anselmo-Franci:** None.

Poster

813. Neuroendocrine Anatomy and Physiology

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 813.18/QQ4

Topic: F.03. Neuroendocrine Processes

Title: A transcriptomic analysis of the female mouse brain: effect of the estrous cycle in 4 brain regions

Authors: *L. M. DICARLO, C. M. VIED, R. S. NOWAKOWSKI;
Biomed. Sci., Florida State Univ. Col. of Med., Tallahassee, FL

Abstract: For many years biomedical and, in particular, neuroscience research, has often focused on male subjects. To examine changes in gene expression in the female brain, we did a transcriptomic analysis of the hypothalamus, hippocampus, neocortex, and cerebellum of female C57BL/6J (B6) mice using 12 animals, 3 from each of the 4 stages of the estrous cycle. At a false discovery rate (FDR) less than 0.05, we found that there are ~10,000 differentially expressed genes (DEGs) between each of the six possible pairs of brain region comparisons which is ~50% of the total number of genes detected. Within each of the four brain regions, between 0.5% and 1% of genes are differentially expressed as a result of the estrous cycle, and only 3 genes are differentially expressed in all 4 brain regions. These results demonstrate that despite large differences in gene expression between the four brain regions >99% of the

transcriptome is unchanged across the 4 phases of the estrous cycle. We expect that our results will be a useful guide for researchers in the field of neuroscience as females are incorporated in future experiments as well as shedding light on the interactions of gene expression in different brain regions.

Disclosures: **L.M. Dicarlo:** None. **C.M. Vied:** None. **R.S. Nowakowski:** None.

Poster

814. Neuropeptides: Physiology And Behavior

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 814.01/QQ5

Topic: F.04. Stress and the Brain

Support: NIH Grant MH096746

Title: Corticotropin-releasing factor (CRF) receptors modulate oxytocin release in the bed nucleus of the stria terminalis (BNST)

Authors: *D. MARTINON, J. A. DABROWSKA;
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Abstract: The neuropeptide oxytocin (OT) plays a key role in the regulation of social and anxiety-like behavior. Previous experiments have indicated that OT neurons send oxytocinergic projections from the paraventricular nucleus of the hypothalamus (PVN) to the dorso-lateral bed nucleus of the stria terminalis (BNST), a forebrain region critically involved in the modulation of anxiety-like behavior. Importantly, these OT terminals in the BNST express corticotropin releasing factor (CRF) receptor type 2 (CRFR2), which suggests that CRFR2 might modulate OT release. There are two putative CRF receptors (CRFR1 and CRFR2) that can be activated by members of CRF peptide family (Urocortin 1, 2, 3 and CRF). Urocortin 3 (Ucn3) binds and activates CRFR2 with high affinity, while CRF has a significantly lower affinity for CRFR2 than for CRFR1. Hence, we employed microdialysis in freely-moving rats to determine the effect of selective CRFR2 agonist (Ucn3) or antagonist (Astressin 2B, As2B) on OT content in the BNST. To determine if CRFR1 is also involved, we used CRFR1 agonist (CRF) and antagonist (NBI35965). All compounds were delivered into the BNST via reverse dialysis. Oxytocin content in dialysates was measured with radioimmunoassay (RIA-gnosis). We demonstrate that blocking CRFR2 by As2B caused an instant and significant increase in the OT release in the BNST, while CRFR2 activation by Ucn3 did not have an effect. Interestingly, CRF alone did not have an instant effect on the OT release, but instead caused a delayed trend in increase of OT content. Furthermore, although CRFR1 antagonist (NBI35965) alone did not have an effect on

OT release, infusion of NBI35965 abrogated the increase of OT release elicited by As2B. This suggests that the effect of As2B on OT release requires concomitant activation of CRFR1. Previous studies have shown that social interactions modulate OT release in posterior BNST. Therefore, in order to determine the effect of social interaction on OT release in the dorso-lateral BNST, single caged rats undergoing microdialysis were paired with novel rats to monitor OT levels during social interaction. Interestingly, social interaction did not have a significant effect on OT release in the dorso-lateral BNST. This suggests that OT release can be evoked by diverse stimuli in different sub-regions of the BNST. In conclusion, our data suggests that members of the CRF peptide family modulate OT release in the BNST via a fine-tuned mechanism that involves both CRFR1 and CRFR2 receptors. Further exploring mechanisms of modulation of endogenous OT by the CRF system is important to grasp the role of this interaction in the regulation of stress response and anxiety.

Disclosures: D. Martinon: None. **J.A. Dabrowska:** None.

Poster

814. Neuropeptides: Physiology And Behavior

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 814.02/QQ6

Topic: F.04. Stress and the Brain

Support: Picto 2013-0065

Title: Ghrelin activates corticotropin-releasing factor neurons of the hypothalamic paraventricular nucleus via regulation of GABA inputs

Authors: *A. CABRAL[1], E. PORSTIANKY[2], E. SÁNCHEZ JARAMILLO[3], J. ZIGMAN[4], M. PERELLO[1];
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Abstract: Ghrelin is a stomach-derived hormone that activates the corticotropin-releasing factor (CRF)-producing neurons of the paraventricular nucleus of the hypothalamus (PVN) and, as a consequence, the hypothalamic-pituitary-adrenal (HPA) neuroendocrine axis; however, the neuronal circuits by which ghrelin engages this neuroendocrine response are unknown. Here, we show that ghrelin-induced activation of PVN CRF neurons does not require neuropeptide Y (NPY) signaling but requires a decrease of γ-aminobutyric acid (GABA) signaling within the

PVN. We also show that ghrelin receptor seems to be mainly located in GABAergic terminals within the PVN and that ghrelin is able to inhibit GABA release from the PVN explants. In addition, we found that peripherally-administered fluorescein-labeled ghrelin is able to gain access to the PVN, and that peripherally-administered ghrelin induces full activation of the PVN CRF neurons in ARC-ablated mice, which otherwise fail to increase food intake in response to the hormone. In contrast, ghrelin fails to activate the PVN CRF neurons of mice with ghrelin receptor expression limited to ARC AgRP neurons, which partially respond to its orexigenic actions. Thus, ghrelin seems to activate PVN CRF neurons via inhibition of a local GABAergic tone, in an ARC-independent manner. These data suggest that the neuronal circuits mediating ghrelin's role as an orexigenic vs. a stress

Disclosures: **A. Cabral:** None. **E. Porstianky:** None. **E. Sánchez Jaramillo:** None. **J. Zigman:** None. **M. Perello:** None.

Poster

814. Neuropeptides: Physiology And Behavior

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 814.03/QQ7

Topic: F.04. Stress and the Brain

Support: NIMH grants MH096086

Title: Chronic stress causes an enhanced NMDA receptor function in the hypothalamic corticotrophin-releasing hormone (CRH)-expressing neurons

Authors: J.-J. ZHOU[1], Z. ZHAO[2], *D.-P. LI[3];
[1]Critical Care, UT MD Anderson Cancer Ctr., Houston, TX; [2]Neurosurg., The Second Hospial of HeBei Med. Univ., Shijiazhuang, China; [3]UT-MD Anderson Cancer Ctr., Houston, TX

Abstract: Chronic stress increases activity of hypothalamic-pituitary-adrenal (HPA) axis and hyperactivity of corticotrophin-releasing hormone (CRH)-expressing neurons in the hypothalamic paraventricular nucleus (PVN). The activity of CRH neurons is regulated by excitatory and inhibitory GABAergic synaptic inputs. In this study we tested a hypothesis that enhance glutamatergic synaptic inputs is responsible for the hyperactivity of CRH neurons in chronic stress. The CRH neurons were identified by expressing green fluorescent protein (GFP) driven by rat CRH promoter. Neuronal activity and synaptic currents of GFP-tagged CRH neurons were assessed by using whole-cell recording. Chronic unpredictable mild stress (CUMS) significantly increased basal firing activity in PVN-CRH neurons. Blocking NMDA receptor with AP5 significantly decreased firing activity in PVN-CRH neurons in CUMS rats but not in

unstressed rats. Furthermore, AP5 decreased frequency of excitatory postsynaptic currents in CUMS rats but had not effect on unstressed rats. Treatment of the slice with AP5 normalized the CUMS-induced increase in $Na^+K^+Cl^-Cl^-$ expression levels in the PVN. In addition, AP5 treatment restored $GABA_A$ receptor antagonist gabazine-induced excitatory effect on PVN-CRH neurons in CUMS rats. These data suggest that chronic stress induces an enhancement of NMDA-mediated glutamatergic control of CRH neurons. The enhanced NMDA receptor function may leads to a reduction of GABAergic inhibition in CUMS rats.

Disclosures: **J. Zhou:** None. **Z. Zhao:** None. **D. Li:** None.

Poster

814. Neuropeptides: Physiology And Behavior

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 814.04/QQ8

Topic: F.04. Stress and the Brain

Support: DA020129

DA013429

Title: Modulation of corticotropin-releasing factor-induced activation of noradrenergic neurons by a cannabinoid type 1 receptor agonist

Authors: ***R. WYROFSKY**[1], B. A. S. REYES[1], L. G. KIRBY[2], E. J. VAN BOCKSTAELE[1]; [1]Pharmacol. & Physiol., Drexel Univ. Col. of Med., Philadelphia, PA; [2]Ctr. for Substance Abuse Res. & Dept. of Anat. and Cell Biol., Lewis Katz Sch. of Med. at Temple Univ., Philadelphia, PA

Abstract: The noradrenergic system has been shown to play a key role in the modulation and regulation of stress responses, arousal, mood, and emotional states. Dysregulation of noradrenergic transmission can lead to the development of several stress-related psychiatric disorders. As the primary mediator of stress-related inputs to the noradrenergic locus coeruleus (LC), corticotropin-releasing factor (CRF) increases LC neuronal discharge rates and induces norepinephrine (NE) release in target regions. The endocannabinoid (eCB) system has been shown to modulate stress responses in multiple brain regions and is thought to act as an “anti-stress” neuromediator. We have previously shown that cannabinoid receptor type 1 (CB1r) and CRF co-localize within axon terminals in the LC, and the types of dually labeled synapses were characterized using immunoelectron microscopy. In the core region of the LC where cell bodies are dense, CB1r and CRF co-localization occurred most frequently in symmetric synapses,

suggestive of a co-existing inhibitory amino acid such as GABA. In the peri-LC where extensive noradrenergic dendrites extend, co-localization of CRF and CB1r was most common in asymmetric synapses, suggestive of a co-existing excitatory transmitter such as glutamate. In the present study, we sought to investigate whether CB1r activation could modulate CRF-induced responses in LC-NE activity. Whole-cell patch-clamp recordings of LC-NE neurons were conducted in 40 μm thick coronal brain slices obtained from 4-5 week old male Sprague-Dawley rats. Preliminary results showed that a 10 nM dose of CRF did not increase LC-NE excitability, but subsequent bath application of 1 μM WIN-55,212-2 (WIN) produced an increase in LC neuronal excitability. This result confirms previous findings showing that a CB1r agonist is capable of increasing the firing rate of LC-NE neurons. Next, we used a higher dose of CRF known to elicit activation of LC-NE neurons. Since previous studies showed that CB1r activation following KCl administration resulted in the attenuation of activity-dependent increases in the LC, we hypothesized that CB1r activation would attenuate CRF-induced increases in LC activity. Bath application of 1μM WIN was able to attenuate CRF-mediated increases in excitability produced by a 100 nM dose of CRF. These electrophysiological results indicate that the CB1r agonist WIN is capable of attenuating CRF-induced excitability of LC neurons. Taken with our previous anatomical data showing co-existence of CB1r with CRF in single afferents innervating the LC, these data indicate a functional interaction between both the CRF and eCB system in this stress-integrative nucleus.

Disclosures: R. Wyrofsky: None. **B.A.S. Reyes:** None. **L.G. Kirby:** None. **E.J. Van Bockstaele:** None.

Poster

814. Neuropeptides: Physiology And Behavior

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 814.05/QQ9

Topic: G.03. Emotion

Title: Corticotropin-releasing factor and a-Helical CRF modulate 50 kHz and 22 kHz ultrasonic calling behavior and anxiety in rats

Authors: *J. O. TAYLOR, V. GJINI, B. COOPER;
TCU, Fort Worth, TX

Abstract: In a given year, 18% of the adult population in the United States will suffer from an anxiety disorder, and the rate increases to 40% over a person's lifetime. This prevalence rate illustrates the need to develop and improve therapeutic treatments for anxiety disorders. Toward that end, we seek to refine behavioral measures of anxiety in laboratory animals by determining

whether specific vocalizations occur when animals are in an elevated state of anxiety. Rat ultrasonic vocalizations (USVs) broadly signal affective state. They can be categorized into one of two frequency ranges, 22 kHz or 50 kHz. The 22 kHz calls are more closely associated with negative affect states, whereas the 50 kHz range is associated with positive affective states. The 50 kHz range consists of calls that can be categorized into multiple subtypes; one USV subtype, flat calls, or constant frequency 50 kHz (CF 50 kHz) calls, are not viewed as signaling an emotional state. We have been testing the hypothesis that these calls are promoted by anxiogenic situations. To test this hypothesis animals are introduced to a novel environment and then exposed to a series of six, temporally predictable, unsignalled footshocks (UFS). Exposure to the novel environment and initial footshocks is the anxiogenic component of the test, and the repeated footshocks should generate fear-related behaviors. In the UFS paradigm, rats initially produce CF 50 kHz calls (baseline and shocks 1-3) and then increase the production of 22 kHz calls following shocks 3-6. In the current experiment, rats were given intraventricular administration of corticotropin-releasing factor (CRF), the CRF antagonist α-Helical CRF, or vehicle control 30 min prior to UFS testing. We hypothesized that CRF and α-Helical CRF would respectively increase or attenuate CF 50 kHz USV production early in the footshock session. The resulting pattern of USV calling behavior was consistent with our hypothesis. Rearing, a measure of risk-assessment, was reduced by the drug treatment, and freezing was increased in the CRF group and reduced in animals receiving α-Helical CRF compared to vehicle control. Animals were subsequently tested on the elevated plus maze. CRF and α-Helical CRF pretreatment oppositely modulated anxiety-related behavior on the elevated plus maze (open arm entries and open arm time) compared to control animals. These results provide further support for the hypothesis that CF 50 kHz USVs are produced when animals are in an elevated state of anxiety, and suggest that including this USV category in behavioral assays of anxiety provides an additional valuable behavioral measure.

Disclosures: J.O. Taylor: None. **V. Gjini:** None. **B. Cooper:** None.

Poster

814. Neuropeptides: Physiology And Behavior

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 814.06/QQ10

Topic: F.04. Stress and the Brain

Support: NIH Grant AA019455

NIH Grant DA019112

NIH Grant MH103950

NARSAD

Vanderbilt DRTC

Title: Control of BNST CRF neurons by norepinephrine and stress

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Abstract: Stress has been implicated as a primary contributor to many disease states. Numerous studies suggest that stress can elevate norepinephrine (NE) levels to enhance corticotropin releasing factor (CRF) signaling and increase neuronal activity in the bed nucleus of the stria terminalis (BNST), a brain region critical to many behavioral and physiologic responses to stressors. We are using both electrophysiological and immunohistochemical techniques to study the effects of stress and NE on BNST CRF neuron excitability and neurotransmission. Through the use of a CRF-tdtomato reporter mouse line (strain B6(Cg)-Crhtm1(cre)Zjh/J crossed with strain B6.Cg-Gt(ROSA)26Sor<tm14(CAG-tdTomato)Hze>/J), we have shown that NE can depolarize BNST CRF neurons, and that this depolarization is sensitive to a β-adrenergic receptor (AR) antagonist. Conversely, NE inhibits glutamatergic transmission onto BNST CRF neurons via an α-AR dependent mechanism, suggesting that AR subclasses may work to balance the excitability of BNST CRF neurons. In order to further understand NE regulation of glutamatergic transmission, we used an optogenetic mapping technique to identify glutamatergic afferents that synapse directly onto BNST CRF neurons. We used an AAV-CamKII-ChR2-YFP virus to express channelrhodopsin in brain regions known to send glutamatergic projections to the BNST and then monitored BNST CRF neurons for the presence of an optically-evoked excitatory post-synaptic current (oEPSC). We find that CRF neurons receive input from both the insular cortex and the parabrachial nucleus. Focusing on the insular cortex input, we found that the α_{2a}-AR agonist guanfacine decreases oEPSC amplitude when stimulating the insular input specifically. To investigate the recruitment of these BNST CRF neurons by stress, we measured cFos expression following 1-hr restraint stress exposure. Restraint stress exposure increased cFos labeling in BNST CRF neurons and this increase was attenuated by either propranolol, a β-AR antagonist or guanfacine. Together, these results suggest a role for the insula to BNST CRF projection as an important site of stress actions and may underlie known actions of guanfacine, including its modulation of depressive phenotypes and body mass.

Disclosures: **T. Fetterly:** None. **E.K. Awad:** None. **Y. Silberman:** None. **D.G. Winder:** None.

Poster

814. Neuropeptides: Physiology And Behavior

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 814.07/QQ11

Topic: F.04. Stress and the Brain

Support: DFG Grant KL 2999/1-1

CIHR Grant 136856

Title: Male and female rats show different behavioral and neuronal responses to central CRF receptor activation

Authors: *S. M. KLAMPFL, Y. YANG, J. CHANG, V. VIAU;
Univ. of British Columbia, Vancouver, BC, Canada

Abstract: Anxiety and depression are among the most common neuropsychiatric disorders, with the incidence being two times higher in women than in men. Stress is one of the leading causes of these mood disorders, frequently accompanied by maladaptive behavioral and neuroendocrine coping responses. As these stress responses are mainly orchestrated by the brain corticotropin-releasing factor (CRF) system, CRF and its family members have emerged as key candidates involved in the development of stress-related mood disorders. However, it is still largely unclear how the CRF system might contribute to sex differences in the development of such disorders. In order to make inroads on sex differences in the central CRF system we compared behavioral and neuronal responses to exogenous CRF in adult male and female rats. We found reliable behavioral differences to intracerebroventricular (icv) CRF administration observed in the home cage, with females showing higher behavioral sensitivity than males. This was reflected by faster increases in self-grooming and greater latencies to return to non-active behaviors in females. Moreover, CRF-treated females showed reduced locomotion compared to vehicle-treated controls, which was not observed in males. The sum of active behaviors (self-grooming, locomotion, burrowing, eating/drinking) was similarly increased by central CRF in both males and females. In addition, icv CRF injection revealed intriguing sex differences in neuronal activation patterns in a variety of limbic, hypothalamic and cortical brain regions. Finally, sex differences in behavioral and neuronal responses did not correlate with variations in gonadal status (plasma estradiol, progesterone and testosterone levels) in males and females.
In summary, male and female rats differentially responded to central CRF receptor activation, providing a framework for further investigation of sex differences in CRF-dependent changes in behavioral and neuroendocrine coping responses.

Disclosures: **S.M. Klampfl:** None. **Y. Yang:** None. **J. Chang:** None. **V. Viau:** None.

Poster

814. Neuropeptides: Physiology And Behavior

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 814.08/QQ12

Topic: F.04. Stress and the Brain

Support: JSPS

Title: Distribution of corticotropin-releasing factor neurons in the mouse brain: a study using corticotropin-releasing factor modified yellow fluorescent protein knock-in mouse

Authors: *K. ITOI[1], J. KONO[1], K. KONNO[2], A. H. TALUKDER[1], T. FUSE[1], K. UCHIDA[1], S. YAMAGATA[1], S. HORIO[3], M. ABE[4], M. WATANABE[2], K. SAKIMURA[4];
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Abstract: Corticotropin-releasing factor (CRF) plays a key role in the regulation of the hypothalamic-pituitary-adrenal axis, but CRF is also distributed broadly in the brain and may play roles as a neurotransmitter and/or modulator. However, there are currently no detailed morphological descriptions of CRF neurons in the mouse brain. The major obstacle in identifying CRF neurons is difficulty in staining CRF neurons by immunohistochemistry using anti-CRF antibodies. In the present study, we examined the morphological features of CRF neurons in a mouse line in which modified yellow fluorescent protein (Venus) was expressed under the CRF promoter. We previously generated the CRF-Venus knock-in mouse (Itoi et al., Endocrinology 155, 4054-60, 2014), from which the pgk-1 promoter-driven neomycin phosphotransferase gene (Neo) was deleted, and a CRF-VenusDeltaNeo mouse was generated. Venus expression is much more prominent in the CRF-VenusDeltaNeo mouse when compared to the CRF-Venus mouse. In addition, most Venus-expressing neurons co-express CRF mRNA. Venus-expressing neurons constitute a discrete population of neuroendocrine neurons in the paraventricular nucleus of the hypothalamus (PVH) that project to the median eminence. Venus-expressing neurons were also found in brain regions outside the neuroendocrine PVH, including the olfactory bulb, the piriform cortex (Pir), the extended amygdala, the hippocampus, the neocortices, Barrington's nucleus, the midbrain/pontine dorsal tegmentum, the periaqueductal gray, and the inferior olivary nucleus (IO). Venus-expressing perikarya co-expressing CRF mRNA could be observed clearly even in regions where CRF-immunoreactive perikarya could hardly be identified. We demonstrated that the CRF neurons contain glutamate in the Pir and IO, while they contain gamma-aminobutyric acid in the neocortex, the bed nucleus of the stria terminalis, the hippocampus, and the amygdala. A population of CRF neurons was demonstrated

to be cholinergic in the midbrain tegmentum. The CRF-VenusDeltaNeo mouse may be useful for studying the structural and functional properties of CRF neurons in the mouse brain.

Disclosures: **K. Itoi:** None. **J. Kono:** None. **K. Konno:** None. **A.H. Talukder:** None. **T. Fuse:** None. **K. Uchida:** None. **S. Yamagata:** None. **S. Horio:** None. **M. Abe:** None. **M. Watanabe:** None. **K. Sakimura:** None.

Poster

814. Neuropeptides: Physiology And Behavior

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 814.09/QQ13

Topic: F.04. Stress and the Brain

Support: Health Research Council (HRC) of New Zealand

Title: Morphological analysis of hypothalamic corticotropin-releasing hormone (CRH) neurons.

Authors: *K. J. IREMONGER, T. BITTAR, B. NAIR;
Univ. of Otago, Dunedin, New Zealand

Abstract: Corticotropin-releasing hormone (CRH) neurons in the paraventricular nucleus (PVN) of the hypothalamus are the final output cells of a complex neural network that controls the neuroendocrine stress response. Activation of CRH neurons ultimately leads to enhanced secretion of stress hormones from the adrenal gland. The morphology of a neuron is important in determining how it integrates and processes information. However, the dendritic and axonal morphology of hypothalamic CRH neurons is currently unknown. This study aimed to examine the morphology of CRH neurons and to determine if there are changes in CRH neuron structure after prolonged exposure to stress hormones. To investigate this, mice were treated for 14 days with 25μg/ml corticosterone (CORT) in the drinking water or vehicle for control. Brain slices were then prepared and patch clamp recordings were obtained to record cellular excitability and fill neurons with neurobiotin. Brain slices were fixed, processed and imaged with confocal microscopy. CRH neurons from control animals were multipolar in appearance with 1-3 primary dendrites emanating from the soma (mean= 2.0 ± 0.1, n=36) and 0-3 secondary dendrites (mean 0.8 ± 0.1). The total dendritic length per cell was 335 ± 24 μm (n=36). The most medial CRH neurons often possessed long dendrites that projected towards and along the ependymal cell layer of the third ventricle. Axons were found to originate from the primary dendrite in 61% of neurons and the soma in 39% of neurons. Axons projected laterally out of the PVN and were not seen to branch over the short distances analyzed. In neurons with axon bearing dendrites, the axon originated at 17.6 ± 2.4 μm from the soma. Exposure to 14 days CORT did not

significantly change any of these parameters (n=33 cells). However, patch clamp recordings confirmed that 14 days CORT significantly reduced CRH neuron intrinsic excitability, consistent with previous reports.
Overall, these data reveal the dendritic and axonal features of CRH neurons for the first time. In addition, these data show that exposure to elevated CORT levels does not lead to large-scale dendritic reorganization.

Disclosures: K.J. Iremonger: None. **T. Bittar:** None. **B. Nair:** None.

Poster

814. Neuropeptides: Physiology And Behavior

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 814.10/QQ14

Topic: F.04. Stress and the Brain

Support: R00MH096746

Title: The effects of oxytocin in the bed nucleus of stria terminalis (BNST) on anxiety and fear

Authors: *M. MOADDAB, J. DABROWSKA;
Chicago Med. Sch. (RFUMS), North Chicago, IL

Abstract: Oxytocin (OT) is a hypothalamic neuropeptide that was shown to reduce anxiety and fear. However, the neural circuitry underlying these effects remains elusive. Bed nucleus of stria terminalis (BNST) is a limbic structure critically involved in the modulation of anxiety, and it expresses high levels of OT receptor (OTR). Therefore, the objective of the study was to determine if OTR neurotransmission in the BNST is involved in the modulation of anxiety and fear. To investigate the effects of OT in the BNST on anxiety-related behavior, we used an acoustic startle response (ASR) paradigm. Male Sprague-Dawley rats were implanted with guide cannulas into the BNST and tested for ASR during exposure to 30 startle eliciting noise bursts. Based on their average ASR, animals were assigned into two treatment groups. On the following day, rats were tested for ASR 10 min after bilateral infusion of either vehicle or OT (100 ng) into the BNST. Our results showed that the ASR was significantly lower in OT-treated animals (294.60 ± 54.09) compared to the vehicle-treated animals (667.30 ± 119.61; $P < 0.05$ Bonferroni's post hoc test). Next, to investigate the role of OTR neurotransmission in acquisition of conditioned fear, we used fear-potentiated startle (FPS) paradigm. Following a baseline ASR test, rats received one session of fear conditioning (training with 10 presentations of the cue light with foot-shock), 10 min after bilateral infusion of either vehicle, OT (100 ng) or OTR antagonist (OTRA; (d(CH2)$_5^1$, Tyr(Me)^2, Thr^4, Orn^8, des-Gly-NH$_2^9$)-vasotocin; 200 ng) into the

BNST. Twenty-four hours later, rats were tested for the FPS, where they were exposed to 30 startle eliciting noise bursts with 10 of them presented in a presence of cue light and the other 20 without the cue light. FPS was calculated as a percent change of startle in a presence of cue. As expected, our results showed that startle amplitude was significantly higher in light-noise trials compared to the noise alone trials (trial type; $F = 21.02$, $P < 0.0001$). OT alone did not have an effect on FPS acquisition. However, FPS was significantly lower in OTRA-treated animals (17.48 ± 26.60) compared to the vehicle-treated animals (164.60 ± 33.85; $P < 0.05$ Bonferroni's post hoc test). Our results show that OT in the BNST might have distinct roles in the regulation of anxiety and fear. While exogenous OT reduced anxiety, it did not affect the FPS acquisition. However, blocking OTR disrupted the acquisition of FPS, suggesting that OTR neurotransmission in the BNST is required for the FPS formation. Taken together, these findings provide evidence for the contribution of OT system in the BNST to anxiety as well as development of fear-related behavior.

Disclosures: M. Moaddab: None. **J. Dabrowska:** None.

Poster

814. Neuropeptides: Physiology And Behavior

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 814.11/QQ15

Topic: F.04. Stress and the Brain

Support: DFG NE 465/27-1

Title: The oxytocin system as regulator of stress and anxiety: underlying molecular mechanisms

Authors: *B. JUREK, I. D. NEUMANN;
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Abstract: Animal and human studies on oxytocin (OXT) are accumulating, reporting a barrage of anti-stress and anxiolytic effects, which largely depend on the context, sex, dosage, and duration of the treatment. This may be in part due to the plethora of signaling cascades that are coupled to the OXT receptor (OXTR), such as MEK/ERK1/2, p38, ERK5, CamK, PI3K, Calcineurin, or PKA/PKC. The signal / target specificity of activated OXTR is brought about by the exclusive or combined activation of a yet unknown subset of signaling cascades, which might lead to altered activity of a defined set of nuclear transcription factors, such as CREB, MEF-2, NRSF, or of translation elongation factors (e.g. eEF2) to alter gene expression. These molecular effects on a cellular level ultimately converge to produce an observable behavioral outcome. We focus on the effects of OT, chronically applied icv (1ng/h or 10ng/h) via osmotic minipumps in

male Wistar rats. Western blot data revealed the phosphorylation/activation of the MEK1/2, ERK1/2, and p90RSK pathway and upregulation of protein levels of downstream transcription factors like CREB and MEF-2. An ELISA-based assay revealed increased binding of MEF-2 to its responsive element after chronic OT treatment, which leads to altered gene transcription of stress-associated factors that contain the MEF-2 binding sequence, like CRH-binding protein, CRH receptors 1/2, urocortin, or BDNF by chronic OT treatment exclusively in the hypothalamic paraventricular nucleus (PVN). Changes in the expression of these stress-related factors have been shown to influence stress- and anxiety-like behaviour, confirming our results of increased anxiety-like behaviour after 14 days of chronic icv OT treatment. A better understanding of the brain OXT system and its regulation of and by other factors is essential for the development of effective treatment strategies for patients suffering, for example, from anxiety disorders with minimal side effects of chronic OXT treatment. Supported by DFG NE 465/27-1

Disclosures: **B. Jurek:** None. **I.D. Neumann:** None.

Poster

814. Neuropeptides: Physiology And Behavior

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 814.12/DP06 (Dynamic Poster)

Topic: F.01. Neuroethology

Support: NIH 5T32 NS07606

Title: Optogenetic activation of oxytocin neurons evokes pain avoidance behaviors

Authors: ***S. LUKS-MORGAN**[1,2], C. L. WEE[3], M. NIKITCHENKO[3], J. GAGNON[3], E. SONG[3], O. RANDLETT[3], I. H. BIANCO[4], A. M. B. LACOSTE[3], A. GRAMA[3], D. G. C. HILDEBRAND[3], A. SCHIER[3], S. KUNES[3], F. ENGERT[3], A. D. DOUGLASS[1];
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Abstract: Oxytocin (OXT) is an evolutionarily ancient neuropeptide that is well known for its pro-social functions. However, it is also involved in many non-social and negative processes, including pain, anxiety, fear and stress, although the precise contributions of OXT to these phenomena, and the underlying physiological mechanisms are not well described. We have utilized brain-wide activity mapping and a combination of optical tools to identify a novel role for hypothalamic OXT neurons in pain-related behaviors in the larval zebrafish. By employing light-mediated activation of the small molecule TRPA1 agonist, optovin, we were able to deliver

noxious stimuli in a spatiotemporally precise manner. Optovin stimulation resulted in large-angle tail bends that are similar to behaviors elicited by natural, noxious stimuli. Calcium imaging revealed that a large fraction of zebrafish OXT neurons show robust responses to optovin-mediated photoactivation of TRPA1. This result was corroborated independently by mapping the brain-wide response to other noxious stimuli. To test the involvement of the OXT neurons in pain-related behaviors, we generated fish which express Channelrhodopsin-2 under the control of the OXT promoter and then exogenously activated neurons using brief pulses of blue light. These manipulations elicited avoidance behaviors in free-swimming and head-fixed animals. Conversely, *oxt-/-* animals were less susceptible to optogenetic manipulation of OXT neurons. Together, these results suggest a central role for oxytocinergic neurons in the acute, locomotor response to pain. We are now using a combination of molecular and neuroanatomical techniques to identify targets of OXT that are relevant to these behaviors. These results will generate a more complete understanding of oxytocin's contribution to pain.

Disclosures: **S. Luks-Morgan:** None. **C.L. Wee:** None. **M. Nikitchenko:** None. **J. Gagnon:** None. **E. Song:** None. **O. Randlett:** None. **I.H. Bianco:** None. **A.M.B. Lacoste:** None. **A. Grama:** None. **D.G.C. Hildebrand:** None. **A. Schier:** None. **S. Kunes:** None. **F. Engert:** None. **A.D. Douglass:** None.

Poster

814. Neuropeptides: Physiology And Behavior

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 814.13/QQ16

Topic: G.03. Emotion

Support: DEGAPA IN 204314

CONACyT CB-2013-220173

Title: Effects of oxytocin and quinpirole in the amygdaloid modulation of anxiety.

Authors: ***A. HERNANDEZ**[1], M. PÉREZ DE LA MORA[1], M. CRESPO RAMIREZ[1], K. FUXE[2];
[1]Cognitive neuroscience, Inst. For Cell. Physiol., Mexico city, Mexico; [2]Dept. of Neurosci., Karolinska Inst., Stockholm, Sweden

Abstract: Amygdala is one of the most important structures in anxiety modulation. Oxytocin & dopamine play a prominent role in traffic information in the the central nucleus of the amygdala (CeA), site in where anxiety-like responses are implemented. Previous results of our laboratory

showed that the administration of 25ng/side of oxytocin in CeA evoked an anxiolytic-like effect in shock probe burying test; as reflect of the decrease of the total time of burying compared with the control group treated with saline solution. Likewise, the administration of 3μg/side of quinpirole, which is a D2 receptor agonist, in CeA provoked an anxiolytic-like effect, decreasing the total amount of time of burying compared with the control group treated with saline solution using the same model of anxiety. Given that oxytocin receptors & dopamine D2 receptors are co-expressed in CeA it is possible they to interact between them to potentiate the anxiolytic effect of the oxytocin & quinpirole. The aim of this work is to behavioraly evaluate whether there is interaction between oxytocin-D2 receptors in central nucleus of the amygdala of the rat using a model of anxiety. The existence of the oxytocinergic & dopaminergic receptors interaction are studied employing four groups 1) sub-optimal dose of oxytocin, 2) sub-optimal dose of quinpirole, 3) co-administration sub-optimal dose of quinpirole + sub-optimal dose of oxytocin, 4) saline solution as control group. All drugs are administrated in CeA. Anxiety behavior is assessed using shock probe burying test. Preliminary results show that the group treated with co-administration of oxytocin & quinpirole has a strong tendency to decrease the total time of burying compared with oxytocin-only, quinpirole-only & control group, whereas the groups treated only with oxytocin or quinpirole are not different to control group. Under these conditions the presence of anxiolytic-like effect provoked by quinpirole & oxytocin co-administration compared with other groups would indicate the existence of interaction between oxytocinergic and dopaminergic transmission systems in amygdaloid modulation of anxiety.

Disclosures: A. Hernandez: None. **M. Pérez de la Mora:** None. **M. Crespo Ramirez:** None. **K. Fuxe:** None.

Poster

814. Neuropeptides: Physiology And Behavior

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 814.14/QQ17

Topic: G.03. Emotion

Support: APA Dissertation Research Award

Title: Oxytocin interacts with GABA in the medial prefrontal cortex to reduce anxiety-like behavior

Authors: *S. SABIHI[1], S. MAURER[1], C. POST[1], B. LEUNER[1,2,3];
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Abstract: Numerous studies in animals and humans have established that the neuropeptide oxytocin (OT) reduces anxiety. In rodents, the prelimbic (PL) subregion of the medial prefrontal cortex (mPFC) is among the brain regions implicated in the anxiolytic actions of OT. However, the mechanisms underlying the anxiolytic effect of OT in the mPFC are unknown. Recent work has shown that oxytocin receptors are located on mPFC GABAergic interneurons and that OT increases GABA levels in the mPFC. Thus, we hypothesize that OT in the mPFC attenuates anxiety by enhancing local GABA activity which in turn inhibits glutamatergic projections from the mPFC to limbic areas implicated in anxiety-like behavior. This hypothesis was tested in two experiments. In experiment one, OT was co-administered with the $GABA_A$ receptor blocker bicuculline methiodide into the PL mPFC of adult male rats prior to testing for anxiety-like behavior in the elevated plus maze and social interaction tests. In experiment two, the extent to which OT in the mPFC affected neuronal activation in the amygdala, a target of the mPFC that is involved in anxiety-like behavior, was assessed using c-Fos immunohistochemistry. Our results show OT in the PL mPFC reduced anxiety-like behavior and this effect was blocked by the $GABA_A$ receptor antagonist which by itself, at the dose administered, had no effect on anxiety-like behavior. Furthermore, administration of OT into the PL mPFC resulted in decreased c-Fos expression in the basolateral amygdala. Together, these results demonstrate that OT in the PL mPFC may attenuate anxiety-related behavior by engaging GABAergic neurons which ultimately suppress downstream brain regions implicated in anxiety-like behavior. In doing so, our results provide novel mechanistic insights into OT's anxiolytic actions for which little is currently known despite its potential therapeutic uses.

Disclosures: **S. Sabihi:** None. **S. Maurer:** None. **C. Post:** None. **B. Leuner:** None.

Poster

814. Neuropeptides: Physiology And Behavior

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 814.15/QQ18

Topic: F.04. Stress and the Brain

Support: The present work was supported by a German Research Foundation (Deutsche Forschungsgemeinschaft, DFG) Grant (HU1202/4-1 and BE 5465/2-1 to R.H. and D.S.).

Title: Oxytocin attenuates neural and behavioral responses to chemosensory stress signals

Authors: *D. SCHEELE, A. MAIER, T. MENBA, F. MOHR, W. MAIER, R. HURLEMANN; Univ. of Bonn, Bonn, Germany

Abstract: Multiple lines of evidence indicate that humans, like other macrosmatic mammals, communicate stress states to conspecifics via chemosensory signals. The hypothalamic peptide oxytocin (OXT) has been found to dampen stress responses in visual and auditory modalities. However, it is still unclear whether OXT also modulates the processing of stress-related body odors. Here we present preliminary data of an ongoing randomized, double-blind, placebo (PLC)-controlled, within-subject design study, in which 26 healthy female participants received a single dose of 40 IU intranasal OXT or PLC. We used functional magnetic resonance imaging to scan the participants while they were confronted with stress-related sweat odors, sport sweat, or a non-social control odor (raspberry). During the odor presentation, participants decided whether an ambiguous face shown for a short duration was fearful or non-fearful. Under PLC, stress-related odors biased the participants to perceive ambiguous faces as more fearful compared to sport odors. This effect was positively associated with stress-specific activations in the left amygdala. OXT abolished this behavioral stress bias. On the neural level, OXT globally inhibited amygdala activity in response to social and non-social odors and reduced stress-specific activations in the anterior cingulate cortex. These preliminary data indicate that OXT produces domain-general anti-stress effects. OXT appears to be a promising adjunct for the treatment of psychiatric disorders, such as schizophrenia or posttraumatic stress disorder, which are characterized by altered olfactory stimuli processing and heightened stress vulnerability.

Disclosures: **D. Scheele:** None. **A. Maier:** None. **T. Menba:** None. **F. Mohr:** None. **W. Maier:** None. **R. Hurlemann:** None.

Poster

814. Neuropeptides: Physiology And Behavior

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 814.16/QQ19

Topic: G.03. Emotion

Support: DGAPA IN 204314

Conacyt CB-2013-220173

Title: Effects of clonidine and oxytocin in the modulation of anxiety in rat.

Authors: *J. HERNANDEZ MONDRAGON, M. PÉREZ DE LA MORA;
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Abstract: Anxiety, is an adaptative response that prepare an individual to contend a potential threat, when this response is disproportionate to the stimulus that is causing it or appears without

apparent cause, then this response is consider to become pathological. The amygdala is a key structure for the modulation of anxiety and within it, both alpha-2 adrenoceptors and oxitocinergic receptors, play an important role in the modulation of anxiety. Because these receptors can be found close from each other in the central amygdala, it is possible that an interaction between both receptors exists and this interaction may cause an increase anxiolytic effects.
The main aim of this study is search the existence of the interaction between oxitocinergic receptors and alpha 2 adrenoreceptors within the amygdala in rat. So, through bilateral microinjections within the central amygdala of clonidine (adrenergic agonist α-2) and oxytocin (OT), we define effective dose and sub-threshold doses of both agonists, these doses was test in the elevated plus-maze (EPM), this test is employ to evaluate anxiety. Our results show that 1.2 µg clonidine increased the time spent in the open arms in elevated plus-maze. While,10 ng OT showed tendency to increase the time spent in the open arms in EPM. Alpha-2 adrenoreceptor activation has anxiolytic effects in elevated plus-maze, nevertheless, oxcitocinergic receptor activation seems elicit anxiolytic effects. In accordance with our results, we will apply jointly sub-threshold doses of both agonists to examine the possible existence of an interaction between oxitocinergic receptors and α-2 adrenoreceptors, and this interaction is involving to increase the anxiolytic effects both receptors have.

Disclosures: J. Hernandez Mondragon: None. **M. Pérez de la Mora:** None.

Poster

814. Neuropeptides: Physiology And Behavior

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 814.17/QQ20

Topic: G.03. Emotion

Support: CONACYT 220173

DGAPA IN203111

Title: Differential activation of vasopressin receptors on the amygdaloid modulation of fear and anxiety in the rat.

Authors: *O. R. HERNANDEZ PEREZ[1], M. CRESPO[2], K. FUXE[3], M. PEREZ DE LA MORA[4];
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Abstract: Vasopressin is a peptide synthesized in the paraventricular nucleus (PVN) and supraoptic (SON) of the hypothalamus. Three different receptors have been so far identified for vasopressin effects (V1a, V1b and V2 receptors). The central vasopressin release contributes to behavioral regulation, emotional states such as fear, depression and anxiety through the V1a and V1b receptors. The effects of vasopressin on anxiety have been shown using vasopressin deficient strains, knock out mice and drug administrations. The amygdala is a key structure in processing anxiety because sensory information integrates and implements responses to aversive stimuli. In the central nucleus of the amygdala it has been reported the existence of V1a and V1b vasopressin receptors using the rat as a model. Various behavioral studies have shown the involvement of V1a and V1b receptors in anxiety using different behavioral paradigms and aiming related structures in anxiety. The aim of this study was to evaluate the possible differential activation of vasopressin receptors within the central amygdaloid nucleus in tests of fear and anxiety. In this study was to evaluate the behavior of rats in the elevated plus-maze and the shock-probe burying and dark light box test following vasopressin administration (1 and 10 ng/side) or simultaneous administration of arginine vasopressin (1 ng/side) and SSR149415 (1 and 10 ng/side), a specific V1b vassopresin receptor antagonist within the central amygdaloid nucleus. The results showed that the bilateral microinjection of arginine vasopressin at lower (1ng /side) but not at higher (10 ng/side) doses significantly increased the time spent by the rats in the open arms of the elevated plus-maze as compared with their saline-treated controls. No effects of this treatment were observed on the total number of entries into open + closed arms of the maze. In contrast, the infusion of arginine vasopressin (1ng/side) increased the burying behavior in the shock-probe burying test. Interestingly, this last behavior was not observed when SSR149415 was administered simultaneously with vasopressin. Our results suggest, that whereas the bilateral administration of arginine vasopressin has an anxiogenic effect in the shock-probe burying test seem to be mediatiad by the activation of arginine vassopresin V1b receptors.

Disclosures: O.R. Hernandez Perez: None. **M. Crespo:** None. **K. Fuxe:** None. **M. Perez de la Mora:** None.

Poster

814. Neuropeptides: Physiology And Behavior

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 814.18/RR1

Topic: F.04. Stress and the Brain

Support: NIMH R01 MH52619

NIA 1K01AG044466

Title: Orexin depolarizes central amygdala neurons via activation of orexin receptor 1 and downstream activity of sodium calcium exchanger

Authors: *E. T. DUSTRUDE[1,3], C. S. BERNABE[2,3,4], S. BHATNAGAR[5], P. L. JOHNSON[2,3], A. I. MOLOSH[1,3], A. SHEKHAR[1,3,6];
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Abstract: Orexin is an excitatory neuropeptide involved in regulation of wakefulness, arousal, and energy homeostasis. Recently, it has been shown that orexin plays an important role in modulation of panic and fear memories. This is consistent with the existence of orexin projections from the perifornical hypothalamus (PeF) to the amygdala, a structure responsible for emotional processing and fear memory. Previous data demonstrates a high density of orexin-positive fibers within the central nucleus of the amygdala (CeA) and that application of orexin within the CeA depolarizes neurons and confers resistance to fear extinction in a cued-induced fear conditioning paradigm. Together, these data highlight the importance of orexin release into the CeA during coordination of fear memories, but molecular determinants of this effect are yet to be elucidated. Our laboratory has previously shown that orexin-mediated depolarization of CeA neurons occurs via activation of orexin receptor 1 (OxR1). To further our understanding of the cellular effects of orexin in the CeA, we utilized whole-cell patch-clamp technique in male rat brain slices. Using a chemogenetic approach, we injected an adeno-associated virus vector within the PeF designed to express a Designer Receptor Exclusively Activated by Designer Drugs (DREADD) coupled to the prepro-orexin promoter to target orexinergic neurons. We then demonstrated that clozapine-N-oxide-mediated stimulation of DREADD excited orexinergic projections from the PeF to induce membrane depolarization of CeA neurons. Additionally, we have found that orexin stimulates glutamate release from presynaptic terminals. Next, our data show that orexin-mediated depolarization of CeA neurons occurred independently of changes to potassium conductance, a mechanism that has been previously implicated in orexin-mediated depolarization of locus coeruleus, median preoptic nucleus, and paraventricular nucleus neurons. Instead, CeA depolarization required high sodium ion reversal potential and driving force. This dependence was further characterized to involve activity of CeA-expressed sodium/calcium exchangers (NCX) through the use of NCX antagonist KB-R7943. Ongoing experiments aim to further dissect the intracellular machinery connecting activation of OxR1 to NCX activity.

Disclosures: **E.T. Dustrude:** None. **C.S. Bernabe:** None. **S. Bhatnagar:** None. **P.L. Johnson:** None. **A.I. Molosh:** None. **A. Shekhar:** None.

Poster

814. Neuropeptides: Physiology And Behavior

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 814.19/RR2

Topic: F.04. Stress and the Brain

Support: VA Advanced Research Fellowship

Great Plains Medical Research Foundation

NIH R15

Title: Topographical organization of perifornical orexin neurons; Implications for stress-induced disorders

Authors: *P. J. RONAN[1], T. D. SKOG[1], J. J. BRUDVIG[1], L. B. CALLAHAN[1], C. H. SUMMERS[2];
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Abstract: Orexin/hypocretin (ORX) and corticotropin releasing factor (CRF) play key, sometimes parallel, roles in a host of arousal/stress responses. They have been implicated in a range of stress-induced psychiatric disorders including addiction, depression and sleep disorders. There is evidence that these systems interact and regulate each other - perhaps providing a feed forward mechanism for enhanced stress responses and a potential mechanism for fine tuning stress responses. Orexin neurons receive inputs from many CRF-rich neuronal fields including the paraventricular nucleus of the hypothalamus (PVN), bed nucleus of the stria terminalis (BNST) and central nucleus of the amygdala (CeA). Using a combination of neuronal tracing methods and immunohistochemistry we sought to build on this earlier work and clarify if these afferent pathways include CRF neurons and secondly, to determine whether these inputs have any topographical organization. We provide further evidence that CRF neurons in these regions specifically project to ORX neuron fields. Additionally, we describe the anatomical organization of afferent pathways from key stress-responsive regions into the ORX cell body region. There appears to be specific topographic distribution of inputs supporting the hypothesis that perifornical ORX neurons preferentially contribute to stress and anxiety responses.

Disclosures: P.J. Ronan: None. **T.D. Skog:** None. **J.J. Brudvig:** None. **L.B. Callahan:** None. **C.H. Summers:** None.

Poster

814. Neuropeptides: Physiology And Behavior

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 814.20/RR3

Topic: G.03. Emotion

Support: CIHR MOP-89758

Title: Role of the orexin (hypocretin) system in contextual fear conditioning in rats

Authors: *H. WANG[1], S. LI[1], G. J. KIROUAC[1,2];
[1]Oral Biol., [2]Psychiatry, Univ. of Manitoba, Winnipeg, MB, Canada

Abstract: Orexin (hypocretin) neurons located in the posterior hypothalamus send projections to multiple areas of the brain involved in arousal. Experimental evidence indicates that the orexin system plays a role in the physiological and behavioral responses to stress. Previous work in our laboratory has also shown that the level of the gene expression for peptide prepro-orexin (ppOX) was increased in the hypothalamus two weeks after exposing rats to footshocks and that systemic injections of a dual orexin antagonist decreased the amount of freezing displayed when shock rats were placed in the shock context (contextual fear condition). The present study examined if systemic injections of a specific antagonist for the orexin 1 receptor (OX1R; SB334867) or the orexin 2 receptor (OX2R; TCSOX229) as well as the dual orexin antagonist TCS1102 attenuated contextual fear. Shocked rats were exposed to footshocks (1.5 mA, 5 × 2 sec with an inter shock period of 10-50 s presented randomly) whereas nonshocked rats were placed in the shock chamber without footshocks. The OX1R antagonist when given at doses of 20 and 30 mg/kg (i.p.) decreased freezing when tested at 14 days postshock while the same doses of the OX2R antagonist had no effect. The dual orexin antagonist given at a dose of 20 mg/kg also decreased contextual freezing. Real-time RT-PCR was used to examine changes in the mRNA levels for ppOX, OX1R and OX2R in the posterior hypothalamus, locus ceoruleus/parabrachial region, and the dorsal midline thalamus at 14 days postshock. We found that the mRNA levels for ppOX and the OX1R were increased in the posterior hypothalamus of shocked rats. An increase in OX1R in the posterior hypothalamus of shocked rats was also established using Western blot. No significant difference was observed in the mRNA levels of OX1R and OX2R in samples of the midline thalamus and locus coeruleus/parabrachial region. The results of the present study show an upregulation of orexin activity and of the OX1R in the hypothalamus following exposure of rats to footshocks and highlight a specific role of OX1R in contextual fear.

Disclosures: H. Wang: None. **S. Li:** None. **G.J. Kirouac:** None.

Poster

814. Neuropeptides: Physiology And Behavior

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 814.21/RR4

Topic: F.04. Stress and the Brain

Support: R21MH102735

Title: Inhibition of orexin neurons by DREADDs promotes resilience to social defeat.

Authors: *D. EACRET, L. GRAFE, S. LUZ, S. BHATNAGAR;
Children's Hosp. of Philadelphia, Philadelphia, PA

Abstract: Chronic exposure to stress in the form of major life events such as bereavement, prolonged conflict or low socioeconomic status is associated with increased incidence of depression, post-traumatic stress disorder and chronic fatigue syndrome. However, some individuals are resilient to the effects of stress while others are more vulnerable. Identifying the substrates underlying resilience and/or vulnerability could lead to novel individualized treatments for enhancing resilience or mitigating vulnerability. Our work has identified a model of repeated social defeat in adult male rats in which two distinct subpopulations emerge with different coping strategies, one that is resilient and one that is vulnerable to the behavioral and neuroendocrine consequences of repeated social defeat. Our preliminary data also show that these two subpopulations differ in the expression of orexins, peptides that are key for arousal, wakefulness and vigilance. The resilient population exhibits lower orexin expression leading to the **hypothesis** that dampened orexin system function is associated with resilience to the effects of repeated defeat. In the current experiment, we developed DREADDS (designer receptors exclusively activated or inhibited by designer drugs) specifically targeted to orexins to inhibit orexin neuron activity in rats exposed to repeated social defeat. Rats were exposed to 5 days of social defeat or no stress, then exposed to another 3 days of defeat or no stress with injections of vehicle or CNO (to activate orexin cells transfected with inhibitory DREADDs) administered prior to each of the 3 days of defeat. All rats were then tested in the forced swim test. We observed that rats classified as vulnerable based on their latencies to be defeated and that were injected with vehicle during the previous 3 days of defeat exhibited increased immobility upon exposure to forced swim, suggesting a pro-depressive profile. This was reversed by inhibition of orexin neurons by CNO. No effects of orexin inhibition were observed in the resilient rats. These results suggest that inhibition of orexins in rats vulnerable to stress can reduce certain aspects of their vulnerability and promote resilience. We are currently testing the effects of stimulation of orexin neurons by DREADDs and determining relevant sites of actions of orexins.

Disclosures: **D. Eacret:** None. **L. Grafe:** None. **S. Luz:** None. **S. Bhatnagar:** None.

Poster

814. Neuropeptides: Physiology And Behavior

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 814.22/RR5

Topic: F.04. Stress and the Brain

Support: McLean-Brookings Fellowship (KL)

MH097860 (WC)

Title: Influence of PACAP on stress related phenotypes

Authors: *K. R. LEZAK, A. J. ALEXANDER, R. J. DONAHUE, A. M. WELLS, W. A. CARLEZON, Jr;
McLean Hospital, Harvard Med. Sch., Belmont, MA

Abstract: Pituitary adenylate cyclase-activating polypeptide (PACAP) and its cognate receptor (PAC1) have been associated with numerous psychiatric illnesses triggered by exposure to stress, including post-traumatic stress disorder and major depressive disorder. In rats, exposure to repeated variate stress increases PACAP and PAC1 expression in brain regions implicated in anxiety- and depression-like behaviors, and stress responsiveness. PACAP signaling is both necessary and sufficient to produce many of the behavioral and molecular consequences of stress. As such, it is conceivable that changes in PACAP signaling contribute importantly to the symptoms of mood and anxiety disorders as well as frequently co-morbid conditions, such as alcohol use disorder (AUD). In the current studies, we treated male C57BL/6J mice with intracerebroventricular (ICV) PACAP (0.0μg/μl, 0.02μg/μl, 0.1μg/μl, 0.25μg/μl, and 0.5μg/μl) and examined social interaction behavior and anxiety-like behavior on the elevated plus-maze. Due to the ability of PACAP to influence motivated behavior (e.g., intracranial self-stimulation), we also characterized the interaction between alcohol consumption and PACAP signaling in mice utilizing two voluntary alcohol consumption paradigms that result in steady-state or escalated alcohol consumption, respectively. Finally, considering that sleep architecture is altered in many psychiatric illnesses, we monitored EEG/EMG activity following ICV PACAP infusion utilizing implantable wireless telemetry devices. Specifically, we examined the impact of PACAP infusion on the various stages of sleep (slow-wave sleep and paradoxical sleep) as well as activity and temperature. Implications for the interactions among these systems and the mechanism for these PACAP induced effects will be discussed.

Disclosures: K.R. Lezak: None. **A.J. Alexander:** None. **R.J. Donahue:** None. **A.M. Wells:** None. **W.A. Carlezon:** None.

Poster

814. Neuropeptides: Physiology And Behavior

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 814.23/RR6

Topic: F.04. Stress and the Brain

Support: CIHR Grant MOP-62921

Fondation du CHU de Québec

Title: Enkephalin and Delta opioïd receptor promote the resilience to chronic stress

Authors: *M. S. HENRY, N. VERNOUX, M.-É. TREMBLAY, G. DROLET;
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Abstract: The capacity to resist the stress is very variable from one individual to an other. Resilience to chronic stress is a complex process involving many brain structures and neurotransmitter systems. Among neuropeptidergic systems, endogenous opioids like enkephalins (ENK) would potentially be involved in this process. We propose the hypothesis that ENK signaling taking place via the Delta opioid receptors (DOR) is specifically involved in resilience to chronic stress.
AIM.
The purpose of this study is to identify and characterize the functional contribution of ENK transmission acting through the DOR in the development of resilience to chronic stress.
METHODS.
The model of chronic social defeat stress allows to study the resilience to stress by mimicking the unpredictable social disruption of daily life. In this 10 days experiment, a "victim" is placed in the vivarium of an "aggressor" for 5 minutes per day. On the 11th day, we evaluate the level of anxiety of the "victim" with a social interaction test to distinguish two groups: resilient and vulnerable to chronic stress. Victims are daily treated (or untreated for control) with a DOR agonist, the SNC80 (s.c. 10 mg / kg) 1 hour before the social defeat. The level of plasma corticosterone was evaluated by ELISA to confirm the release of stress hormones and thus the effectiveness of the stress paradigm. mRNA levels of ENK, the DOR and the neurotrophic factor, the brain-derived-neurotrophic-factor (BDNF) which is stimulated by ENK signaling, are quantified in different brain areas receiving ENK projections by radioactive *in situ* hybridization.
RESULTS.
The administration of SNC80 induces a resilient phenotype on most tested individuals. The ENK mRNA is increased in resilient individuals compared to vulnerable ones in the basolateral nucleus of the amygdala (BLA) (11 vs 10, $p < 0.05$). The DOR mRNA and BDNF are increased in resilient individuals compared to vulnerable ones in the CA1 region of the hippocampus (11

vs 10, $p < 0.05$).
CONCLUSIONS.
A privileged dialogue between the BLA and CA1 of the hippocampus acting through ENK transmission (via DOR and BDNF downstream recruitment) takes part in the development of resilience to chronic stress.

Disclosures: **M.S. Henry:** None. **N. Vernoux:** None. **M. Tremblay:** None. **G. Drolet:** None.

Poster

814. Neuropeptides: Physiology And Behavior

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 814.24/RR7

Topic: F.04. Stress and the Brain

Support: NIH Grant NS048602

Title: Anatomical, morphological, and electrophysiological properties of central amygdala dynorphin neurons

Authors: ***J. G. MCCALL**, B. A. COPITS, V. K. SAMINENI, R. W. GEREAU, IV; Anesthesiol., Washington Univ., Saint Louis, MO

Abstract: The central amygdala (CeA) is a critical anatomical substrate for emotional regulation in response to stress, pain, and drugs of abuse. While much is known the identity of cell-types composing the CeA, much less is understood about the unique properties of these molecularly defined neurons. Here we focus on a subset of neurons in the CeA expressing the neuropeptide dynorphine (Dyn+), the endogenous ligand of the kappa opioid receptor. To genetically identify dynorphinergic (Dyn) neurons, we crossed the Cre-dependent tdTomato (Ai9) reporter mouse to a mouse that expresses Cre recombinase under the same promoter as preprodynorphin (Dyn-Cre). In this model, only dynorphinergic cells express tdTomato, allowing complete visualization of dynorphinergic circuitry throughout the brain. Consistent with previous *in situ* hybridization results, we find robust dynorphin expression in cell bodies throughout the central amygdala. These animals enable targeted whole-cell recordings in amygdala slices. We report the intrinsic properties of these neurons including the input resistance, resting membrane potential, and firing profiles compared to neighboring Dyn- CeA neurons. We also identify incoming spontaneous and evoked synaptic transmission to these neurons. Furthermore, the morphology of these Dyn+ neurons is defined by filling the cells with Neurobiotin. In addition to its local circuitry, the CeA is also a major output nuclei of the amygdala. To determine the long-range connectivity of Dyn+ CeA neurons, we utilize cell-type selective expression of reporter viruses in tandem with

retrograde labeling to identify these molecularly-defined projections throughout the brain, including brainstem targets in the parabrachial nucleus and locus coeruleus. Together these data provide a base knowledge for further cell-type selective manipulation and observation *in vivo*. Understanding the mechanisms by which the dynorphin/kappa opioid system regulates emotional processing in the context of stress, chronic pain, and addiction will provide valuable insight into potential therapeutic targets for these neurological and neuropsychiatric disorders.

Disclosures: J.G. McCall: None. **B.A. Copits:** None. **V.K. Samineni:** None. **R.W. Gereau:** None.

Poster

814. Neuropeptides: Physiology And Behavior

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 814.25/RR8

Topic: F.04. Stress and the Brain

Support: MH-097988 to SEH

Title: The effects of prior stress on anxiety-like responding to intra-BNST pituitary adenylate cyclase activating polypeptide (PACAP) in male and female rats.

Authors: *S. B. KING[1], B. BRUMBAUGH[1], D. VORMSTEIN-SCHNEIDE[1], V. MAY[2], S. E. HAMMACK[1];
[1]Psychological Sci., Univ. of Vermont, Burlington, VT; [2]Dept. of Neurolog. Sci., Univ. of Vermont Col. of Med., Burlington, VT

Abstract: Chronic or repeated exposure to stressful stimuli can result in several maladaptive consequences, including increased anxiety-like behaviors and altered peptide expression in anxiety-related brain structures. Among these structures, the bed nucleus of the stria terminalis (BNST) has been implicated in emotional behaviors as well as regulation of hypothalamic-pituitary-adrenal (HPA) axis activity. In male rodents, chronic variate stress (CVS) has been shown to increase BNST pituitary adenylate cyclase activating polypeptide (PACAP) and its cognate PAC1 receptor transcript, and BNST PACAP signaling may mediate the maladaptive changes associated with chronic stress. Here, we examined whether chronic variate stress (CVS) would sensitize the behavioral and/or endocrine response to a subthreshold BNST PACAP infusion. Male and cycling female rats were exposed to a 7 day CVS paradigm previously shown to upregulate BNST PAC1 receptor transcripts; control rats were not stressed. 24 hr following the last stressor, rats were bilaterally infused into the BNST with 0.5 μg PACAP. We found an increase in startle amplitude and plasma corticosterone levels 30 minutes following intra-BNST

PACAP infusion in male rats that had been previously exposed to CVS. CVS did not enhance the startle response in cycling females. Equimolar infusion of the VPAC1/2 receptor ligand vasoactive intestinal polypeptide (VIP) had no effect on plasma corticosterone levels even in previously stressed male rats. These results suggest that repeated exposure to stressors may differentially alter the neural circuits underlying the behavioral and endocrine responses to intra-BNST PACAP and may result in different anxiety-like responses in males and females.

Disclosures: S.B. King: None. **B. Brumbaugh:** None. **D. Vormstein-Schneide:** None. **V. May:** None. **S.E. Hammack:** None.

Poster

814. Neuropeptides: Physiology And Behavior

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 814.26/RR9

Topic: F.04. Stress and the Brain

Support: CIHR 86501

Brain Canada

AIHS CRIO 201200828

Title: Experimentally-induced colitis promotes anxiogenesis — a possible role for central amygdala CRH neurons

Authors: *B. HUNT[1], K. D. NYUYKI[2], Q. J. PITTMAN[2], K. A. SHARKEY[2], J. S. BAINS[2]; [1]Neurosci., [2]Univ. of Calgary, Calgary, AB, Canada

Abstract: Peripheral inflammation can profoundly affect behaviour and mood, but relatively little is known about mechanisms linking inflammation in the periphery with brain and behavioural changes. The central amygdala (CeA) is a key structure for behavioral control. Here we hypothesize that peripheral inflammation, induced by dextran-sodium sulphate (DSS), alters the intrinsic membrane and synaptic properties of corticotropin-releasing hormone (CRH) neurons in the central amygdala (CeA). Since CeA CRH neurons participate in a circuit that promotes anxiety, these alterations may underlie the anxiogenic phenotype mice with DSS-induced colitis display. Inflammation was induced in the gut by adding DSS to the drinking water of C57BL/6J mice for five days. This treatment significantly increased anxiety-like behaviour on the elevated plus maze EPM. DSS treated mice spent less time in open arms (control: 20.5 + 2.4%; n =15 vs DSS: 6.35 $\pm$ 1.7%; n=15, $p<0.0001$) and more time in closed arms (control: 63.8 $\pm$ 2.5% n=15 vs DSS: 80.6 $\pm$ 2.5%; n=15, $p<0.001$), when compared to

control animals. To identify CRH neurons in the CeA, we utilized *Crh-IRES-Cre;Ai4* mice, which express red tdTomato fluorescence in all CRH producing neurons, including those in the CeA. Whole-cell current clamp recordings revealed that tdTomato+ neurons, from DSS-treated mice, exhibited a decrease in excitability (control: 9.25 $\pm$ 0.9 APs; n= 8 vs DSS: 5.67 $\pm$ 0.9 APs; n = 15, $p<0.001$.); and an increase in latency to first spike when compared to control animals (control: 26.7 $\pm$ 6 msec; n=8 vs DSS: 68.4 $\pm$ 9 msec; n=15). Whole-cell voltage-clamp recordings, in the presence of picrotoxin, revealed no changes in spontaneous excitatory post-synaptic currents following DSS (Amplitude; control: 28.56 $\pm$ 3 pA vs DSS: 23.65 $\pm$ 1 pA; $p>0.05$; Frequency; control: 1.5 $\pm$ 0.4 Hz; n=6 vs DSS: 2.4 $\pm$ 0.3 Hz; n=12, $p>0.05$). There was a decrease in the paired-pulse ratio (PPR) when compared to control animals (control: 1.01 $\pm$ 0.07; n=7 vs DSS: 0.81 $\pm$ 0.03; n=10, $p<0.01$). When the NMDA receptor-mediated current was unmasked and compared to the AMPA receptor-mediated current (AMPA:NMDA ratio), there was no difference between DSS-treated and control animals (6.6 $\pm$ 1.3; n=7 vs 4.4 $\pm$ 0.5; n=7, $p>0.05$). DSS-treated animals show an anxiogenic phenotype, decreased neuronal excitability and decreased glutamate release probability in CeA CRH
neurons. These observations provide a platform to investigate a precise mechanism by which peripheral inflammation alters the excitability of CRH neurons in the CeA and allow us to understand how these neurons function/dysfunction in anxiety and stress related circuits.

Disclosures: B. Hunt: None. **K.D. Nyuyki:** None. **Q.J. Pittman:** None. **K.A. Sharkey:** None. **J.S. Bains:** None.

Poster

815. Circadian Mechanisms

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 815.01/RR10

Topic: F.08. Biological Rhythms and Sleep

Support: CONACyT (239403)

PAPIIT-UNAM (I6200314)

Title: Constant light during lactation programs circadian and metabolic functions in rat pups

Authors: *M. PALMA, I. OSNAYA, A. BALDERAS, D. ORTEGA, D. ORTEGA, C. ESCOBAR BRIONES;
Anat., UNAM, mexico city, Mexico

Abstract: Epidemiological and experimental evidence support an association between constant light (LL) expossure and an increased incidence of overweight and metabolic disease in rats. The present study aimed to describe the effects constant light (LL) during lactation on the development of the suprachiasmatic nucleus (SCN), on body weight and metabolism in rat pups. New born rats were randomly assigned to one of three groups: Control photoperiod 12:12 (LD), Constant darkness (DD) or Constant light (LL). Lighting conditions were maintained along lactation from P0 to P21. In order to specifically evidence the effects of light conditions in the pups, the nursing mothers had a normal LD cycle. At P21 after weaning we determined daily rhythms of glucose, general activity, Vasoactive Intestinal Peptitde (VIP), Argininge Vasopresine Peptide (AVP) and the clock protein PER1 in the SCN.
General activity was assessed from P14 to P21 and we found that in LD conditions 100% of animals litters in LD conditions, 33.33% of litters in DD conditions and 16.67% of litters in LL were rhytmic, [(percentage: arrhytmic animals/total animals)*100)]. In pups exposed to DD and LL rhythm was observed for the peptides AVP and VIP and the clock protein PER1 in the SCN additionally the number of positive inmunoreactive cells of VIP and AVP was decreased in DD and LL conditions. In LL-exposed animals body weight gain was significantly increased as well as fat mass, the glucose rhythm was lost in both DD and LL conditions. The body weight remained higher until the day P90 in animals exposed to LL during lactation.
Overall our results show that expossure to LL as well as DD affects the development of the SCN leading to adecreaed VIP and AVP cell number and a loss of rhythmicity. These animals also had metabolic disturbance and increased weight gain. Present point out the relevance of a normal LD cycle for the development of the SCN and urge to revise the conditions in Neonatal Intensive Care Units as well as in the house enviroment in order to avoid long lasting perturbations in the metabolic and circadian systems.

Disclosures: **M. Palma:** None. **I. Osnaya:** None. **A. Balderas:** None. **D. Ortega:** None. **D. Ortega:** None. **C. Escobar Briones:** None.

Poster

815. Circadian Mechanisms

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 815.02/RR11

Topic: F.08. Biological Rhythms and Sleep

Support: NSF Grant IOS 11-18792

NIDCR T32DE014320

Title: Parental exposure to dim light at night prior to mating alters offspring adaptive immunity

Authors: *Y. M. CISSE[1], R. J. NELSON[2];
[1]Neurosci., [2]The Ohio State Univ. Wexner Med. Ctr., Columbus, OH

Abstract: Environmental light is the most potent signal for synchronizing the circadian system. Disruption of natural light/dark cycles by light at night (LAN) dampens endogenous biological rhythms that maintain optimal function of various systems, including the endocrine and immune systems. Dim LAN (dLAN) exposure impairs innate and cell mediated immune responses in Siberian hamsters (*Phodopus sungorus*). Circadian disruption studies have thus far focused on adults, but impaired maternal immune and endocrine function affects offspring immune phenotype. Because of potential transgenerational effects of dLAN, we hypothesized that parental exposure to dLAN *prior* to mating influences offspring immune function. Adult male and female Siberian hamsters were exposed to either dark nights (Dark) or dLAN for 9 weeks, then paired, mated, and thereafter housed in dark nights. Pairings resulted in four groups: Dark/Dark (Male/Female), Dark/dLAN, dLAN/Dark, and dLAN/dLAN. Adult offspring were tested for cell-mediated, humoral, and innate immunity. Male offspring of dams exposed to dLAN dampened cell-mediated swelling reactions. Male offspring of Dark/dLAN and dLAN/Dark parents produced more antibodies in response to a novel antigen. In female offspring, maternal and paternal exposure to dLAN decreased swelling response. Female offspring of dams exposed to dLAN produced more antibodies in response to a challenge. Global splenic DNA methylation was assessed as a mediator of altered offspring immune function. Paternal exposure to dLAN decreased splenic methylation and altered DNA methyltransferase 1 expression (DMNT1) in an offspring sex-specific manner. Overall, parental exposure to dLAN decreased offspring cell-mediated immunity and enhanced humoral immunity in a parent and offspring sex-specific manner. These phenotypes may be mediated by global alterations in the epigenetic landscape of immune tissues, suggested by global alterations in methylation and altered methylation machinery. Altered immune responsiveness in offspring that have experienced dLAN in the germline indicates that seemingly innocuous nighttime lighting may have transgenerational effects on immune function.

Disclosures: Y.M. Cisse: None. **R.J. Nelson:** None.

Poster

815. Circadian Mechanisms

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 815.03/RR12

Topic: F.08. Biological Rhythms and Sleep

Support: PAPIIT UNAM IN212715

Title: Circadian misalignment between hypothalamus and ovary in obese mice Neotomodon alstoni

Authors: M. PEREZ-MENDOZA[1], C. R. JUAREZ-TAPIA[1], G. MARTINEZ-MORALES[1], M. CARDENAS LEON[2], *M. MIRANDA-ANAYA[1];
[1]Facultad De Ciencias, UNAM, Querétaro, Mexico; [2]2.Instituto de Ciencias Médicas y de la Nutrición, Salvador Zubirán, Mexico City, Mexico

Abstract: Obesity has become a serious health problem in industrialized countries. Obesity seems to be related to the disturbances of circadian misalignment between central and peripheral oscillators, which may negatively affect physiological functions such as reproduction. Studies on diverse animal models are needed to understand the consequences of obesity. The volcano mouse *Neotomodon alstoni*, develops obesity in some animals with no need of high caloric diets, while some other animals remain lean, which represent a different animal model in which we can address this research. The aim of this work was to compare, between lean and obese female mice, whether the clock protein BMAL1 and Estrogenic Receptors present a different daily profile in hypothalamus and ovary. We also compared the circulating levels of Estrogen and LH along the estrous cycle; 20 lean (45±5 g) and 20 obese females (65±5 g) were used. Animals were kept at 18-23°C, and light-dark cycles 12:12 hours (photo phase: 06:00-18:00, 200-250 lx). Tissue samples of females in diestrous (brain and ovary) were collected at 10:00, 15:00, 19:00, 24:00 and 05:00 h. Estrogen Receptors (ER), Leptin receptors and BMAL1 were evaluated by Western Blot. Circulating Leptin, Estrogen and LH hormones were quantified by means of ELISA. Results indicate that the daily rhythms of BMAL1, Leptin and Estrogen Receptors in hypothalamus show reduced amplitude and different profile in obese compared to lean mice. Also differences in BMAL1 were found in ovary. Obese mice present irregular estrous cycle, and a stationary phase in diestrous associated to differences in endocrine signals. Obese mice had higher concentrations of Leptin, Estrogen, and low concentration of LH hormones than lean mice. Interactions between Estradiol and Leptin are critical hormones in the regulation of body weight. These results indicate that in obese females *Neotomodon alstoni* a circadian misalignment is associated with the endocrine disruption between hypothalamus and ovary signalling.

Disclosures: M. Perez-Mendoza: None. **C.R. Juarez-Tapia:** None. **G. Martinez-Morales:** None. **M. Cardenas Leon:** None. **M. Miranda-Anaya:** None.

Poster

815. Circadian Mechanisms

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 815.04/RR13

Topic: F.08. Biological Rhythms and Sleep

Support: STW grant OnTime, project 12195

Title: Acute effects of light at night on glucose metabolism in rats

Authors: *A. KALSBEEK[1,2], A.-L. OPPERHUIZEN[2], D.-J. STENVERS[1], R. D. JANSEN[2], E. FOPPEN[1], E. FLIERS[1];
[1]Academic Med. Ctr. (AMC), Dept Endocrinol & Metab, Amsterdam, Netherlands;
[2]Hypothalamic Integration Mechanisms, Netherlands Inst. for Neurosci. (NIN), Amsterdam, Netherlands

Abstract: Light is the most important cue for the brain biological clock in the suprachiasmatic nuclei (SCN) to synchronize its endogenously generated rhythmic activity with the outside world. The SCN *master clock* translates 'environmental time' to 'endogenous time' via hormones and the autonomic nervous system (ANS) to optimally prepare bodily physiology for recurring daily changes. The SCN directly controls (organs involved in) glucose homeostasis, including basal glucose levels and glucose tolerance. Nowadays, electrical lighting is widely used around the world, but possible harmful effects of the 24/7 presence of light have become apparent only recently. In particular, use of light at night (LAN) is considered potentially disruptive, as this is an unnatural time for organisms to deal with light signals. LAN has been correlated with increased risk to develop cancer, depression, insomnia, overweight and obesity. Besides human epidemiology, rodents exposed to nocturnal (dim)light for several days or weeks, have been shown to increase body weight and develop glucose intolerance and insulin resistance. Acute experiments revealed alterations in the release of hormones, such as melatonin and corticosterone. Furthermore, 1-h of nocturnal light altered gene expression of clock and metabolic genes within multiple organs, including liver, pineal and heart. Surgical removal of the autonomic input to liver or adrenal reversed these effects of LAN, confirming the potential of light to affect the ANS. The correlation between LAN and metabolic disorders together with the power of light to control the SCN and downstream targets, such as the liver, made us hypothesize that LAN might affect glucose homeostasis acutely. We investigated this hypothesis by exposing Wistar rats to glucose and insulin tolerance tests at different times of day in abnormal lighting conditions. Light exposure at ZT15 and ZT21, as well as exposure to darkness at ZT3, acutely induced glucose intolerance. The specific effects of light were dependent on time-of-day, resulting in increased glucose, but unaltered insulin responses at ZT15 and ZT3, and an increased insulin but unaltered glucose response at ZT21. Furthermore, we showed that at ZT15 the effect of light was dose dependent in terms of intensity and exposure duration. Currently we are investigating whether the effects of light are wavelength dependent. Additional experiments are aimed at revealing the mechanism of glucose tolerance, as insulin sensitivity was not affected and also changes in corticosterone and activity were not explanatory, as well as the neuro-anatomical substrate using co-staining's for c-fos and hypothalamic neuropeptides.

Disclosures: **A. Kalsbeek:** None. **A. Opperhuizen:** None. **D. Stenvers:** None. **R.D. Jansen:** None. **E. Foppen:** None. **E. Fliers:** None.

Poster

815. Circadian Mechanisms

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 815.05/RR14

Topic: F.08. Biological Rhythms and Sleep

Support: FC-UNAM2016

Title: Chronic lead exposition affects neuronal activation of the suprachiasmatic nuclei of the male rat.

Authors: *H. A. MOLINA[1], J. ROJAS-CASTAÑEDA[2], P. DURAN[1];
[1]Lab. de Biología Animal Exptl., Univ. Nacional Autónoma De México, Mexico City, Mexico;
[2]Lab. de Biología de la Reproducción, Inst. Nacional de Pediatría, Mexico City, Mexico

Abstract: In mammals, the hypothalamic suprachiasmatic nuclei (SCN) is considered as the circadian pacemaker, which communicates with many others peripheral oscillators in the organism, in order to respond to the environmental cyclic alterations in a rhythmic and organized way. The SCN receives the photic information through the retina, where the ganglion cells traduce the information and transmitted by a monosynaptic pathway, the retino-hypotalamic tract (RHT) and reaches the SCN. It has been reported that lead (Pb), despite having any known biological function, induces abnormailties in the SCN cells morphology and density so this alterations can induce disorders in the photic transmission to the pacemaker. The aim of this study was to evaluated the effects of chronic exposition to Pb on the neuronal activation induce by light in the SCN of the male rat at 3 different hours. Female Wistar rats were exposed during gestation and lactation to a Pb solution containing 320 ppm of lead acetate through drinking water. After weaning, the male pups were maintained with the same drinking water than its mothers. Then after 90 days maintained in a 12:12 light/dark cycle we changed the photoperiod to 3 days of constant dark. Each treatment was divided into 2 groups; the first one the rats were sacrificed at three different hours (CT7, CT14 and CT24), the other group were given a light pulse during an hour at 3 different hours(CT6, CT13 and CT23) then after the ligth pulse the rats were sacrificed at three different hours (CT7, CT14 and CT24). Two representative sections from the middle level of the SCN were selected of each animal to evaluate the density of immunoreactive cells to neuronal nitric oxide synthetase (NOSn) and c-fos. Meanwhile another group of male rats were sacrificed at 90 days old to determine Pb levels in blood and hypothalamus through an atomic absorption spectrophotometer. Pb levels in blood and hypothalamus were significantly increased in the experimental group. In the Pb group, we found a decrease on cells numbers regarding to control group. The immunoreactive cells for NOSn and c-fos are significantly decreased in Pb groups. This difference is higher in CT 24 and CT14, those hours corresponds to the subjective night. So this may explain the deficits in circadian

rhythmicity documented in Pb-exposed animals. The alteration than the Pb cause in the activation of neuronal activity in the SCN may occurs because Pb has chemical properties similar to calcium (Ca^{+2}) so it can be replace Ca^{+2} altering the signaling cascades.

Disclosures: H.A. Molina: None. **J. Rojas-Castañeda:** None. **P. Duran:** None.

Poster

815. Circadian Mechanisms

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 815.06/RR15

Topic: F.08. Biological Rhythms and Sleep

Support: NIH Grant AG-019100

NIH Grant AG-023477

NIH Grant AG-026472

NIH Grant AG-029612

NIH Grant AG-036670

NIH Grant OD-011092

Title: Characterization of the rhesus monkey suprachiasmatic nucleus during aging

Authors: *D. H. EGHLIDI[1,2], V. T. GARYFALLOU[2], S. G. KOHAMA[2], H. F. URBANSKI[2]; [1]Beth Israel Deaconess Med. Ctr. and Harvard M, Boston, MA; [2]Oregon Natl. Primate Res. Ctr., Beaverton, OR

Abstract: The suprachiasmatic nucleus (SCN) plays an important role in maintaining sleep-wake cycles and other rhythmic physiological functions, many of which undergo marked age-related changes. Here we summarize our research into age-related changes within the SCN of a diurnal and long-lived primate species, the rhesus macaque (*Macaca mulatta*). First, we performed immunohistochemistry (using antibodies against VIP, AVP and REV-ERBα) on sections from the anterior hypothalamus; this enabled us to accurately delineate the anatomical boundaries of the SCN, which we subsequently corroborated with RNA-seq using RNA extracted from this isolated brain region. The same boundaries were then used as guides in the extraction of RNA from the SCN of young (~12 years, n = 6) and old (~26 years, n=6) males collected at 10AM (lights on at 7AM); for comparison, RNA was also extracted from the SCN of old (~26 years, n=6) males that had received androgen treatment for ~6 months, as well as from

old controls (~21 years, n=4) in which the SCN were collected at 10PM. Affymetrix Rhesus Gene Chip 1.0 ST Arrays and RMA analysis was then used to profile gene expression differences between the four groups. As expected, core-clock genes (including *CLOCK*, *NPAS2*, *BMAL1*/*2*, *PER1-3*, *CRY1* and *2*, *DEC1*, *NR1D1*/*2*, *RORA*-*C*, and *CSNK1E*) and output signals (including *VIP*, *VPAC2*, and *AVP*) were all highly expressed in the SCN. Globally, however, there was no difference in SCN gene expression between the young, old, and old androgen-supplemented groups. On the other hand, most of the SCN genes showed significantly lower expression at 10PM than at 10AM, although expression of *NPAS2*, *CRY2*, *NR1D1* (*REV-ERBα*), and *VPAC2* was higher ($P < 0.05$). *NPAS2* expression was confirmed with real-time PCR and showed the same diurnal pattern of significantly higher expression at 10PM than 10AM ($P < 0.05$). Overall, the data failed to disclose any deleterious effect of aging on gene expression in the SCN, or any modulatory influence of sex steroids. This suggests that global gene expression in the SCN remains relatively robust during healthy aging. However, as we only profiled gene expression at 10AM we cannot rule out the possibility that significant age-dependent and/or steroid-dependent changes occur at other times of the day.

Disclosures: D.H. Eghlidi: None. **V.T. Garyfallou:** None. **S.G. Kohama:** None. **H.F. Urbanski:** None.

Poster

815. Circadian Mechanisms

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 815.07/RR16

Topic: F.08. Biological Rhythms and Sleep

Support: NIH Grant GM10499102

UNCF/Merck Postdoctoral Fellowship

Title: Kv12-encoded channels selectively regulate nighttime firing rates in the suprachiasmatic nucleus

Authors: *T. HERMANSTYNE[1], D. GRANADOS-FUENTES[2], E. D. HERZOG[2], J. M. NERBONNE[1];
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Abstract: In-situ hybridization and RNA-seq data have shown that voltage-gated K^+ (Kv) channel subunits in the KCNH (Kv12) subfamily, Kv12.1 and Kv12.2, which generate outwardly

rectifying K^+ currents in the subthreshold voltage range, are highly expressed in the suprachiasmatic nucleus (SCN). We explored the hypothesis that Kv12.1 and/or Kv12.2 contribute to the daily variations in the resting and active properties of neurons in the SCN that are critical for circadian rhythms in physiology and behavior. We generated short hairpin RNAs (shRNAs) selectively targeting Kv12.1 or Kv12.2 and used these to provide acute *in vivo* "knockdown" of Kv12.1 or Kv12.2 expression in the adult mouse SCN. Whole-cell current-clamp recordings from SCN neurons in acute slices revealed that "knockdown" of either Kv12.1 or Kv12.2 selectively altered cellular excitability at night. The mean input resistances of SCN neurons at night, for example, were significantly ($P < 0.05$) higher in Kv12.1- (1.2 ± 0.3 GΩ) and Kv12.2- (1.8 ± 0.3 GΩ) targeted shRNA-expressing SCN neurons, compared with WT SCN neurons (0.9 ± 0.1 GΩ). In addition, mean ± SEM nighttime action potential thresholds were significantly ($P < 0.05$) more hyperpolarized in Kv12.1-targeted shRNA-expressing (-32.6 ± 2.1 mV) and Kv12.2-targeted shRNA-expressing (-30.1 ± 2.2 mV), than in WT (-24.1 ± 1.8 mV), SCN neurons. Furthermore, compared to WT SCN neurons (-46.2 ± 1.4 mV), the mean ± SEM nighttime resting membrane potential was significantly ($P < 0.05$) more depolarized in Kv12.1-targeted shRNA-expressing SCN neurons (-37.3 ± 3.3 mV) and trending towards significance in Kv12.2-targeted shRNA-expressing SCN neurons (-43.0 ± 1.5 mV). Mean ± SEM repetitive firing rates measured at night were also significantly ($P < 0.01$) higher in Kv12.1- (4.9 ± 1.1 Hz) and Kv12.2- (3.6 ± 0.8 Hz) targeted shRNA-expressing SCN neurons when compared with WT SCN neurons (0.7 ± 0.2 Hz). Parallel daytime experiments revealed no significant differences in mean input resistances, mean action potential thresholds, mean resting membrane potentials and mean repetitive firing rates in WT, Kv12.1-, and Kv12.2-targeted shRNA expressing SCN neurons. Taken together, these results reveal that the targeted "knockdown" of Kv12.1 or Kv12.2 pore-forming α-subunits selectively regulate nighttime firing rates in the SCN with very little to no effect on daytime firing activity. These observations suggest a critical role for Kv12.1- and Kv12.2- encoded K+ channels in regulating the "down-state" nighttime electrical activity in the SCN. This work was supported by NIH grant GM10499102 to EDH and JMN and UNCF/Merck Postdoctoral Fellowship to TOH.

Disclosures: **T. Hermanstyne:** None. **D. Granados-Fuentes:** None. **E.D. Herzog:** None. **J.M. Nerbonne:** None.

Poster

815. Circadian Mechanisms

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 815.08/RR17

Topic: F.08. Biological Rhythms and Sleep

Title: An eIF2α kinase GCN2 regulates circadian clock timing and entrainment

Authors: ***R. CAO**[1], N. D. ZAVALÍA[2], L. ZHU[3], K.-F. STORCH[3], S. AMIR[2], N. SONENBERG[4];
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Abstract: Circadian (~24h) rhythms in behavior, physiology, and gene expression are observed throughout the animal kingdom and are imperative to normal development and successful adaptation to the external cyclic environment. In mammals, these rhythms are governed by a master circadian pacemaker located in the suprachiasmatic nucleus (SCN) of the hypothalamus. GCN2 (general control nonderepressible 2) is a serine/threonine-protein kinase that controls mRNA translation by phosphorylation of the eukaryotic initiation factor 2α kinase (eIF2α) at serine 51. Previous studies have demonstrated a role of GCN2 in a number of functions within the central nervous system, including regulation of synaptic plasticity, learning and memory. In the current study we investigated a potential role of GCN2 in regulating the SCN circadian clock. We found that the level of GCN2 protein in the SCN was regulated by the circadian clock. Accordingly, the phosphorylation of its target protein, the eIF2α kinase also exhibited significant circadian rhythms. GCN2 null mice were poorly entrained to the 12h/12h light/dark cycles as compared to their wild-type (WT) littermates. Under constant dark conditions, these mice exhibited a longer circadian period of wheel-running activities than the WT mice (24.14±0.03h vs. 23.90±0.05h, $P<0.05$). In the brains of the GCN2 KO mice, the levels of the clock protein PERIOD1 and PERIOD2 were decreased, which can be explained by inhibited translation of the transcription factor ATF4 (CREB2). Together, these data indicate that GCN2 is a key regulator of the circadian clock through translation control of ATF4.

Disclosures: R. Cao: None. **N.D. Zavalía:** None. **L. Zhu:** None. **K. Storch:** None. **S. Amir:** None. **N. Sonenberg:** None.

Poster

815. Circadian Mechanisms

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 815.09/RR18

Topic: F.08. Biological Rhythms and Sleep

Support: National Institutes of Health (Grant code: MH103361)

National Science Foundation (Grant code: 1354612)

Title: The phosphorylation of CREB at Serine-133 contributes to both SCN clock timing and entrainment.

Authors: K. L. WHEATON[1], K. HANSEN[2], S. ATEN[2], *K. R. HOYT[1], K. OBRIETAN[2]; [1]Pharmacol., Ohio State Univ. Col. of Pharm., Columbus, OH; [2]Neurosci., Ohio State Univ. Col. of Med., Columbus, OH

Abstract: Within the suprachiasmatic nucleus (SCN), the locus of the master mammalian circadian clock, transcriptional regulation mediated by the CREB/CRE pathway has been implicated in the functioning of the molecular clock timing process, and has been shown to be a critical conduit through which photic input entrains the SCN oscillator. A key event driving CRE-mediated transcription is the phosphorylation of CREB at Serine-133. Indeed, numerous studies have shown that that point mutagenesis of Serine-133 to an Alanine potently abrogates CREB-mediated transcription. Here, we sought to examine the contribution of Serine-133 to the functional role of CREB in SCN timing and entrainment in vivo. To this end, we utilized a CREB Serine 133-to-Alanine-133 (CREB S/A) knock-in mouse strain to test the role of this phosphorylation event in SCN clock physiology. Control experiments showed that the gross morphology of the SCN was not affected by the S/A mutation and that total CREB levels in the SCN of CREB S/A were not different from the levels detected in WT mice; However, as expected, the Serine-133 phosphorylated form of CREB was not detected in CREB S/A mice. Under a standard 12 hr light/dark cycle CREB S/A mice exhibited a marked alteration in clock gating of wheel running activity. Thus, relative to WT mice, CREB S/A mice exhibited highly fragmented bouts of locomotor activity during the night phase, elevated daytime activity, and a delayed phase angle of entrainment. Further, under free running conditions, CREB S/A mice exhibited a significantly longer tau than WT mice. Photic entrainment, as assessed using Aschoff type 1 light pulse assays and 'jet lag' re-entrainment paradigms, revealed significant deficits in the response properties of CREB S/A mice. Together, these data indicate that CREB activation via Serine-133 phosphorylation contributes to both SCN clock entrainment and to the period of the SCN oscillator.

Disclosures: K.L. Wheaton: None. **K. Hansen:** None. **S. Aten:** None. **K.R. Hoyt:** None. **K. Obrietan:** None.

Poster

815. Circadian Mechanisms

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 815.10/RR19

Topic: F.08. Biological Rhythms and Sleep

Support: NIH Grant T32DA007262

NIH Grant R01NS036607

Title: Cannabinoids change circadian timing and recruit astrocytes to modulate GABAergic neurotransmission within the SCN

Authors: *L. M. HABLITZ, C. N. ALLEN;
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Abstract: Aberrant endocannabinoid signaling is implicated in epilepsy, mood disorders, and neurodegenerative diseases, all of which frequently present with sleep/wake and circadian disturbances indicating that the endocannabinoid system may be involved in daily timekeeping. However, little research has been done to study the effects of endocannabinoids on the timing of the circadian clock. Endocannabinoid receptor agonists (CB1/2) block the phase shifting effects of light and inhibit GABAergic neurotransmission in the suprachiasmatic nucleus (SCN), but the mechanism underlying the inhibition of GABAergic neurotransmission remains unknown. In other areas of the brain, endocannabinoid signaling-induced alterations in neurotransmission are mediated, in part, by astrocytes. We hypothesize that endocannabinoids change the function of the SCN neural network by recruiting astrocytes to modulate neurotransmission. We found that application of the CB1/2R agonist WIN 55,212-2 (3 μM) decreases the frequency of GABA(A) receptor-mediated mIPSCs by ~25% without significantly altering the mIPSC amplitude. These data are consistent with a direct effect of cannabinoids to reduce the release of GABA from presynaptic terminals. Fluorocitrate (1 μM), a metabolic inhibitor of astrocytes, attenuates the effects of WIN on mIPSCs, indicating a potential role for astrocytes in mediating cannabinoid-induced changes on GABAergic neurotransmission. To study the response of astrocytes to cannabinoids a floxed GCamP6 calcium reporter was stereotaxically injected into the SCN of mice expressing Cre recombinase driven by the GFAP promoter. WIN (3 μM) application increased the cytoplasmic calcium concentration in astrocytes. Finally, we found that daytime (1 hr between ZT 4-7) application of WIN (3 μM) phase advanced Per2 bioluminescence rhythms by ~2 hours. This study demonstrates that astrocytes play an active role in modulating the circadian pacemaker and cannabinoid signaling can change clock timing, which may explain the circadian disruptions observed in chronic marijuana users.

Disclosures: L.M. Hablitz: None. **C.N. Allen:** None.

Poster

815. Circadian Mechanisms

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 815.11/RR20

Topic: F.08. Biological Rhythms and Sleep

Support: NSF DMS 1412571

NSF DMS 1412119

Title: Multiscale mathematical modeling of vigilance state feedback on the circadian clock

Authors: ***C. DINIZ BEHN**[1,3], M. MURRAY[2], V. BOOTH[4];
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Abstract: Suprachiasmatic nucleus (SCN) neuron electrophysiology varies with time of day. In addition to modulating SCN outputs, this variable electrophysiology allows SCN neurons to gate responses to neuronal inputs. Previous work has demonstrated a functional connection between the laterodorsal tegmental nucleus (LDT) and the SCN. This connection may transmit information about vigilance states to the clock, but the mechanisms linking neuronal inputs to effects on the clock are not well understood. To investigate the mechanisms by which LDT activity affects the molecular clock in SCN neurons, we used a multiscale mathematical model representing the interaction between SCN per1 neuron electrophysiology and a simplified gene feedback network to simulate LDT inputs at different times of day.
To identify the role of electrophysiology in gating the response of the SCN neuron, we first considered the time-of-day differences in the effects of general excitatory/inhibitory inputs on individual per1 SCN neurons. Then we simulated projections from LDT neurons to determine how resulting changes in intracellular calcium concentration affected gene regulation and the timing of the internal clock. We found that the distinct electrophysiological properties demonstrated by SCN neurons at different circadian phases resulted in altered time courses for 24-h intracellular calcium concentrations. These changes, in turn, advanced or delayed the phase of the gene network. Thus, simulated LDT inputs generated phase-dependent responses in the clock. This model suggests mechanisms by which variable electrophysiology of SCN neurons gates inputs such as those coming from neurons involved in sleep/wake regulation. Since such inputs are vigilance state-dependent, these findings have implications for the effects of waking and sleeping out of phase with the endogenous clock as may occur with jet lag or shift work.

Disclosures: **C. Diniz Behn:** F. Consulting Fees (e.g., advisory boards); Merck and Co.. **M. Murray:** None. **V. Booth:** None.

Poster

815. Circadian Mechanisms

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 815.12/RR21

Topic: F.08. Biological Rhythms and Sleep

Support: the European Commission (ERC Advanced Grant MeloVision) to R.J.L

Title: Realignment of behavioural state and sub-cortical brain activity following chemogenetic activation of melanopsin retinal ganglion cells (mRGCs)

Authors: *N. MILOSAVLJEVIC[1], J. CEHAJIC-KAPETANOVIC[2], C. A. PROCYK[1], R. J. LUCAS[1];
[1]Neurosci., The Univ. of Manchester, Manchester, United Kingdom; [2]Ctr. for Ophthalmology & Vision Sciences, Inst. of Human Development, Fac. of Med. and Human Sci. and Manchester Royal Eye Hosp., Manchester, United Kingdom

Abstract: Functional imaging and psychometric assessments indicate that the quality and quantity of environmental light can modulate mood, attention and cognitive performance in humans. Indirect evidence links these events to light detection by intrinsically photosensitive melanopsin-expressing retinal ganglion cells (mRGCs) [1]. However, there is currently no direct demonstration that mRGCs can have such an immediate effect on mood or behavioural state in any species. We addressed this deficit by using chemogenetics to selectively activate mRGCs, recreating the effects of bright light on this cell type in dark housed mice. This specific manipulation evoked circadian phase resetting and pupil constriction (known consequences of mRGC activation). It also induced c-Fos (a marker of neuronal activation) in multiple nuclei in the hypothalamic, thalamic and limbic structures that influence numerous aspects of autonomic and neuroendocrine activity and are typically active during periods of wakefulness/arousal. By contrast, c-Fos was absent from the lateral habenula (associated with negative reward prediction) and ventrolateral preoptic area (VLPO; active during sleep). In standard behavioural tests (open field, elevated plus maze, forced swim test), mRGC activation induced behaviours commonly interpreted as anxiety-like or as signs of increased alertness, but not depression. These data demonstrate that selectively activating mRGCs is sufficient to change behavioural motivation towards a more alert, risk averse state. They also highlight the ability of this small fraction of retinal ganglion cells to realign activity in brain regions defining widespread aspects of physiology and behaviour.
1. Vandewalle, G., Maquet, P., and Dijk, D.J. (2009). Light as a modulator of cognitive brain function. Trends in cognitive sciences 13, 429-438

Disclosures: **N. Milosavljevic:** None. **J. Cehajic-Kapetanovic:** None. **C.A. Procyk:** None. **R.J. Lucas:** None.

Poster

815. Circadian Mechanisms

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 815.13/RR22

Topic: F.08. Biological Rhythms and Sleep

Support: NIH Grants R01 NS036607 (CNA) & R01 NS077003 (PJS, GEP)

Title: Photoentrainment and glutamatergic synaptic transmission in the SCN of ipRGC conditional vGlut2 KO mice

Authors: M. MOLDAVAN[1], P. J. SOLLARS[2], *C. N. ALLEN[1], G. E. PICKARD[2,3]; [1]OR Inst. Occup. Hlth. Sci., Oregon Hlth. Sci. Univ., Portland, OR; [2]Sch. of Vet. Med. and Biomed. Sci., Univ. of Nebraska, Lincoln, NE; [3]Dept. of Ophthalmology and Visual Sci., Univ. of Nebraska Med. Ctr., Omaha, NE

Abstract: Melanopsin-expressing intrinsically photosensitive retinal ganglion cells (ipRGCs) convey retinal signals to the suprachiasmatic nucleus (SCN) via glutamatergic neurotransmission. These signals entrain the SCN to the day/night cycle. ipRGCs use the vesicular glutamate transporter 2 (vGlut2) to package glutamate into synaptic vesicles. In addition to glutamate ipRGCs also package pituitary adenylate cyclase activating polypeptide (PACAP) into vesicles and PACAP may modulate glutamatergic neurotransmission in the SCN. To examine the role of ipRGC glutamatergic input to the SCN we generated conditional vGlut2 knock-out (KO) mice by crossing mice in which Cre-recombinase expression is driven by the melanopsin promotor ($Opn4^{Cre/+}$) with mice in which the second exon of vGlut2 is flanked by loxP sites ($vGlut2^{flx/flx}$) producing mice with one copy of melanopsin and unable to package glutamate into ipRGCs expressing Cre-recombinase ($Opn4^{Cre/+}$, $vGlut2^{flx/flx}$); and control mice ($Opn4^{+/+}$, $vGlut2^{flx/flx}$). Mice were maintained under various L:D conditions, constant dark and constant light. $Opn4^{Cre/+}$,$vGlut2^{flx/flx}$ mice, exhibited various degrees of photoentrainment but typically with positive phase angles of entrainment. These mice had free-running circadian activity rhythms under constant conditions and re-entrained when re-introduced to L:D conditions; the phase angle of entrainment was light intensity dependent. Coronal brain slices were prepared from $Opn4^{Cre/Cre}$,$vGlut2^{flx/flx}$; $Opn4^{Cre/+}$,$vGlut2^{flx/flx}$; $Opn4^{+/+}$,$vGlut2^{flx/flx}$ and wild-type (WT) mice and excitatory postsynaptic currents (EPSCs) were recorded *in vitro* from SCN neurons. EPSCs were evoked by a single stimulus, paired-pulse stimulation (PPS) or stimulus trains applied to the optic chiasm to simulate the discharges of ipRGCs. Knocking-out vGlut2 did not significantly alter the magnitude, rise time or time to peak of the evoked EPSCs (eEPSCs) nor the stimulus threshold required to evoke EPSCs. The eEPSC decay time constant (tau) was significantly decreased in $Opn4^{Cre/+}$,$vGlut2^{flx/flx}$ mice compared to WT or $Opn4^{+/+}$,$vGlut2^{flx/flx}$ mice. During 5-25 Hz PPS, the number of neurons demonstrating facilitation

was significantly higher in WT than in Opn4$^{Cre/+}$,vGlut2$^{flx/flx}$, or Opn4$^{+/+}$,vGlut2$^{flx/flx}$ mice. The EPSCs amplitudes during short-term synaptic depression induced by stimulus trains at 0.08-25 Hz frequencies were not different between vGlut2 KO and control mice. We conclude that vGlut2 KO only partially affected glutamate transmission in the retinohypothalamic tract by shortening the eEPSC duration and decreasing the release probability at high stimulus frequencies.

Disclosures: M. Moldavan: None. **P.J. Sollars:** None. **C.N. Allen:** None. **G.E. Pickard:** None.

Poster

815. Circadian Mechanisms

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 815.14/SS1

Topic: F.08. Biological Rhythms and Sleep

Title: Circadian phase shifts induced by matrix metalloproteinase-2/-9 inhibition in the suprachiasmatic nucleus correlate with an endogenous rhythm in enzymatic activity.

Authors: *K. ABRAHAMSSON, R. PROSSER;
Biochem. and Cell and Mol. Biol., Univ. of Tennessee, Knoxville, TN

Abstract: Neurons in the master clock, or suprachiasmatic nucleus (SCN), of the brain exhibit near 24-hr, or circadian, rhythms that synchronize mammalian behavior and physiology to the environment. It is known that molecular signaling pathways inside SCN neurons regulate circadian neuronal activity, but the involvement of extracellular-matrix (ECM) molecules in SCN clock phase regulation is unclear. Day vs. night differences in extracellular proteases and glial cell morphology in the SCN set precedent for the involvement of ECM proteins in regulating these changes. Two candidate proteins, matrix metalloprotease (MMP)-2 and MMP-9, may be the link between the ECM and circadian firing output of the SCN. Classically known as ECM remodelers, MMP-2/-9 can become activated when neuronal activity increases. MMP-2/-9 are also involved in regulating N-methyl D-aspartate receptor (NMDAR) activity, a critical element of the photic phase shifting pathway. To examine the role of MMP-2/-9 in the SCN, acute SCN tissue slices (from adult, male C57/BL6 mice housed in a 12:12 LD cycle) were prepared and maintained in an interface perfusion chamber, then treated with the MMP-2/-9 inhibitor BiPS. We chose to inhibit MMP-2/-9 at time points when activation of NMDARs can phase delay (Zeitgeber time: ZT 16, where ZT 0 is lights-on and ZT 12 is lights-off) or phase advance (ZT 23) the clock. During the day after drug treatment, single cell, extracellular activity recordings were taken from SCN neurons for 10 hours. Analysis of the time of peak activity

showed that BiPS application at ZT 16 produced a 3 h phase delay. Co-application of the NMDAR antagonist AP5 with BiPS blocked the BiPS induced phase shift. On the contrary, treating SCN slices with BiPS at ZT 23 did not induce a significant phase shift. Surprisingly, application of BiPS at ZT 6 also resulted in a significant phase advance. Previous research has shown that NMDAR activation at this time does not produce a phase shift, but we saw that co-application of BiPS and AP5 blocked BiPS- induced phase shifts at ZT 6. Evaluation of total MMP-2/-9 expression in SCN tissue using Western blotting did not reveal day vs. night differences of either MMP. However, gelatin zymography (to assess enzymatic activity) of SCN protein extracts show that MMP-9 is more active than MMP-2. We also saw that MMP-9 activity at ZT 6 and ZT 16 is higher than it is during the late night (ZT 23). Our results suggest that BiPS induced phase shifts only occur during times when MMP-2/-9 activity level is high. Further studies investigating MMP-2/-9 and their relationship with NMDARs could reveal how these extracellular proteases participate in circadian phase modulation in the SCN.

Disclosures: K. Abrahamsson: None. **R. Prosser:** None.

Poster

815. Circadian Mechanisms

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 815.15/SS2

Topic: F.08. Biological Rhythms and Sleep

Support: IH NS078220

NS092545

Title: Excitatory $GABA_A$ receptor responses in the suprachiasmatic nucleus control phase shifts of circadian rhythms

Authors: *J. K. MCNEILL, IV, J. WALTON, E. ALBERS;
Georgia State Univ., Atlanta, GA

Abstract: Over 90% of suprachiasmatic nucleus (SCN) neurons expressγ-aminobutyric acid (GABA). The acute activation of $GABA_A$ receptors ($GABA_ARs$) can inhibit the phase shifting effects of photic cues. The sustained activation of $GABA_ARs$ can mimic the phase delaying effects of light and the sustained inhibition of $GABA_ARs$ can inhibit the phase delaying effects of light. Although GABA is commonly viewed as an inhibitory neurotransmitter, *in vitro* studies suggest the activation of $GABA_A$ receptors can produce excitatory responses in the adult SCN. The ratio of excitatory to inhibitory responses to GABA depends on the balance of chloride

influx by $Na^+/K^+/Cl^-$ co-transporter 1 (NKCC1) and chloride efflux by K^+/Cl^- co-transporters (KCCs). Excitatory GABA responses in the adult SCN disappear upon inhibition of the inward chloride co-transporter, $Na^+/K^+/Cl^-$ co-transporter 1 (NKCC1). We have previously shown that the actions of NKCC1 regulate phase shifts to light. The following experiments aimed to further characterize the role of chloride co-transporter activity in entrainment. Adult male Syrian hamsters were housed in constant dark conditions until the formation of stable free-running activity rhythms. Hamsters received varying doses of bumetanide (a NKCC1 inhibitor) or vehicle into the SCN region in the subjective day (CT 6), and in the early (CT 13.5) and late (CT 19) subjective night. Phase shifts were calculated using regression lines fitted to activity onsets. Acute NKCC1 inhibition during the subjective day did not alter the phase of the free-running rhythm but appeared to inhibit $GABA_AR$ induced advances. NKCC1 inhibition in the late subjective night produced phase delays in a dose-dependent manner. These data suggest that excitatory responses to GABA are important in determining the phase of the circadian pacemaker.

Disclosures: **J.K. McNeill:** None. **J. Walton:** None. **E. Albers:** None.

Poster

815. Circadian Mechanisms

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 815.16/SS3

Topic: F.08. Biological Rhythms and Sleep

Support: DGAPA-PAPIIT grant IN215513

CONACYT grant 236908.

Title: Impairment of the rat estrous cycle as a consequence of a 2 hour restricted feeding protocol

Authors: J. P. HERNANDEZ, 09230[1], P. ESTEVEZ[2], M. I. GUTIERREZ[2], G. D. CORTES[2], C. Y. JAVIER[2], *A. FLORES[2], C. C. SILVA[2];
[1]FES Zaragoza-UNAM, Mexico, Mexico; [2]FES Zaragoza-UNAM, Mexico City, Mexico

Abstract: Circadian systems coordinating endogenous rhythms probably evolved as a property that conveys the capability of anticipation and thus of energy optimization. In order to match the endogenous period with that of the earth, circadian systems are entrained by environmental recurrent cues. In mammals, the light-dark cycle rules most of the rhythms through the synchronization of the suprachiasmatic nucleus (SCN), which in turn couples peripheral

oscillators and effectors. Food availability is also a robust entraining signal that seems to act throughout a different pacemaker than light. Experiments testing the properties of this putative Food Entrainable Oscillator (FEO) use nocturnal SCN-intact rodents and allow them to eat only for a few hours during the day, modifying the animal natural active phase. The aim of this study was to test if restricted feeding (RF) paradigms that oppose the activity of the FEO with that of the SCN can impact negatively on female reproduction. Parallel, we assessed the influence of social interaction on the deleterious effects of the RF paradigm. Adult and cyclic female rats where housed individually (n=10) or in groups (n=30) under a 14:10 light-dark cycle, lights on at 05:00 h. Animals were feed either, ad libitum (AL) or from 10:00 h to 12:00 h (RF group) with a standard pelleted diet for lab rats. Vaginal smears were taken and modifications to the estrous cycles were compared. Abnormalities of the cycles were observed immediately after the start of the RF protocol. After a few irregular cycles, single-housed rats became acyclic with permanent predominance of leucocytes in the smears. Grouped rats also became acyclic, but presented spontaneous cycles intercalated with periods of acyclicity. AL rats continued to be cyclic for the rest of the experiment no matter if they were isolated or not. These results could be the effect of the induction of a high catabolic state as a consequence of food restriction, even if it has been proved that RF rats usually eat the same amount of food than AL rats. Another possibility is that competing entraining signals from the SCN and FEO result in arhythmicity on peripheral oscillators located at the pituitary and/or ovaries, if this is true, social interaction is a weak stimulus preventing desynchrony, even in social mammals. Further studies assessing the activity of brain structures related with the FEO and also of SCN and GnRH neurons of rats under a RF protocol are in progress. Experiments involving females and RF paradigms must consider the modification of estrous cycles and thus of estradiol secretion as this hormone has relevant effects on the amplitude of the locomotor activity, as well as in other circadian rhythms.

Disclosures: **J.P. Hernandez:** None. **P. Estevez:** None. **M.I. Gutierrez:** None. **G.D. Cortes:** None. **C.Y. Javier:** None. **A. Flores:** None. **C.C. Silva:** None.

Poster

815. Circadian Mechanisms

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 815.17/SS4

Topic: F.08. Biological Rhythms and Sleep

Title: Behavioral & neural response to variation in the timing of restricted feeding

Authors: *A. RASTOGI, E. M. MINTZ;
DEPARTMENT OF BIOLOGICAL SCIENCES, KENT STATE UNIVERSITY, Kent, OH

Abstract: Food anticipatory activity (FAA) is a classical behavioral phenotype, which appears in response to a daily restricted feeding condition in rodents, and normally develops 2-3h before the time of food presentation. When a single window of food availability is placed at different times of the day, the timing and duration of FAA is altered. To study this, experiments were performed using memory deficient tissue-type plasminogen activator knock out ($tPA^{-/-}$) male mice and wild type ($tPA^{+/+}$, C57BL/6J) males. $tPA^{-/-}$ mice are severely deficient in long-term potentiation, long-term depression, and hippocampal-based learning and memory tasks, and show reduced nocturnal wheel-running activity but not reduced FAA. Mice were individually maintained in 18L:6D photoperiod with *ad libitum* (AL) food. After entraining to LD conditions, mice (n=6 each group) had their access to food restricted to a 4-hr window from either ZT5-9 (ZT0: lights onset) or ZT12-16, and perfused after 1 week in the middle of FAA at ZT4 or ZT11, respectively. Another group (n=12) was maintained in AL and perfused at similar ZTs (n=6 / ZT) to serve as controls. Body weight data showed that all food-restricted groups lost body weight. A genotypic difference was detected with higher body weight loss in $tPA^{-/-}$ mice than $tPA^{+/+}$s. Interestingly, variation in FAA generation and duration was detected as a function of the timing of food restriction. Mice fed at ZT5 developed FAA with 3h duration and also showed elevated post-feeding, day time activity, which extended into the dark phase. However, mice fed at ZT12 developed FAA for a longer duration ranging from 5-7h. Also, in response to restricted feeding, total locomotor activity/day increased for both food restriction time periods ($tPA^{+/+}$s: 60-70%; $tPA^{-/-}$s: 70-140%) compared to AL. Fos-immunohistochemistry data suggests that Fos expression in dorsomedial hypothalamus (DMH) and arcuate nucleus (ARC) was higher in $tPA^{-/-}$ mice than $tPA^{+/+}$s with either food restriction timing. Unexpectedly, in $tPA^{+/+}$s it remained unchanged in both restricted feeding and AL groups, except in mice fed at ZT12, where Fos was higher in ARC and reduced in SCN compared to respective controls and mice fed at ZT5. These data suggest that the underlying mechanisms of generation and duration of FAA are flexible and may be altered when food presentation is given at different times of the day. In addition, the loss of tPA may reduce the masking effect of light on locomotor activity and reduce the influence of the SCN on the timing of activity.

Disclosures: **A. Rastogi:** None. **E.M. Mintz:** None.

Poster

815. Circadian Mechanisms

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 815.18/SS5

Topic: F.08. Biological Rhythms and Sleep

Support: CIHR M00204

Title: Locomotor sensitization and circadian food entrainment

Authors: *H. N. OPIOL[1,2], N. DE ZAVALIA[2], T. DELORME[2], P. SOLIS[2], S. RUTHERFORD[2], S. AMIR[2];
[1]Psychology, Ctr. For Studies In Behavioral Neurobiology, Con, Montreal, QC, Canada;
[2]Concordia Univ., Montreal, QC, Canada

Abstract: Restricted feeding (RF), a feeding regimen that restricts feeding to a specified allotted time each day, allows the body to realign the internal timing of many behavioral and physiological functions such that they anticipate the new feeding time. The mechanism by which the body is able to shift circadian processes responsible for food entrainment remains unknown. Our work examines the process of locomotor sensitization in the food entrainment pathway by measuring cross-sensitization to an acute injection of amphetamine (AMPH). We show that RF results in locomotor sensitization after 2 weeks of RF but not after 1, 3 or 7 days into RF. When food is returned and rats regain their body weight, locomotor sensitization is present when tested 10-14 days post-RF. Food restriction that is not circadian, e.g. variable RF does not result in cross-sensitization. Food entrainment without caloric restriction, e.g. daily access to a time-restricted treat, also does not result in cross-sensitization. Further, when RF is timed to the dark phase, cross-sensitization is observed only at night; however RF timed to the light phase results in cross-sensitization that is present during day and night. It appears that locomotor sensitization is a unique outcome of circadian defined RF that requires a period of incubation for its behavioral expression. Given that locomotor sensitization involves reorganization of dopamine-regulated motor circuitry, our work provides further support for the existing hypothesis of dopamine in the food entrainment pathway.

Disclosures: H.N. Opiol: None. **N. de Zavalia:** None. **T. Delorme:** None. **P. Solis:** None. **S. Rutherford:** None. **S. Amir:** None.

Poster

815. Circadian Mechanisms

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 815.19/SS6

Topic: F.08. Biological Rhythms and Sleep

Support: ONR grant N00014-13-1-0285

Title: Entrainment in a polyphasic light regime is affected by sex, age, activity, and light levels.

Authors: *T. J. WALBEEK[1], D. A. MAY[1], I. MISHRA[2], M. R. GORMAN[1];
[1]Dept of Psychology, UCSD, LA Jolla, CA; [2]Dept. of Zoology, Univ. of Delhi, Delhi, India

Abstract: Mice (C57BL/6j) exposed to a polyphasic light regime consisting of two light and two dark phases every 24h (Light:Dark:Light:Dark; LDLD) can adopt a bifurcated entrainment pattern with roughly equal amounts of running wheel activity in each of the two nights. This rhythm "bifurcation" has significant after-effects on increased circadian adaptability: Mice that have been bifurcated show accelerated rates of re-entrainment after a sudden phase shift and have an expanded range of entrainment. Identifying environmental and physiological factors that facilitate or prevent rhythm bifurcation in LDLD conditions will contribute to an understanding of neurophysiological mechanisms underlying enhanced circadian plasticity. Here we present a collection of experiments showing the effects of sex, age, light levels, activity levels, melatonin, and diet composition on bifurcation rates of animals exposed to LDLD. There is robust evidence that females exhibit higher prevalence of bifurcated rhythms compared to males. Also younger animals (< 20 weeks) are more likely to symmetrically bifurcate activity compared to older animals (>30 weeks). Additionally and independently, levels of bright light correlate with bifurcation symmetry such that higher levels of light (~500 lux) predict more symmetric entrainment than low levels of light (~50 lux). Without a running-wheel, mice do not express bimodal activity patterns (as measured by passive infrared), which indicated that high levels of (aerobic) activity are necessary to induce and maintain rhythm bifurcation. Neither a life time exposure to melatonin administered in the drinking water nor a high fat diet affects rates of bifurcation in addition to the previously mentioned factors. Combined, these findings provide a strong basis for a rodent model for studying the mechanisms of increased circadian plasticity. Follow-up experiments can specifically target the effects and feedback of for example sex hormones or activity on plastic circadian regulation, information crucial to ameliorate negative consequences previously associated with repeated jet-lag or rotating shift-work.

Disclosures: **T.J. Walbeek:** None. **D.A. May:** None. **I. Mishra:** None. **M.R. Gorman:** None.

Poster

815. Circadian Mechanisms

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 815.20/SS7

Topic: F.08. Biological Rhythms and Sleep

Support: Howard Hughes Medical Institute through the Undergraduate Science Education Program

Nyenhuis grant from Hope College

Startup funds from the Division of Social Sciences at Hope College to AG

Title: Effects of superior colliculus (SC) lesions on circadian rhythms and masking in diurnal grass rats

Authors: O. KHACHERIAN, A. GOODWIN, *A. J. GALL;
Psychology, Hope Col., Holland, MI

Abstract: The circadian system regulates daily rhythms of physiology and behavior and thus, it affects many aspects of daily life. Although there has been tremendous progress elucidating the mechanisms responsible for the workings of the circadian system in nocturnal species, little is known about the mechanisms that support a diurnal profile of activity. Recent data has shown that retinorecipient brain areas such as the intergeniculate leaflet (IGL) and olivary pretectal nucleus (OPT) are critical for the display of normal patterns of daily activity in diurnal grass rats (*Arvicanthis niloticus*) (Gall et al., 2013, 2014). Specifically, grass rats with IGL and OPT lesions behave in ways similar to nocturnal animals. Importantly, both the IGL and OPT project to one another in nocturnal species, and there is evidence that these two brain regions also project to the superior colliculus (SC). The superior colliculus (SC) receives direct retinal input, is involved in the triggering of REM sleep in nocturnal rats (Miller et al., 1998), and is disproportionately large in the diurnal grass rat (Gaillard et al., 2013). The objective of the current study was to use diurnal grass rats to test the hypothesis that the SC is critical for the expression of diurnal behavior and physiology. We performed bilateral electrolytic lesions of the SC to examine the diurnal behavioral patterns and acute responses to light in these animals. This research has implications for understanding Alzheimer's Disease (AD) and Parkinson's Disease (PD), neurological disorders in which diurnal behavior is severely disrupted. Data collection for this experiment is currently ongoing. We anticipate that these data will shed light on the mechanisms involved in the display of diurnal activity patterns, and will reveal the functional implications of interconnections between the IGL, OPT, and SC in a diurnal species.

Disclosures: O. Khacherian: None. **A. Goodwin:** None. **A.J. Gall:** None.

Poster

815. Circadian Mechanisms

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 815.21/SS8

Topic: F.08. Biological Rhythms and Sleep

Support: CIHR Grant 142458

Title: Circadian characterization of a VPA induced model of autism in rats

Authors: *S. FERRARO, N. DE ZAVALIA, S. AMIR;
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Abstract: Autism Spectrum Disorder (ASD) is a pervasive developmental disorder which is characterized by impairments in social interaction and communication, as well as repetitive patterns of behaviour that occur within the first few years of life. ASD is often accompanied by various comorbid conditions whereby a large percentage of patients report disturbances in sleep-wake cycles, thus potentially delineating alterations in the circadian timing system. The objective of this study is to assess and phenotypically characterize the circadian system in an animal model of autism in response to various circadian challenges. The administration of Valproic Acid (VPA) to pregnant rats is used as an environmentally triggered model of autism which exhibits strong clinical validity. Pregnant rats were administered a 600 mg/kg dose of VPA on day twelve of gestation, corresponding to the developmental time point before neural tube closure. Analysis of baseline activity under a standard 12:12 light-dark (LD) cycle revealed a significant decrease in overall locomotor activity in VPA animals, whereby further investigation revealed a significant decrease in night activity, but not in day activity. The constant dark (DD) cycle allows for the determination of the endogenous free running period in these animals. Although the period was not significantly different between both groups, there was a significant decrease in locomotor activity in the VPA group, similar to what was obtained in the baseline analysis. Under the constant light cycle (LL), which allows for the assessment of light's masking effect on rhythms and locomotor activity, there was a significant increase in overall activity in VPA rats when compared to controls. Moreover, the VPA group had a tendency to show an overall increase in the number of days needed to reach arrhythmicity when compared to controls, however these results were not significant and need to be further replicated. These results propose that the perception of light in VPA animals is altered, such that the normal, necessary neuronal signaling which would decrease overall locomotor activity cannot be achieved. This is can perhaps be attributed to differential clock gene expression within the suprachiasmatic nucleus, or due to an aberration of the molecular clock in response to this protocol. Further studies are necessary to elucidate the molecular cause behind resistance to the constant light protocol, as it pertains highly to what is observed in clinical practice.

Disclosures: **S. Ferraro:** None. **N. de Zavalia:** None. **S. Amir:** None.

Poster

815. Circadian Mechanisms

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 815.22/SS9

Topic: F.08. Biological Rhythms and Sleep

Support: Kent State University Department of Biological Sciences

Kent State University Department of Biomedical Sciences

Title: Transgenerational epigenetic effect of cocaine on circadian behavior and cocaine reward

Authors: *A. YAW[1], A. SHEMERY[1], R. A. PROSSER[2], J. D. GLASS[1];
[1]Biomed. Sci., Kent State Univ., Kent, OH; [2]Univ. of Tennessee, Knoxville, TN

Abstract: Cocaine irreversibly lengthens circadian period (tau), which could underlie the significant health issues of cocaine addiction. Others have reported that rewarding effects of paternal cocaine use are transgenerational. We hypothesize that the disruptive effects of cocaine on tau may also be transgenerational, causing altered subjective cocaine reward response in offspring (F1). Male C57Bl/6J mice ~6 wks were exposed to forced cocaine-water (0.5 mg/ml; experimental) or water (control) for 6 wks. Immediately following this treatment, the mice were harem-mated with cocaine naïve females. Offspring (22 male, 21 female) were weaned after three weeks and then behaviorally phenotyped for cocaine or sucrose (to test for reward specificity) preference using a dual bottle (water and drug [0.15 mg/ml cocaine: 15% ethanol] or water and sucrose [2%]) free-choice regimen. Circadian behaviors were analyzed in individual mice by measuring circadian activity using passive infrared activity sensors and ClockLab analysis. A long-term (possibly permanent) lengthening of tau after drug withdrawal was evident in sires with forced cocaine compared to water controls (24.18± 0.17 h vs. 24.07±0.02 h; $p<0.05$). Tau, alpha, and subjective daytime bouts were not altered in the F1's. However, preference for cocaine was decreased in cocaine-sired F1 males compared to those from control sires (49.36±0.67 vs. 54.929±0.78; $p<0.05$). In contrast, cocaine preference in cocaine-sired F1 females was increased compared to those from control sires (57.74±0.77 vs. 53.21±0.74; $p<0.05$). There were no such differences in F1 sucrose preference or ethanol preference. These data reveal that there is no transgenerational transmission of a cocaine-lengthened tau phenotype. Significantly, however, paternal cocaine exposure significantly altered F1 preference for cocaine, but not sucrose or ethanol, suggesting a selective effect on cocaine reward mechanisms. Thus, cocaine addiction could be influenced by a transgenerational paternal mode of epigenetic inheritance.

Disclosures: **A. Yaw:** None. **A. Shemery:** None. **R.A. Prosser:** None. **J.D. Glass:** None.

Poster

815. Circadian Mechanisms

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 815.23/SS10

Topic: F.08. Biological Rhythms and Sleep

Support: Creation of Innovation Centers for Advanced Interdisciplinary Research Areas Program, Ministry of Education, Culture, Sports, Science and Technology, Japan

Title: *In vivo* imaging of clock gene expression in multiple tissues of freely moving mice

Authors: *T. HAMADA[1], S. KENNETH[2], M. ISHIKAWA[5], N. MIYAMOTO[2], S. HONMA[3], H. SHIRATO[4], K. HONMA[3];
[1]Hokkaido Univ., Sapporo, Japan; [2]Div. of Med. Physics and Engin., [4]Dept. of Radiation Med., [3]Hokkaido Univ. Grad. Sch. of Med., Sapporo, Japan; [5]Hokkaido Univ. Grad. Sch. of Hlth. Sci., Sapporo, Japan

Abstract: Clock genes are expressed in many tissues, both inside and outside the hypothalamic suprachiasmatic nucleus, the master clock controlling circadian rhythm. To understand the role of ubiquitous clock gene expression, we developed a novel *in vivo* imaging technique that enables whole-body imaging of multiple tissues in freely moving mice over extended periods. Quantification of gene expression in a steadily moving target was achieved by using dual-focal 3D tracing technology and a signal intensity calibration technique that identifies, traces, and quantifies gene expression in a target area. Using these techniques, we were able to measure circadian rhythms of clock gene expression over a prolonged period in multiple areas, including the olfactory bulb, dorsal skin, left and right ears, left and right cerebral cortices. In addition, the kinetic relationship between gene expression in these tissues and physiological responses to experimental cues was simultaneously monitored. Thus, our novel system successfully quantified clock gene expression in multiple tissues in freely moving mice for a period sufficient to analyze circadian dynamics.

Disclosures: **T. Hamada:** None. **S. Kenneth:** None. **M. Ishikawa:** None. **N. Miyamoto:** None. **S. Honma:** None. **H. Shirato:** None. **K. Honma:** None.

Poster

815. Circadian Mechanisms

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 815.24/SS11

Topic: F.08. Biological Rhythms and Sleep

Support: NIH NS078220

NIH NS092545

Title: Intracellular calcium in the suprachiasmatic nucleus and the resetting of circadian phase.

Authors: *J. C. WALTON, J. K. MCNEILL, IV, H. E. ALBERS;
Neurosci. Inst. and Ctr. for Behavioral Neurosci., Georgia State Univ., Atlanta, GA

Abstract: The mammalian suprachiasmatic nuclei (SCN) of the hypothalamus functions as a central circadian clock that entrains an organism's physiology and behavior to environmental light-dark cycles. Individual neurons within the SCN display circadian rhythms in cytosolic Ca^{2+}, which are dependent upon ryanodine receptor (RyR) mediated Ca^{2+} release from the endoplasmic reticulum and are independent of Ca^{2+} rhythms driven by voltage gated Ca^{2+} flux across the neuronal cell membrane. Recent studies have directly linked these intracellular Ca^{2+} rhythms to the core clock gene transcriptional-translational feedback loop, but few studies have examined the role of Ca^{2+} from intracellular Ca^{2+} stores in circadian entrainment. Toward this end, we investigated the effects of intracellular Ca^{2+} antagonists on photic phase resetting *in vivo* using Syrian hamsters implanted with cannula aimed at the SCN. In the early subjective night, microinjection of the general intracellular Ca^{2+} antagonist 8-(Diethylamino)octyl 3,4,5-trimethoxybenzoate hydrochloride; 3,4,5-Trimethoxybenzoic acid 8-(diethylamino)octyl ester hydrochloride (TMB-8) induced phase delays that were not different from those caused by a 150 lux 15 minute light pulse. TMB-8 given in conjunction with a light pulse enhanced the phase delaying ability of the light pulse. Antagonizing RyR mediated Ca^{2+} release with dantrolene did not affect photic phase delays, nor did dantrolene alone have an effect on circadian phase. We are currently investigating the role of inositol triphosphate (IP3) mediated Ca^{2+} release on photic phase delays and whether intracellular Ca^{2+} release from stores through RyR or IP3 channels has a role in photic phase advances.

Disclosures: J.C. Walton: None. **J.K. McNeill:** None. **H.E. Albers:** None.

Poster

815. Circadian Mechanisms

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 815.25/SS12

Topic: F.08. Biological Rhythms and Sleep

Support: Office of Naval Research (RJH and TJW)

Title: Effects of photoperiod alteration on the hypothalamic-pituitary-adrenal stress axis and behavior in male C57BL/6J mice fed soy-based and soy-free diets

Authors: *B. M. BAUMAN[1], R. J. HANDA[2], T. J. WU[1];
[1]Uniformed Services Univ., Bethesda, MD; [2]Biomed. Sci., Colorado State Univ., Fort Collins, CO

Abstract: The hypothalamic-pituitary-adrenal (HPA) axis functions to synchronize physiological systems with environmental cues and rhythms, in addition to its role in the hormonal response to stress. Dysregulation of the HPA axis in cases of altered photoperiods can lead to increased depressive-like behaviors and metabolic anomalies. Likewise, exposure to dietary soy has been implicated in the regulation of the neurocircuitry mediating these processes. In the current study, we determined the effect of exposure to a short-day (SD) photoperiod (shortened active period) in mice, as well as examined the role of dietary soy in depressive-like behaviors and body weight change. Male C57BL/6J mice were fed either soy-based or soy-free diets and acclimated to a normal (12 h light:12 h dark) photoperiod, after which time they were exposed to either a normal or SD (16 h light:8 h dark) photoperiod. After photoperiod alteration, mice fed a soy-based diet displayed an increase ($p < 0.05$) in body weight in the SD photoperiod relative to controls. Additionally, mice fed a soy-free diet and exposed to a SD period gained less weight ($p < 0.05$) than those fed a soy-based diet exposed to the same period. The effects of photoperiod alteration on depressive-like behaviors were examined with an Open Field test that included the use of a novel object. Animals fed a soy-based diet and exposed to the SD period experienced a decrease ($p < 0.05$) in both total distance traveled and mobile time, as well as an increase ($p < 0.05$) in immobile time, compared to those exposed to the normal period. Mice fed a soy-free diet in the altered photoperiod displayed an increase ($p < 0.05$) in total distance traveled and mobile time and a decrease ($p < 0.05$) in immobile time relative to those fed a soy-based diet in the same photoperiod. The soy-free diet also appeared to alleviate basal anxiety levels as mice fed the soy-free diet and maintained in the normal photoperiod spent more time ($p < 0.05$) in the center of the Open Field relative to those fed a soy-based diet and maintained in the same photoperiod. Using a second behavioral measure, the Elevated Plus Maze, mice exposed to the SD period and fed a soy-based diet displayed a decrease ($p < 0.05$) in total distance traveled and average speed, compared to that of the normal photoperiod. Mice exposed

to the altered photoperiod and fed a soy-free diet showed a decrease ($p < 0.05$) in closed arm time relative to the normal photoperiod. Our results suggest that exposure to an altered photoperiod leads to anxiogenic-producing effects in male mice fed a soy-based diet, which is reversed in males fed a soy-free diet.

Disclosures: B.M. Bauman: None. **R.J. Handa:** None. **T.J. Wu:** None.

Poster

815. Circadian Mechanisms

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 815.26/SS13

Topic: F.08. Biological Rhythms and Sleep

Support: NIH Grant MH075968

NSF Grant IOS-1456706

Title: Diurnal corticosterone is necessary but not sufficient for optimal conditioned fear extinction learning in male rats

Authors: *E. R. WOODRUFF[1], L. E. CHUN[1], D. TIRADO[2], R. L. SPENCER[1]; [1]Psychology/Neuroscience, Univ. of Colorado At Boulder, Boulder, CO; [2]Univ. of Miami, Miami, FL

Abstract: Circadian rhythms are highly conserved 24h fluctuations in physiology and behavior. Optimal organismal health and tissue functioning relies on the integrity of the circadian system. At the molecular level these rhythms consist of a core set of so-called “clock genes” (*Bmal1*, *CLOCK*, *Period*, and *Cryptochrome*) which are expressed in an oscillatory fashion. Glucocorticoid hormone (CORT) exhibits a robust diurnal rhythm with peak circulating levels occurring around the onset of the active phase (morning in humans and evening in nocturnal rodents). In peripheral tissues clock gene expression and subsequent tissue functioning is strongly modulated and/or entrained by diurnal CORT. We have recently shown that in male rats normal clock gene expression in the prefrontal cortex (PFC) relies on the presence and correct phase timing of CORT. In a set of follow-up experiments we found that rats learn conditioned fear extinction, a PFC-dependent behavior, better when trained and tested during their active phase (zeitgeber time, ZT16) compared to those trained and tested during their inactive phase (ZT4). Furthermore, we found this enhanced learning is abolished by both *Period1* knockdown in the infralimbic PFC and removal of endogenous CORT by way of adrenalectomy (ADX). Here we examined whether diurnal CORT replacement was sufficient to restore enhanced

extinction learning in ADX rats trained and tested at ZT16. Briefly, one week into a two-week acclimation period rats received either ADX or sham-ADX surgery. Immediately afterwards ADX rats were given either 0.9% saline drinking water or 0.9% saline drinking water with 25μg/ml CORT in order to mimic the diurnal circulation pattern of endogenous CORT. 1 week after surgery rats were trained and tested across 4 sessions: conditioned fear acquisition, extinction, extinction recall, and fear renewal. We observed that replacing diurnal CORT in the drinking water was not sufficient to restore optimal extinction learning in ZT16 ADX rats. We posit that diurnal CORT, rather than enabling enhanced extinction learning at ZT16 per se, primes PFC cells to be more responsive at that time of day to testing-induced acute CORT release, which was absent in CORT replaced ADX rats. Future studies will thoroughly examine this prospect.

Disclosures: **E.R. Woodruff:** None. **L.E. Chun:** None. **D. Tirado:** None. **R.L. Spencer:** None.

Poster

815. Circadian Mechanisms

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 815.27/SS14

Topic: F.08. Biological Rhythms and Sleep

Support: BGSU JP Scott Center

Title: Stem-like cells of the adult mouse suprachiasmatic nucleus examined in explant cultures

Authors: D. BELIGALA[1], A. DE[1], A. MALIK[2], *M. E. GEUSZ[1];
[1]Dept. of Biol. Sci., Bowling Green State Univ., Bowling Green, OH; [2]Cincinnati Children's Hosp. and Med. Ctr., Cincinnati, OH

Abstract: Reports have described cells with stem-like protein expression in the hypothalamic suprachiasmatic nucleus (SCN), which contains the principal circadian pacemaker of the body. In particular, SOX-2, a regulator of embryonic and adult neurogenesis is expressed in the SCN of adult rodents. Similarly, some SCN cells express doublecortin, a marker characteristic of differentiating cells committed to becoming neurons. To test whether SCN stem-like cells persist under conditions that favor the culture of neural stem cells rather than mature neurons or glia, SCN explant cultures from brain slices were maintained in serum-free stem cell medium containing fibroblast growth factor 2 and epidermal growth factor. Because neurogenesis continues throughout the lifetime, we examined the SCN of mice at 21 days to 17 months of age. The optic chiasm and ependymal cell layer were surgically removed from the nearby SCN to eliminate any potential sources of stem cells or progenitor cells. Cell proliferation was assayed

indirectly by measuring cross-sectional areas of SCN explants. During the first five days in culture, explants showed a significant daily increase of 15.23% (SD ±2.98, average of 7 explants) and then maintained an enlarged but slightly smaller size. The tissue reorganized while in culture, and explants developed spheroid-like structures associated with neural stem cell proliferation. After seven days in culture, immunocytochemistry and confocal imaging revealed nuclear SOX-2 expression in cells that also expressed GFAP, a feature of multipotent neural stem cells. Similar evidence of stem cells was found in cells expressing both nestin and GFAP after 4 weeks in culture. Nestin and GFAP were also expressed separately. Hoechst nuclear staining revealed multiple pockets devoid of cells. Although the culture conditions of stem cell medium were not suitable for many SCN cells, some cell types survived for as long as 7 weeks according to firefly luciferase bioluminescence and live-dead staining using propidium iodide dye exclusion and Hoechst staining. Although not yet conclusive, these results provide additional evidence that the mature SCN has cells that may provide unique regenerative properties. This plasticity could be induced in the SCN in response to pathological conditions or it may enable SCN circadian rhythms to adjust to changing environmental timing cues, seasonal behavioral cycles or aging. Supported by the BGSU JP Scott Center for Neuroscience, Mind, and Behavior.

Disclosures: D. Beligala: None. **A. De:** None. **A. Malik:** None. **M.E. Geusz:** None.

Poster

815. Circadian Mechanisms

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 815.28/SS15

Topic: F.08. Biological Rhythms and Sleep

Support: Univ of Pittsburgh CTSI Pilot Study Grant

Title: Circadian rhythms of adolescent rodents and the effects of adolescent circadian misalignment on mood and alcohol sensitivity

Authors: *C. A. VADNIE, B. P. HASLER, P. K. PAREKH, M. L. BERTHOLOMEY, J. D. OLIVER-SMITH, E. J. FITZGERALD, C. A. MCCLUNG;
Dept. of Psychiatry, Univ. of Pittsburgh, Pittsburgh, PA

Abstract: During adolescence, circadian phase and sleep/wake times are delayed. When given the choice on the weekend, teens prefer to stay up late and sleep in. However, on weekdays adolescents must wake up early for school. The repeated weekend-weekday shifts, termed “social jet lag”, cause the internal clock to become desynchronized from the environment. Social jet lag has been linked with mood disturbances and increased alcohol use in adolescents. Imaging

studies on adolescent humans indicate that the effects of social jet lag are associated with altered medial prefrontal cortex and striatal activity. However, the specific neurobiological mechanisms by which adolescent social jet lag may lead to mood disturbances and increased alcohol use are unknown. Rats have been shown to exhibit an evening chronotype during adolescence similar to humans, and thus we chose to investigate the effects of social jet lag-like shifts in circadian activity on adolescent rat behavior and corticostriatal molecular rhythms. We hypothesized that adolescent rats have delayed phase and altered amplitude of corticostriatal circadian gene expression. Our preliminary findings suggest that adolescent rats may have decreased *Drd3* expression in the dorsal striatum. Then to examine if adolescent social jet lag disturbs mood and alters alcohol sensitivity in rats, adolescent rats (P31-P44) were forced to experience weekend-weekday activity advances by treadmill walking. On weekdays rats were placed on the treadmills from ZT6-ZT14, and on the weekends rats were on the treadmills from ZT12-ZT20. Control rats remained on the treadmills from ZT12-ZT20 each day. Following two weeks of timed treadmill walking, mood-related behaviors were assessed by open field, elevated plus maze, and forced swim tests. Then we examined alcohol sensitivity by assessing locomotor activity and striatal c-fos levels after an alcohol (2 g/kg, *i.p.*) challenge. Our preliminary data indicates that our social jet lag paradigm may increase risk taking behavior and produce hyperactivity. This data suggests that we can successfully model social jet lag and its behavioral effects in adolescent rats.

Disclosures: C.A. Vadnie: None. **B.P. Hasler:** None. **P.K. Parekh:** None. **M.L. Bertholomey:** None. **J.D. Oliver-Smith:** None. **E.J. Fitzgerald:** None. **C.A. McClung:** None.

Poster

816. Control of Sleep

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 816.01/SS16

Topic: F.08. Biological Rhythms and Sleep

Support: NIH 02-25520000-50000-8078-13

Title: State-dependent population synchrony in prefrontal cortex of freely moving non-human primate

Authors: *R. MILTON, N. SHAHIDI, V. DRAGOI;
Neurobio. and Anat., Univ. of Texas Hlth. Sci. Ctr. At Houst, Houston, TX

Abstract: Neural activity in a particular brain region results from the integration of bottom-up sensory inputs with top-down, internally-generated signals. The state of the animal, e.g., sleep or wakefulness, is a prominent global variable involved in shaping neuronal activity in all cortical

regions. In this study, we sought to better characterize the neuronal activity associated with resting and waking states in the dorsolateral prefrontal cortex of freely moving primates. We recorded from populations between 29 and 50 single neurons, in addition to 96 channels of local field potential recordings. All recordings were made in a freely-moving, naturalistic experimental setting. We computed the population distribution of single unit characteristics including firing rate and inter-spike interval histograms. Higher-order influences were also investigated. We quantified higher-order characteristics of the neuronal populations by computing pairwise correlations and a population synchrony index. We also computed the power spectra of the local field potentials. Significant state-dependent changes in the ratio of low LFP power (2-12Hz) to high LFP power (40-100Hz) were detected in agreement with findings in other cortical regions. We found that rest is associated with a significant decrease in the spontaneous firing rates of individual neurons. We also demonstrated that the pairwise correlations and population synchrony index are both increased during the resting state compared with wakefulness. These findings demonstrate that global cognitive states exert widespread influences on the activity of single units and the neuronal populations in the dorsolateral prefrontal cortex in freely-behaving rhesus macaque.

Disclosures: **R. Milton:** None. **N. Shahidi:** None. **V. Dragoi:** None.

Poster

816. Control of Sleep

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 816.02/SS17

Topic: F.08. Biological Rhythms and Sleep

Support: NIH Grant R01NS075545

Title: A novel role of Arc gene in sleep

Authors: ***A. SUZUKI**, R. W. GREENE;
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Abstract: Cumulative findings suggest that one of the most important roles of sleep is the maintenance of homeostatic synaptic plasticity. Potentiated synaptic strength during waking duration is released during sleep duration as delta power dependent manner. An immediate early gene, Arc plays a critical role in synaptic homeostasis to down-regulate synaptic plasticity induced by several physiological stimuli. Also, prolonged waking in rodents induces large increases in brain Arc gene expression in association with prolonged waking induced sleep need. Its expression is highly distributed in cortex, an important target for NREM and REM sleep

function. Nevertheless, the role of ARC in sleep/wake regulation or function is not well understood. To address these issues, we evaluated wild type (WT) and Arc KO mice sleep/wake activity. Although Arc is a light-inducible gene and expressed in SCN, Arc KO mice clearly showed normal circadian sleep phenotype; that is greater time spent in sleep in the light phase and wake in the dark phase, respectively. Also, knockout of Arc gene had no effect on the EEG. Arc KO mice exhibited longer time spent in REM sleep due to higher frequency of REM sleep episodes (no change in REM episode duration) compared to WT. Interestingly, the NREM to REM, and REM to NREM transitions were also increased but REM to wake transition was not affected. NREM sleep episode duration, and REM sleep latency were similar in both genotypes. On the other hand, Arc KO mice did not show REM sleep rebound following 4-h selective REM sleep deprivation. In addition, 4-h total sleep deprivation failed to induce any rebound in either NREM or REM sleep duration, regardless of the normal induction of delta power rebound. Our results suggest that Arc gene is necessary for normal REM sleep regulation, as well as the NREM and REM sleep duration response to sleep deprivation.

Disclosures: **A. Suzuki:** None. **R.W. Greene:** None.

Poster

816. Control of Sleep

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 816.03/SS18

Topic: F.08. Biological Rhythms and Sleep

Support: NIH Grant MH097037-01

Title: Knockdown of AT1 receptor expression in sleep-promoting areas improves sleep in a rodent model of stress-induced insomnia

Authors: *G. CANO, A. F. SVED;
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Abstract: Primary insomnia is triggered by stress in predisposed individuals. Central Angiotensin II (Ang II) is involved in stress, and blockade of brain Ang II AT1 receptors (AT1R) strongly attenuates stress responses. We have previously reported that pharmacologic blockage of brain AT1R prevents the emergence of sleep disturbances induced by stress in a rat model of insomnia. We hypothesize that the mechanism responsible for the improved sleep was the inhibition of AT1R located in key components of the brain circuitry activated during insomnia, such as the limbic and arousal systems. Nevertheless, there is high density of AT1R in the sleep-promoting areas, the median and ventrolateral preoptic areas (MnPO and VLPO,

respectively). We have verified the location of AT1R in these areas with RNAscope in situ hybridization in rat brain sections, as well as in sections from BAC transgenic mice that express AT1R-GFP in the brain. To explore the role of AT1R located in sleep-promoting areas in insomnia, we knocked down AT1R expression through RNA interference using a lentiviral vector (SPWGAT1R, 4 x 10^6 transducing units/ul) injected bilaterally in the VLPO (0.33 ul; lenti-VLPO) or MnPO (0.5 ul; lenti-MnPO). Three weeks after injections, rats were exposed to a psychosocial stressor (cage exchange), which consists in placing a rat into a dirty cage previously occupied during a week by another rat. This paradigm induces changes in the pattern of sleep several hours after stress exposure similar to those observed in humans. EEG/EMG activity was recorded using telemetric transmitters. Rats with the AT1R knocked down showed increased total sleep during the 5 hour period after cage exchange compared to intact rats. The % nREM sleep was 70.5 $\pm$ 2.7 (lenti-VLPO) and 63.7 $\pm$ 2.0 (lenti-MnPO) vs. 46.9 $\pm$ 8.8 (intact rats); the % REM sleep was 13.1 $\pm$ 1.5 (lenti-VLPO) and 8.05 $\pm$ 3.05 (lenti-MnPO) vs. 2.28 $\pm$ 1.06 (intact rats). Sleep latency was decreased in lenti-VLPO (43.1 + 3.5 min) compared to intact rats (68.2 +10.7), whereas fragmentation (number of state bouts) was decreased in lenti-MnPO rats (73 $\pm$ 12) compared to intact rats (99 $\pm$ 10.8). Lenti-VLPO rats fell asleep faster and stayed mostly asleep during the first 2 hours after cage exchange, whereas lenti-MnPO rats displayed much longer sleep latency but slept more during the 3-4th hours after cage exchange. Our results suggest that AT1R in VLPO and MnPO are distinctively involved in disturbances in sleep induction and maintenance, respectively, in the insomnia model. These observations suggest that AT1R in VLPO and MnPO could be a novel target for pharmacologic treatment of sleep disorders associated with decreased activity of sleep-promoting neurons.

Disclosures: G. Cano: None. **A.F. Sved:** None.

Poster

816. Control of Sleep

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 816.04/SS19

Topic: F.08. Biological Rhythms and Sleep

Support: Brain/MINDS (AMED/MEXT, H.R.U.)

Basic Science and Platform Technology Program for Innovative Biological Medicine (AMED/MEXT, H.R.U.)

Grant-in-Aid for Scientific Research (S) (JSPS, 25221004, H.R.U.)

Grant-in-Aid for Scientific Research on Innovative Areas (JSPS, 23115006, H.R.U.)

The strategic programs for R&D (RIKEN, H.R.U.)

Intramural Grant-in-Aid (RIKEN QBiC, H.R.U.)

Grant-in-Aid for JSPS Fellows (JSPS, 25-1565, G.N.K.)

Title: Involvement of interneuronal peptides in sleep duration in mammals

Authors: *G. N. KANDA[1,2], K. SUMIYAMA[1], R. G. YAMADA[1], H. R. UEDA[1,3,2];
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Abstract: Sleeping is essential for humans and most animals, and disruption of sleep critically interferes with our health. Although there has been lots of research to elucidate the neural networking of the sleep/wake cycle, identification of homeostatic regulators of sleep is not complete. To identify these molecules, we focused on peptidic neurotransmitters expressed in interneurons, which regulate sleep by repression of cortical excitatory neurons via GABA. Interneurons are classified by their morphology, connection, and marker genes. However the function of these peptides is still unclear. In this study, we hypothesized that peptidic neurotransmitters in interneurons act as a brake on the sleep/wake cycle. First, we characterized *Sst*, *Npy*, and *Cck* expressing neurons by tyramide-amplified immunohistochemistry-fluorescence in situ hybridization (TAI-FISH) of brain slices, and confirmed that almost all *Sst*, *Npy* and *Cck* expressing neurons are GABAergic. In addition, both the ratio of *c-fos* (+) neurons in *Sst* (+) neurons and the ratio of *c-fos* (+) neurons in *Npy* (+) neurons increased at night in the cortex, which indicates an increase in activity in these interneurons. These results suggest that an increase in activity in *Sst* and *Npy* expressing interneurons at night represses cortical excitatory neurons to promote sleep. Now we are generating *Sst*, *Npy* and *Cck* deficient mice by CRISPR/Cas microinjection and measuring sleep time using a respiration-based fully automated non- invasive sleep phenotyping system, the Snappy Sleep Stager (SSS, Sunagawa et al. 2016).

Disclosures: G.N. Kanda: None. **K. Sumiyama:** None. **R.G. Yamada:** None. **H.R. Ueda:** None.

Poster

816. Control of Sleep

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 816.05/SS20

Topic: F.08. Biological Rhythms and Sleep

Support: NS084477

NS079940

NS052287

Veterans Administration Medical Research

Title: Optogenetic activation of MCH neurons in MCH knockout mice increases sleep at night

Authors: *R. KONADHODE[1], D. PELLURU[1], C. BLANCO-CENTURION[1], M. LIU[1], P. SHIROMANI[1,2];
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Abstract: Melanin concentrating hormone (MCH) neurons become active during sleep and silent during waking (Hassani et al. 2009). We discovered that optogenetic activation of MCH neurons in wildtype (C57BL6/J) mice robustly increased both NREM and REM sleep (Konadhode et al. 2013). What is released from the MCH neurons that increases sleep? Is it the MCH peptide that increases sleep? To test our hypothesis we optogenetically activated the MCH neurons in MCH knockout mice.
MCH knockout mice were administered excitatory (rAAV-MCH-hChR2 (H134R)-EYFP) opsin into the lateral hypothalamus (LH) and implanted with sleep recording electrodes under 2% isoflurane anesthesia. Three weeks later a 48 h baseline sleep recording was obtained (0 Hz). At the start of the lights-off (night) period the mice were stimulated with 5, 10 or 30 Hz (random order) of blue light pulses (10 msec duration). The light pulses were delivered for 1 minute every 5 minutes for 24h, and 36h elapsed between the three stimulation rates.
Activation of MCH neurons (10Hz) in MCH knockout mice (n=8) for the 6h night period significantly decreased waking ($P<0.033$), increased NREM ($P<0.043$) and REM ($P<0.02$) sleep compared to baseline (0Hz). Activation of MCH neurons at 5 and 30Hz had no effect on sleep compared to baseline (0Hz).
These results in MCH knockout mice show that other factors such as GABA, released from the MCH neurons may also induce sleep in the absence of MCH peptide. Pharmacological activation of MCH neurons could potentially treat insomnia.

Disclosures: R. Konadhode: None. **D. Pelluru:** None. **C. Blanco-Centurion:** None. **M. Liu:** None. **P. Shiromani:** None.

Poster

816. Control of Sleep

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 816.06/SS21

Topic: F.08. Biological Rhythms and Sleep

Support: Howard Hughes Medical Institute

Title: Dorsomedial hypothalamus circuits for sleep regulation.

Authors: *K.-S. CHEN[1,2], M. XU[1,2], Y. DAN[1,2];
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Abstract: Mammals and birds have three distinct brain states - wakefulness, rapid eye movement (REM) sleep and non-REM sleep. Sleep is regulated by both circadian and homeostatic processes. The dorsomedial hypothalamus (DMH) in the hypothalamus is an important nucleus mediating circadian regulation of sleep, feeding, and thermogenesis. However, the mechanism by which the DMH regulates sleep is poorly understood. Using microendoscopic calcium imaging *in vivo*, optogenetic manipulations and virus-mediated circuit tracing we characterized the DMH circuits for sleep regulation.

Disclosures: K. Chen: None. **M. Xu:** None. **Y. Dan:** None.

Poster

816. Control of Sleep

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 816.07/SS22

Topic: F.08. Biological Rhythms and Sleep

Support: NIH Grant MH087592

NARSAD Grant

ELSC postdoctoral fellowship

Title: VTA dopaminergic neurons regulate sleep-wake states

Authors: *A. EBAN-ROTHSCHILD[1], G. ROTHSCHILD[2], W. J. GIARDINO[1], J. R. JONES[1], L. DE LECEA[1];
[1]Stanford Univ., Palo Alto, CA; [2]Dept. of Physiol. and Ctr. for Integrative Neurosci., Univ. of California, San Francisco, San Francisco, CA

Abstract: Dopaminergic ventral tegmental area (VTA) neurons are critically involved in a variety of behaviors that rely on heightened arousal, but whether they directly and causally control the generation and maintenance of arousal is unknown. We combined fiber-photometry

calcium imaging, chemogenetic and optogenetic manipulations and polysomnographic recordings in freely-behaving mice. We reveal state-dependent alterations in neuronal activity of VTA dopaminergic neurons. We show that VTA dopaminergic neurons are necessary for arousal and that their chemogenetic inhibition suppresses wakefulness to promote sleep; even in the face of ethologically relevant salient stimuli. Moreover, prior to inducing sleep, chemogenetic inhibition of VTA dopaminergic neurons promotes goal-directed and sleep-related nesting behavior. Optogenetic stimulation, in contrast, initiates and maintains wakefulness and suppresses sleep and sleep-related nesting behavior. We further show that different afferent projections of VTA dopaminergic neurons differently modulate arousal. Collectively, our findings uncover a fundamental role for VTA dopaminergic circuitry in the maintenance of the wake state and ethologically relevant sleep-related behaviors.

Disclosures: A. Eban-Rothschild: None. **G. Rothschild:** None. **W.J. Giardino:** None. **J.R. Jones:** None. **L. de Lecea:** None.

Poster

816. Control of Sleep

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 816.08/SS23

Topic: F.08. Biological Rhythms and Sleep

Support: Dept. of Veterans Affairs (VA merit, I01 BX001356 to RWM & VA CDA, IK2 BX002130 to JMM), NIMH RO1 MH039683 (RWM), NHLBI HL095491 (RWM). JTM received partial salary compensation and funding from Merck MISP, but has no conflict of interest with regards

Title: Optogenetic manipulation of basal forebrain parvalbumin neuron terminals in TRN modulates sleep spindles and NREM sleep

Authors: *S. THANKACHAN, J. M. MCNALLY, J. T. MCKENNA, C. YANG, R. E. STRECKER, R. E. BROWN, R. W. MCCARLEY;
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Abstract: Sleep spindle abnormalities are observed in psychiatric disorders such as schizophrenia (Sz). Spindles are EEG oscillations (12-15 Hz in humans, 8-15 Hz in rodents) occurring during NREM sleep. The thalamic reticular nucleus (TRN), a structure composed primarily of inhibitory GABAergic neurons, many of which contain the calcium binding protein parvalbumin (PV), is the generator of sleep spindles. Abnormalities of GABA/PV neocortical neurons are linked to Sz and there is evidence that they may be abnormal in TRN; we thus

speculate that abnormalities in PV neurons cause spindle abnormalities in Sz. For instance, one recent GWAS study found the gene coding for the CaV 3.3 channel, which is highly expressed in TRN and is required to generate low threshold calcium spikes underlying spindles, is a risk gene for Sz. Given this evidence, it is important to understand the normal state-dependent regulation of TRN PV neurons in order to correct spindle abnormalities in Sz. Anatomical evidence strongly shows basal forebrain (BF) PV neurons project extensively into TRN. Thus, here we investigate whether BF PV neurons control TRN PV neurons and in so doing modulate spindles & NREM sleep.

Experiments were performed in mice that express Cre recombinase in PV neurons (PV-Cre). We injected adeno-associated virus (AAV)-ChR2-EYFP or AAV-ArchT-GFP bilaterally into BF or TRN in PV-Cre mice. These mice were implanted with EEG/EMG screw electrodes to record sleep and histology confirmed that the bilateral optical fibers were located in TRN. Laser illumination was performed using either 473 nm solid state laser (for ChR2 activation) or 532 nm laser (for ArchT activation). In vitro work confirmed that the PV-labeled TRN neurons had low threshold spikes.

ChR2 optical excitation of BF PV terminals in TRN (n=2 animals) at 40Hz for 5s reliably blocked ongoing spontaneous trains of spindles for 8s compared with sham stimulation. Moreover, during a 6hr recording, 40 Hz stimulation for 5s/min decreased spindle density (spindles/min during NREM sleep) and NREM sleep. This effect was similar to TRN direct inhibition experiments, where ArchT inhibition of TRN PV cells blocked spindles and decreased NREM sleep/increased wake (N=7).

The data suggest that BF PV neurons directly modulate TRN PV cells in generating spindle activity and NREM sleep. These data provide further evidence for the essential role of TRN PV neurons in spindle generation. These results also point to targets for pharmacological development of compounds for spindle deficits in Sz that are based on TRN or BF PV neuronal abnormalities.

Disclosures: S. Thankachan: None. **J.M. McNally:** None. **J.T. McKenna:** A. Employment/Salary (full or part-time): Merck MISP. B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution; Merck MISP. C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Merck MISP. **C. Yang:** None. **R.E. Strecker:** None. **R.E. Brown:** None. **R.W. McCarley:** None.

Poster

816. Control of Sleep

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 816.09/SS24

Topic: F.08. Biological Rhythms and Sleep

Title: Octopamine regulation of sleep and arousal

Authors: *D. SITARAMAN[1], V. RAMIREZ[2];
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Abstract: The Drosophila mushroom body (MB) is an associative learning network that is important for the control of sleep. We have recently identified particular intrinsic MB Kenyon cell (KC) classes that regulate sleep through synaptic activation of particular MB output neurons (MBONs) whose axons convey sleep control signals out of the MB to downstream target regions. Specifically, we found that sleep-promoting KCs increase sleep by preferentially activating cholinergic sleep-promoting MBONs, while wake-promoting KCs decrease sleep by preferentially activating glutamatergic wake-promoting MBONs. Further, we have identified specific neuromodulatory neurons that innervate the sleep and wake microcircuits and likely underlie the persistence of sleep and wake states. Here we use a combination of genetic and physiological approaches to identify two distinct classes of the wake-promoting neurons that release Octopamine a biogenic amine homologous to norepinephrine in humans. These studies will reveal the precise nature of connectivity and sleep regulation by octopamine and provide a framework for the design of analogous experiments in understanding how norephinephrine controls sleep in genetically tractable vertebrate model systems such as zebrafish and mice.

Disclosures: D. Sitaraman: None. **V. Ramirez:** None.

Poster

816. Control of Sleep

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 816.10/SS25

Topic: F.08. Biological Rhythms and Sleep

Support: NSFC Grant 91432306

Title: Role of the cholinergic transmission from the nucleus basalis of Meynert to the thalamic reticular nucleus in sleep regulation

Authors: *P. DONG, X.-J. HOU, K.-M. NI, P. JIANG, X.-M. LI;
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Abstract: The cholinergic neurons of the basalis of Meynert (nbM) provide widespread projections to the cortex, but its connection with other brain areas are poorly understood. The thalamic reticular nucleus (TRN) mainly receives cholinergic projection from the brainstem. Interestingly, we detected projections from the nbM cholinergic neurons to TRN parvalbumin (PV) neurons. By using optogenetics, electrophysiology, and fiber-recording system, we found that the nbM cholinergic neurons provide direct excitatory and inhibitory synaptic transmission to TRN PV neurons via α7 nicotinic acetylcholine receptors (α7 nAChRs) and M1 muscarinic acetylcholine receptors (M1 mAChRs), respectively. Our results also suggest that the nbM-TRN projection is involved in sleep regulation. Detailed characterization of the nbM-TRN circuitry may improve our understanding of the pathophysiology of diseases such as sleep disorders associated with TRN dysfunction.

Disclosures: **P. Dong:** None. **X. Hou:** None. **K. Ni:** None. **P. Jiang:** None. **X. Li:** None.

Poster

816. Control of Sleep

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 816.11/SS26

Topic: F.08. Biological Rhythms and Sleep

Support: AHA 15POST25510020

VA 1I01RX001640

NIH 1K02NS093014

BWF 1009855

Title: Optogenetic inhibition of spiking during slow wave activity prevents consolidation of neuroprosthetic learning.

Authors: *T. GULATI, L. GUO, D. RAMANATHAN, A. HISHINUMA, A. BODEPUDI, K. GANGULY;
Neurology, UCSF, San Francisco VA Med. Center/ UCSF, San Francisco, CA

Abstract: Introduction: A large body of work shows that reactivation of neural activity during sleep plays a role in memory consolidation. However, it remains debated if these reactivations result in either exclusive strengthening or renormalization of functional connectivity. Using neuroprosthetic learning, where we can experimentally control the causality between neural firing & behavior, we found link between the microstructure of sleep reactivations & renormalization, with selective preservation of task activity & downscaling of non-task activity. In a subset of experiments, we optogenetically inhibited the neural activity during sleep which prevented task unrelated activity's renormalization & also, the offline gains in performance.
Methods: We recorded spikes & LFPs in the M1 of 9 rats. 3 of these animals were also injected with a halorhodopsin encoding plasmid 'Jaws' (pAAV-hsyn-Jaws-KGC-GFP-ER2) - which is a red-shifted, light-driven inward chloride pump used to silence activity. Post surgeries, rats were trained to exert direct neural control over a mechanical actuator in a session we termed BMI_1. A decoder was used that converted the firing of 2 randomly selected units ('directs') into the angular velocity of the actuator. For optogenetic expts., these were so chosen that they responded by silencing with light stim. We also recorded a host of other units that were not causally linked to actuator movements ('indirects'). We also recorded two spontaneous recording sessions before & after the BMI_1 - $Sleep_1$ & $Sleep_2$. We studied task-related modulations of all units & performance changes in a second BMI session (BMI_2) after $Sleep_2$. In optogenetic experiments, we delivered stimulation during SWA oscillations in $Sleep_2$.
Results: We found that from BMI_1 to BMI_2, the task-related firing modulation persisted only for direct units, while it renormalized for indirects. This was concomitant with performance gains. In opto expts., we found that stimulation when delivered during high power in SWA or during 'On' states prevented rescaling of indirect activity. There were also no performance gains in BMI_2 in these experiments. Surprisingly, in 2 sessions, light stim. was restricted to 'Off' states in $Sleep_2$ & we saw performance gains as well as rescaling of indirect units' activity.
Conclusion: We found that the coupling of spiking to SWA is required for the renormalization of task-related activity. Our results support the notion that reactivations during sleep may renormalize task activity & thereby improve the signal-to-noise of neural networks during task performance.

Disclosures: T. Gulati: None. **L. Guo:** None. **D. Ramanathan:** None. **A. Hishinuma:** None. **A. Bodepudi:** None. **K. Ganguly:** None.

Poster

816. Control of Sleep

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 816.12/TT1

Topic: F.08. Biological Rhythms and Sleep

Support: MEXT Grant 26220207

MEXT Grant 15H05935

Title: Forward genetic screening in mice identifies a novel sleep-regulating gene

Authors: *H. FUNATO[1,2], C. MIYOSHI[2], M. SATO[2], A. IKKYU[2], M. KAKIZAKI[2], N. HOTTA[2], S. KANNO[2], K. HARUNA[2], S. WAKANA[3], M. YANAGISAWA[2];
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Abstract: Sleep is an animal behavior ubiquitously conserved from invertebrates to vertebrates, and tightly regulated in a homeostatic manner. Each animal species has a characteristic time spent in sleep determined by a homeostatic sleep need, which works as a driving force for sleep/wakefulness switching. Although recent advances in optogenetic and chemogenetic research have enabled us to directly examine executive neural circuitries regulating sleep/wakefulness states, the molecular and cellular mechanism that determines the propensity of switching between wakefulness and non-REMS (NREMS) remains unknown. Here we identified a genetic mutation affecting sleep/wakefulness through electroencephalogram (EEG) / electromyogram (EMG)-based screening of randomly mutagenized mice. A splicing mutation of a protein kinase gene, termed *Sleepy*, causes a profound decrease in total wake time. Increased sleep time of *Sleepy* mutant mice does not seem to be due to a defect in wake-promoting system, but rather due to an increased inherent sleep need.

Disclosures: H. Funato: None. **C. Miyoshi:** None. **M. Sato:** None. **A. Ikkyu:** None. **M. Kakizaki:** None. **N. Hotta:** None. **S. Kanno:** None. **K. Haruna:** None. **S. Wakana:** None. **M. Yanagisawa:** None.

Poster

816. Control of Sleep

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 816.13/TT2

Topic: F.08. Biological Rhythms and Sleep

Support: RO1-NS088482

PO1-AG09975

PO1-HL095491

Title: Optogenetic activation of VLPO galaninergic neurons promotes sleep in mice.

Authors: *D. KROEGER, L. L. FERRARI, E. ARRIGONI, T. E. SCAMMELL, C. B. SAPER, R. VETRIVELAN;
BIDMC / Harvard Univ., Boston, MA

Abstract: Much research suggests that the ventrolateral preoptic area (VLPO) is a key region for promoting sleep in mammals. The VLPO contains neurons that are active during sleep, and lesions of the VLPO reduce NREM and REM sleep in rats. As a heterogeneous nucleus, some neurons in the VLPO can contain GABA, glutamate, galanin (GAL) and other neuropeptides. Since specifically GAL neurons in the VLPO express c-Fos after periods of increased sleep and project to key wake-promoting regions, we hypothesize that GAL neurons are the crucial sleep-promoting population within the VLPO. However, the ability of GAL neurons to promote sleep has not been determined. To test this question, we used optogenetics to selectively activate GAL neurons in mice and studied changes in sleep/wake behavior. We injected an adeno-associated viral vector (AAV) coding for channelrhodopsin (ChR2) and the fluorescent tag mCherry (AAV8-ChR2-mCherry) into the VLPO of transgenic mice expressing Cre recombinase (cre) specifically in GAL neurons (GAL-Cre mice). A control group of GAL-cre mice received injections of an AAV coding for only mCherry (AAV8-mCherry). Both groups were implanted with optical fibers for light stimulation and electrodes for EEG and EMG recordings. After 3-4 weeks of postoperative recovery, we performed blue light (473 nm) or sham (no light) stimulation during the dark (active) period and assessed sleep/wake behavior. Photostimulation of ChR2-expressing galaninergic VLPO neurons increased NREM sleep ~75% compared to sham stimulation in the same mice or blue light stimulation in mCherry-expressing controls. REM sleep increased similarly. These results demonstrate that GAL neurons in the VLPO are capable of promoting sleep even during the dark period when the circadian drive for wake is high, providing further evidence that GAL neurons are the key sleep-promoting system within the VLPO.

Disclosures: D. Kroeger: None. **L.L. Ferrari:** None. **E. Arrigoni:** None. **T.E. Scammell:** None. **C.B. Saper:** None. **R. Vetrivelan:** None.

Poster

816. Control of Sleep

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 816.14/TT3

Topic: F.08. Biological Rhythms and Sleep

Support: NS078167

NS078304

Title: Cation composition changes in brain interstitial space control the sleep-wake cycle

Authors: *F. DING, J. O'DONNELL, Q. XU, N. KANG, N. GOLDMAN, M. NEDERGAARD; Univ. of Rochester, Rochester, NY

Abstract: Neuronal excitability is sensitive to changes in the composition of extracellular ions. For example, elevations of extracellular $[K^+]_e$ in the bath solution increase spontaneous and evoked excitatory activity in hippocampal slices and can at higher concentrations trigger seizure-like activity. Astrocytes are believed to play a critical role in buffering $[K^+]_e$ elevations during neural activity. However, studies in peripheral tissue have documented the resting level $[K^+]_e$ is regulated by neuromodulators. We have here tested whether $[K^+]_e$ is regulated by the sleep-wake cycle and whether the release of neuromodulators during the transition from sleep to wakefulness increases $[K^+]_e$. In cortical slices prepared from adult mice, we found that a cocktail of neuromodulators (norepinephrine, acetylcholine, histamine, dopamine, and orexin) consistently elevated $[K^+]_e$ in cortical slices electrically silenced by tetrodotoxin. In vivo, arousal was linked to AMPA receptor-independent elevations of $[K^+]_e$. Opposite, natural sleep or isoflurane anesthesia reduced $[K^+]_e$. Moreover, local cortical activity of sleeping mice could be readily converted to the stereotypical EEG pattern of wakefulness by simply imposing a change in the extracellular ions composition. Thus, we propose that extracellular $[K^+]_e$ and possible other ions control the state-dependent patterns of neural activity, which is most likely regulated by concerted release of neuromodulators in brain.

Disclosures: F. Ding: None. **J. O'Donnell:** None. **Q. Xu:** None. **N. Kang:** None. **N. Goldman:** None. **M. Nedergaard:** None.

Poster

816. Control of Sleep

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 816.15/TT4

Topic: F.08. Biological Rhythms and Sleep

Support: NIH R01 NS073613

NIH K99 MH103399

Title: Differential regulation of wake, sws and rem sleep by pontomedullary gabaergic, glutamatergic and phox2b-expressing neurons.

Authors: *C. ANACLET, P. M. FULLER;
BIDMC Harvard, Boston, MA

Abstract: We have previously reported that acute and selective activation of GABAergic (VGAT+) parafacial zone (PZ) neurons is sufficient to produce slow wave sleep (SWS) and associated cortical slow wave activity (SWA), independent of the time of day. The PZ, however, also contains intermingled glutamatergic and Phox2B-expressing neurons whose roles in these processes remain unknown.
We first asked whether Phox2B might be co-expressed with GABAergic (VGAT+) and/or glutamatergic (VGLUT2+) PZ neurons. We then tested whether activation of PZ glutamatergic and Phox2B-expressing neurons affects sleep-wake behavior and compared these responses to activation of neighboring glutamatergic neurons implicated in wake promotion, i.e. parabrachial nucleus (PB) or in REM sleep promotion, i.e. sublaterodorsal nucleus (SLD). We first found that PZ Vglut2+, but not PZ VGAT+, neurons co-expressed Phox2b, suggesting a similar role for PZ glutamatergic and Phox2b neurons in sleep-wake control. To explicitly test this, we placed bilateral injections of a viral vector containing a cre-enabled excitatory receptor system [hM3Dq-AAV10] into the PZ of Vglut2-cre and Phox2b-cre mice. We found that selective activation of PZ glutamatergic or Phox2B-expressing neurons (CNO, 0.3mg/kg, IP, ZT3 & 12) did not reliably induce SWS, wake or REM sleep. By contrast, selective activation of neighboring PB or SLD glutamatergic neurons, also using hM3Dq, induced sustained wakefulness or decreased REM sleep latency and increased REM sleep amount, respectively. These results 1) fail to implicate PZ glutamatergic and Phox2B-expressing neurons in sleep-wake control; 2) confirm differential sleep-wake regulatory roles for delimited nodes of glutamatergic neurons within the pontine tegmentum-rostral medulla continuum; and 3) provide new mouse models of wake- and REM sleep-enhancement that offer the advantages of being non-invasive and non-pharmacologic and, as such, serve as complements to the recently published PZ mouse model of SWS enhancement. These mouse models will facilitate a greater understanding of the influence of these three vigilance stages *per se* in other neurological functions.

Disclosures: C. Anaclet: None. **P.M. Fuller:** None.

Poster

816. Control of Sleep

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 816.16/TT5

Topic: F.08. Biological Rhythms and Sleep

Support: NIMH #60670

NIH T32 Systems and Integrative Biology

Rackham Merit Fellowship

Title: The effects of Locus Coeruleus optogenetic stimulation on sleep Traits and Memory Consolidation

Authors: *K. SWIFT, B. GROSS, A. SERGEEVA, D. BAUER, G. POE;
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Abstract: It has been shown that the proper modulation of norepinephrine release across sleep states is essential for sleep dependent memory consolidation. The supplier of norepinephrine, the locus coeruleus (LC), actively secretes norepinephrine throughout the brain, except during rapid eye movement (REM) and and sleep spindles during transition to REM (TR) sleep, when it falls silent. While norepinephrine acts to strengthen synaptic connections, the cessation of norepinephrine during periods of LC quiescence uniquely allows synaptic weakening. Furthermore, REM sleep, and sleep spindles found during TR have been mechanistically associated with sleep dependent memory consolidation. We hypothesize that these transient periods allow bidirectional synaptic plasticity necessary for the incorporation of new memories or ideas into preexisting schema. To test our hypothesis male Long-Evans rats were trained on a hippocampally dependent-spatial learning task to find food with less than one error/lap. Rats we then outfitted with microdrives, optic fibers, and viral vector containing channelrhodopsin2. Following recovery rats were tested on the familiar spatial task, and then given a novel spatial task and optogenetically stimulated during the subsequent five hours of sleep for two days. Normal sleep was allowed following three more days of running. Results showed that 2 Hz optogenetic stimulation of the LC during sleep caused a significant reduction in sleep spindles during REM and TR sleep and a decrease in sigma band power during TR. Also stimulation during sleep after training impaired novel learning of reward shifts in the spatial maze task. We conclude that periods of norepinephrine cessation are essential for proper sleep-dependent memory consolidation. These results also indicate that elevated LC activity during REM and TR sleep is maladaptive to tasks requiring alterations in pre-existing schema.

Disclosures: **K. Swift:** None. **B. Gross:** None. **A. Sergeeva:** None. **D. Bauer:** None. **G. Poe:** None.

Poster

817. Thirst and Water Balance

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 817.01/TT6

Topic: F.09. Thirst and Water Balance

Support: OCAST HR12-196

Title: Glial immunolabeling in female rats after short term vs long term furosemide treatment

Authors: *S. L. CORE, K. CURTIS;
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Abstract: During osmotic challenges glia interact with neurons to influence signaling in hypothalamic areas associated with body fluid balance. Glia located in or near circumventricular organs (CVOs), the central sites at which changes in circulating hormones and osmolytes are detected, may also affect neural signaling and the modulatory effects of estradiol are unknown. Furosemide, a natriuretic-diuretic, increases urinary sodium loss within an hour after treatment but an 18-24 hour delay typically transpires before rats consume sodium solutions. We hypothesized that sodium loss and/or the associated volume loss is detected by glial cells which, in turn, influence central signaling, and that this effect may be altered by estradiol. Our objectives were to assess the effect of estradiol on water and salt intake following furosemide treatment, compare glial presence after Na+ depletion using immunolabeling, and determine whether any differences in glial abundance depend upon the presence of estradiol. Adult female Sprague Dawley rats were OVX under pentobarbital anesthesia (Pbt; 50mg/kg bw, i.p.), treated with Meloxicam (1.5mg/kg bw) for postoperative pain management, and allowed 7 days to recover; then given estradiol benzoate (EB; 10 µg/0.1 ml sesame oil, s.c.) or sesame oil vehicle (OIL; 0.1 ml, s.c.) on an intermittent schedule. Rats were given two s.c injections 1-hour apart of 0.15 M NaCl (ISO; 1.0 mL/kg bw) or furosemide (5 mg/kg bw) in one of two protocols. For the short-term protocol, one hour after the 2nd injection, rats were given a two-bottle test (0.5 M NaCl and water) or were anesthetized with Pbt and perfused with paraformaldehyde. Brains were removed and cut in 40 µ sections. For the long-term protocol, rats were returned to their cages for 18 hours after the 2nd injection, and then treated as described. For immunolabeling, free-floating sections were labeled for glial fibrillary acidic protein (GFAP; Millipore; 1:10,000). Rats consumed 0.5 M NaCl after furosemide in the long-term, but not the short-term protocol. GFAP immunolabeling after furosemide appeared to be most abundant in the CVO's of rats from the long-term protocol, but did not appear to be substantially different between EB- and OIL- treated rats. These data suggest a role for glia in CVOs in responses to established sodium loss and/or volume loss that does not appear to depend on estradiol. All procedures were approved by the Oklahoma State University Center for Health Sciences Animal Care and Use Committee.

Disclosures: S.L. Core: None. **K. Curtis:** None.

Poster

817. Thirst and Water Balance

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 817.02/TT7

Topic: F.09. Thirst and Water Balance

Support: CNPQ - 150266/2015-4

CNPQ - 150055/2016-1

FAPESP - 2011/03368-3

FAPESP - RCUK - 2011/52108-4

BBSRC - BB/J015415/1

Title: Maternal salt overloading changes behavioral, neuroendocrine and transcriptome responses in adult offspring

Authors: *M. SANTOS DA SILVA[1], F. LUCIO-OLIVEIRA[1], C. HINDMARCH[2,3], A. S. MECAWI[4], M. P. GREENWOOD[2], L. L. K. ELIAS[1], D. MURPHY[2,3], J. ANTUNES-RODRIGUES[1];
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Abstract: It is well stablished that pregnancy and postnatal periods are important for offspring health. During these periods, stressful conditions can program physiological systems of the adult offspring, and potentially leads to diseases. However, the effect of osmotic challenges, due to maternal salt overloading, is unknown in adult offspring. Thus, our aims were to evaluate transcriptome in control adult offspring as well as, water intake, vasopressin (AVP), oxytocin (OT) and corticosterone secretion in adult offspring submitted or not, to water deprivation. For this, dams were assigned into two groups; mothers with access to either water (MW) or isotonic saline (MS) during the entire pregnancy-lactation period. All litters received only water after weaning until 60 postnatal days, when they were submitted or not to water deprivation for 48h (WD). Thus, experimental groups were: MW-Control, MW-WD, MS-Control and MS-WD. In our study, we analyzed differential paraventricular (PVN) and supraoptic (SON) nuclei genes expressions induced by salt overloading during perinatal and postnatal periods. Genes tracking of MW-Control and MS-Control groups were compared to the rat reference genome. Results indicated that a total of 7.509 PVN genes and 639 SON genes expressions were altered in MS group compare to MW group. Importantly, expressions of some genes were significantly altered in both nuclei, and it could represent an important function to the hydromineral balance, such as

AVP, angiotensinogen, cholecystokinin, nitric oxide synthase 1 neuronal and epoxide hydrolase 2. Confirmation of the altered expression of these genes, as being significantly regulated by maternal salt loading treatment, was done by qPCR. Our results interestingly showed that, differently from MW-WD group, offspring from the MS-WD group, did not exhibit a significant increase in cumulative intake of water compared to MS-Control group. Neuroendocrine data identified a significant main effect of water deprivation on vasopressin (AVP) ($p<0.001$), oxytocin (OT) ($p<0.001$) and cortiscosterone ($p<0.001$) plasma concentrations. Post-hoc analyses indicated that AVP release was significant ($p<0.05$) lower in MS-WD group compared to MW-WD. No programming effects were observed on OT and cortiscosterone secretion. Overall, our data suggest that the ontogenic period is a critical stage for the development of behavioral, neuroendocrine and genetic adaptative mechanisms to better cope with a hydromineral challenge in the future.

Disclosures: **M. Santos Da Silva:** None. **F. Lucio-Oliveira:** None. **C. Hindmarch:** None. **A.S. Mecawi:** None. **M.P. Greenwood:** None. **L.L.K. Elias:** None. **D. Murphy:** None. **J. Antunes-Rodrigues:** None.

Poster

817. Thirst and Water Balance

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 817.03/TT8

Topic: F.09. Thirst and Water Balance

Title: Chronic dehydration induced brain plasticity and exhibited high expression of vasopressin and renal water channel aquaporin type 2 of meriones shawi

Authors: *A. ELGOT[1,2], O. ELHIBA[3], H. GAMRANI[3];
[1]biology, Cadi Ayyad Univ. (UCAM), Fac. of Sci., Marrakech, Morocco; [2]laboratory of biomedical sciences, Higher Inst. of Hlth. Sciences, Hassan First University, Complexe Universitaire, route de Casablanca B.P 555 Settat, Morocco., Settat, Morocco; [3]Lab. of Neurosciences, Pharmacol. and Environment, Cadi Ayyad Univ. (UCAM), Fac. of Sci. Semlalia, B.P. 2390, Marrakesh, Morocco, Marrakech, Morocco

Abstract: Introduction: Supraoptic (SON) and paraventricular (PVN) nuclei are part of the hypothalamic system, they constitute the main source for vasopressin (AVP) and they represent obvious examples of activity-dependent neuroglial plasticity. Under severe dehydration, AVP neurons, release AVP which stimulates the expression of the kidney water channel named aquaporines type 2 (AQP-2), necessary for the reabsorption of water and reduces significantly the dieresis. The aim of the present investigation is to clarify the underlying central and

peripheral mechanisms allowing the desert rodent *Meriones shawi* to resist to dehydration. **Materials and Methods:** Glial fibrillary acidic protein (GFAP), AVP and AQP-2 immunoreactivities were used successively as activation indicators of astrocytes, AVP neurons and medulla kidney AQP-2. Hence, we studied the immunoreactivity in various hydration states: water ad libitum, one and three months of dehydration. **Results:** Our results showed that dehydration of *Meriones* induced a significant decrease of GFAP accompanied by an increase of AVP immunoreactivities, the latter concerns both cell bodies and fibers in both SON and PVN. Peripherally, a significant increase of AQP-2 immunoreactivity in the kidney medulla was simultaneously seen. **Conclusion:** These results show that both astrocytes and neurons display structural and physiological plasticity on both SON and PVN allowing an excessive release of AVP, which acts probably on AQP-2 allowing probably to *Meriones* a great ability to water retention.These various changes at both central and peripheral levels might be the basis of control of body water homeostasis, providing to *M. shawi* a strong resistance against dehydration.

Disclosures: **A. Elgot:** None. **O. Elhiba:** None. **H. Gamrani:** None.

Poster

817. Thirst and Water Balance

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 817.04/TT9

Topic: F.09. Thirst and Water Balance

Title: Reproductive status does not affect phasic activity patterning in hypothalamic vasopressin neurons

Authors: *C. H. BROWN[1], R. A. AUGUSTINE[2];
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Abstract: The antidiuretic hormone, vasopressin, promotes water retention by the kidney. Vasopressin secretion is inhibited by reduced plasma osmolality, as well as by increased plasma volume. During pregnancy and lactation, plasma osmolality is reduced and plasma volume is increased but, remarkably, circulating vasopressin is not decreased. Vasopressin release from the posterior pituitary gland is triggered by action potential firing of magnocellular neurosecretory neurons that are mainly located in the hypothalamic supraoptic nucleus and paraventricular nucleus. Vasopressin neurons fire action potentials in a phasic pattern comprised of alternating bursts of activity and silence, each lasting tens of seconds. Here, we made extracellular single unit recordings of spontaneous phasic activity of supraoptic nucleus vasopressin neurons in urethane-anaesthetized virgin (n = 58), pregnant (n = 15) and lactating (n = 25) rats. Despite

lower plasma osmolality in pregnant and lactating rats than in virgin rats (P = 0.004, one-way ANOVA), there were no differences in overall firing rate (P = 0.46), intra-burst firing rate (P = 0.35), burst duration (P = 0.62) or inter-burst interval (P = 0.49) in phasic vasopressin neurons. Hence, vasopressin neurons maintain normal phasic activity patterning during pregnancy and lactation, which might underpin the decreased osmotic set-point for vasopressin secretion evident during pregnancy and lactation.

Disclosures: C.H. Brown: None. **R.A. Augustine:** None.

Poster

817. Thirst and Water Balance

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 817.05/TT10

Topic: F.09. Thirst and Water Balance

Support: NSF Graduate Research Fellowship

UCSF Discovery Fellowship

Title: Thirst neurons anticipate the homeostatic consequences of eating and drinking.

Authors: *C. A. ZIMMERMAN, Y.-C. LIN, D. E. LEIB, L. GUO, E. L. HUEY, G. E. DALY, Z. A. KNIGHT;
UCSF, San Francisco, CA

Abstract: Thirst motivates animals to drink in order to maintain fluid balance. Traditionally, thirst has been viewed as a homeostatic response to changes in the blood volume or tonicity. However most drinking behavior is regulated too rapidly to be controlled by blood composition directly, and instead appears to anticipate homeostatic imbalances before they arise. How this is achieved remains unknown. We recently discovered an unexpected role for a specific molecularly-defined population of neurons in the anticipatory regulation of thirst. We show by deep-brain calcium imaging that these thirst-promoting neurons respond to inputs from the oral cavity during eating and drinking, which they then integrate with information about the composition of the blood. This integration allows these neurons to predict how ongoing food and water consumption will alter fluid balance in the future and then adjust behavior preemptively. We used complementary optogenetic manipulations to further refine our understanding of the role that this rapid anticipatory modulation, and this population of excitatory neurons in general, play in the real-time control of drinking behavior in multiple contexts. These findings provide a neural mechanism to explain longstanding behavioral observations, including the prevalence of

drinking during meals, the rapid satiation of thirst, and the fact that oral cooling is thirst-quenching.

Disclosures: **C.A. Zimmerman:** None. **Y. Lin:** None. **D.E. Leib:** None. **L. Guo:** None. **E.L. Huey:** None. **G.E. Daly:** None. **Z.A. Knight:** None.

Poster

817. Thirst and Water Balance

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 817.06/TT11

Topic: F.09. Thirst and Water Balance

Support: Canadian Institutes of Health Research (FDN 143337)

Title: High salt intake activates microglia-mediated astrocytes remodeling to modulate the excitability of vasopressin neurons

Authors: ***M. PRAGER-KHOUTORSKY**, K. Y. CHOE, T. W. FARMER, D. I. LEVI, K. K. MURAI, C. W. BOURQUE;
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Abstract: The supraoptic nuclei (SON) of the hypothalamus display a remarkable anatomical plasticity during the physiological and pathological conditions associated with strong and sustained release of neurohypophysial hormones (e.g. dehydration, lactation, and chronic hypernatremia). This plasticity is characterized by a pronounced reduction in astrocytic coverage of SON neurons, resulting in an increased number and extent of synaptic contacts. While the impact of this glial plasticity on synaptic transmission and neuronal activity has been studied, the mechanism that mediates the reduction in the astrocytic coverage remains unknown. Previous studies suggested that microglia in the SON become activated during chronic hypernatremia achieved by 7-day salt loading. Our data show that salt loading causes a dramatic reduction in the astrocytic coverage of SON neurons secreting vasopressin (an antidiuretic hormone). This effect is significantly attenuated when microglia activation is inhibited by minocycline. These results suggest that activation of microglia may be involved in the reduction of the astrocytic coverage of vasopressin neurons, thereby contributing to the modulation of their activity in chronic hypernatremia.

Disclosures: **M. Prager-Khoutorsky:** None. **K.Y. Choe:** None. **T.W. Farmer:** None. **D.I. Levi:** None. **K.K. Murai:** None. **C.W. Bourque:** None.

Poster

817. Thirst and Water Balance

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 817.07/TT12

Topic: F.09. Thirst and Water Balance

Support: INPRFM NC093290.0 (MLO)

CONACYT/ Doctorado en Ciencias Biomédicas, FM, UNAM (294229 MYAG)

Dr. Harold Gainer (NIH, Bethesda, USA) for donation of the vasopressin antibody

Dr. Prasada Rao S. Kodavanti (USEPA) for donation of DE-79

Mr. Feliciano Camacho for the technical assistance

Title: Perinatal exposure to commercial mixture of polybrominated diphenyl ethers DE79 affects vasopressin content and mRNA expression in hypothalamic nuclei of adult rats

Authors: *M. Y. ÁLVAREZ-GONZÁLEZ[1], E. SÁNCHEZ-ISLAS[1], S. MUCIO-RAMÍREZ[1], P. DE GORTARI[2], M. I. AMAYA[2], M. LEÓN-OLEA[1];
[1]Neuromorfología Funcional, [2]Neurofisiología Mol., Inst. Nacional De Psiquiatría Ramón De La Fuente, Ciudad De México, Mexico

Abstract: The polybrominated diphenyl ethers (PBDEs) are extensively used as additive flame retardant in different daily products. PBDEs are lipophilic and bioaccumulated in animals and in the environment. They are classified as endocrine disruptors causing adverse effects in human health. PBDEs exist as 209 possible congeners based on the number and position of bromines (mono- through deca-BDE). The DE-79, a commercial octabromodiphenyl ether (octaBDE) mixture, was banned from the market on 2004, but persists in the environment. The decaBDEs are currently in use, but these compounds undergo biodegradation to lower brominated congeners. The aim of this study was to determine the effects of DE-79 exposure during gestation and lactation on the vasopressin (AVP) content and mRNA expression of the hypothalamic paraventricular (PVN) and supraoptic nuclei (SON) of rats under osmotic challenge. Pregnant Wistar dams were given orally DE-79 at doses of 0 (control), 1.7 and, 10.2 mg/kg/day dissolved in corn oil from gestational day 6 to postnatal day 21. Male offspring were allowed to grow up to 3 months old. One group was processed for AVP immunofluorescence in coronal brain sections (30 um) of PVN and SON. Photomicrographs were taken and AVP immunoreactivity (AVP-IR) changes were quantified integrated optical density (IOD). Another group was processed to obtain AVP mRNA by RT-PCR assay in PVN and SON punches. Both groups included dehydrated (drinking 2% saline *ad libitum* for 4 days) and hydrated rats (*ad libitum* access to tap water*)*. Plasma osmolality was measured by vapor pressure osmometry.

Data were analyzed with a two-way ANOVA. IOD values showed increased AVP-IR in hydrated animals with dose of 1.7 and decreased with 10.2 dose compared to control; these differences were significant only in SON. In response to the osmotic challenge there was a significant dose-related decrease of AVP-IR in both nuclei. The AVP mRNA expression significantly increased with dose 10.2 compared to control but did not increase after dehydration as expected. The osmolality showed increased dose-related tendency in dehydrated animals. These results suggested that perinatal exposure to octaBDEs affected AVP content and mRNA expression in adult rats, which compromises osmoregulation. These outcomes are consistent with our previous reports of less brominated congeners.

Disclosures: **M.Y. Álvarez-González:** None. **E. Sánchez-Islas:** None. **S. Mucio-Ramírez:** None. **P. de Gortari:** None. **M.I. Amaya:** None. **M. León-Olea:** None.

Poster

817. Thirst and Water Balance

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 817.08/TT13

Topic: F.09. Thirst and Water Balance

Support: The Canadian Institutes for Health Research

Title: Direct actions of adropin on hypothalamic paraventricular nucleus neurons

Authors: *S. P. LOEWEN, A. V. FERGUSON;
Dept. of Biomed. and Mol. Sci., Queen's Univ., Kingston, ON, Canada

Abstract: Adropin, a peptide hormone encoded by the Energy Homeostasis Associated (*Enho*) gene, has been observed to have metabolic roles in the periphery, including effects on glucose and lipid homeostasis. Central administration of adropin has recently been shown to inhibit water intake in rats; however, the site at which this novel CNS action occurs has yet to be determined. The hypothalamic paraventricular nucleus (PVN) is an important autonomic control center required for regulating energy balance and fluid homeostasis, and is therefore a potential target for centrally acting adropin. In the present study, we used whole-cell patch clamp techniques to examine the effects of adropin on the excitability of neurons within the PVN of the rat. All three neuronal subpopulations (magnocellular neurosecretory, parvocellular preautonomic, and parvocellular neuroendocrine) in the PVN were found to be responsive to bath application of 10 nM adropin, which elicited responses in 69% of cells (n=70), with 59% depolarizing (mean: 5.2 ± 0.3 mV) and 10% hyperpolarizing (mean: -4.1 ± 1.1 mV). Concentration-dependent (100 pM-100 nM) depolarizations were observed in all three types of neurons (mean depolarizations: 100

pM, 3.8 ± 0.3 mV, n=11; 10 nM, 5.2 ± 0.3 mV, n=33; 100 nM, 6.0 ± 1.9 mV, n=5), while no neurons tested (n=6) responded to 1 pM adropin (mean: 1.1 ± 0.3 mV). The depolarizing effects of 10 nM adropin were maintained in the presence of tetrodotoxin in 86% of neurons tested (mean: 4.9 ± 1.0 mV, n=7). Furthermore, voltage-clamp analysis demonstrated that adropin had no effect on the amplitude or frequency of excitatory postsynaptic currents, suggesting the peptide exerts direct postsynaptic actions on PVN neurons. These findings provide insight into the cellular events by which central adropin may exert its physiological effects.

Disclosures: S.P. Loewen: None. **A.V. Ferguson:** None.

Poster

817. Thirst and Water Balance

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 817.09/TT14

Topic: F.09. Thirst and Water Balance

Support: CIHR FDN 143337

MUHCRI Studentship

Title: Clock-driven vasopressin neurotransmission mediates anticipatory thirst prior to sleep

Authors: *C. GIZOWSKI, C. ZAELZER, C. W. BOURQUE;
Res. Inst. of the MUHC, Montreal, QC, Canada

Abstract: Circadian rhythms have evolved to anticipate and adapt animals to the constraints of earth's 24-hour light cycle. Although molecular processes establishing periodicity in clock neurons of the suprachiasmatic nucleus (SCN) are well established, the mechanisms by which axonal projections from the central clock drive behavioural rhythms are unknown. We found that the sleep period in mice (Zeitgeber time, ZT0-12) is preceded by an increase in water intake promoted entirely by the central clock, and not motivated by physiological need, such as hyperosmolality, increased body temperature, or hypovolemia. Mice denied this surge experienced significant dehydration, indicating that this behaviour is physiologically relevant. We show this effect relies specifically on the activity of SCN vasopressin (VP) neurons that project to thirst neurons in the OVLT (organum vasculosum lamina terminalis) where VP is released as a neurotransmitter. In vitro recordings of SCN VP and OVLT neurons showed an increase in the spontaneous electrical activity during the anticipatory period (AP, ZT21.5-23.5). Furthermore, electrical stimulation of the SCN in angled horizontal hypothalamic slices caused detectable VP release within the OVLT as detected by HEK293 cells engineered to serve as

dynamic VP biosensors. Using whole cell recordings, we investigated the effects of SCN stimulation on OVLT neurons. Stimulation caused a reversible depolarization and excitation of OVLT neurons, an effect specifically dependent on VP V1a receptors and downstream non-selective cation channels. The role of this SCN-OVLT pathway was further explored using transgenic mice expressing accelerated channelrhodopsin (ChETA) or archaerhodopsin-3 (ArchT) in VP neurons, and delivering light to the axon terminals of these cells in the OVLT. Optogenetic induction of VP release by application of blue light (473 nm) prior to the AP (basal period, BP; ZT19.5-21.5) excited OVLT neurons in vitro and prompted a surge in water intake in vivo. Conversely, optogenetic inhibition of VP release by yellow light (589 nm) inhibited the firing of OVLT neurons, and prevented the corresponding increase in water intake during the AP. Collectively, these findings reveal the existence of anticipatory thirst, and demonstrate this behaviour to be driven by excitatory peptidergic neurotransmission mediated by VP release from central clock neurons.

Disclosures: **C. Gizowski:** None. **C. Zaelzer:** None. **C.W. Bourque:** None.

Poster

817. Thirst and Water Balance

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 817.10/UU1

Topic: F.09. Thirst and Water Balance

Support: HL-091911

DK-098841

Title: Sex differences in angiotensin II-induced behavioral desensitization are not mediated by activational or organizational effects of gonadal hormones.

Authors: *J. SANTOLLO, D. DANIELS;
Psychology, Univ. at Buffalo Dept. of Psychology, Buffalo, NY

Abstract: Previous *in vivo* studies from our laboratory and *in vitro* studies by others demonstrate that the angiotensin type 1 receptor (AT1R) rapidly desensitizes after repeated exposure to angiotensin II (AngII). To date, one behavioral effect of this desensitization, a decrease in the dipsogenic potency of Ang II treatment, has been studied exclusively in male rats. Because sex differences in the dipsogenic potency of AngII are well established, it is plausible to hypothesize that sex differences exist in the desensitization of the AT1R. Here we tested the influence of sex and hormone treatment on water intake after repeated AngII treatment. As expected, when male

rats were pretreated with three 300 ng injections of AngII spaced 20 min apart, they drank less water after a 100 ng test injection of AngII than did rats pretreated with vehicle ($p < 0.05$). Intact cycling female rats, however, drank similar amounts of water after 100 ng AngII-treatment regardless of AngII pretreatment. Next, we tested the hypothesis that activational effects of gonadal hormones mediate this sex difference. Female rats were ovariectomized, treated with either oil, 20 µg estradiol benzoate (EB), or 20 µg EB plus 500 µg progesterone for two consecutive days, and 48 h after the second hormone treatment were tested for desensitization after repeated AngII. We found no evidence for desensitization in these rats in any of the hormone conditions. To test if androgens are required for the desensitization observed in male rats, we tested the response to repeated injections of AngII in sham or castrated male rats and found no effect of castration. Collectively, these findings suggest that activational effects of gonadal hormones do not mediate the observed sex difference. Ongoing experiments are testing for organizational effects using neonatal rats treated with oil, 250 µg testosterone, or 250 µg DHT within 6 h of birth and again 24 h later. The female rats from these litters were ovariectomized as adults and tested for desensitization. Preliminary results suggest that neonatal androgens do not produce an adult that shows desensitization after repeated AngII, ruling out the possibility of hormonally mediated organization. Together, these data reveal a striking sex difference in the response to elevated AngII that is not mediated by either acitivational or organizational effects of gonadal hormones.

Disclosures: J. Santollo: None. **D. Daniels:** None.

Poster

817. Thirst and Water Balance

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 817.11/UU2

Topic: F.09. Thirst and Water Balance

Support: R01-DA025634

UIC University Fellowship

Title: Nucleus accumbens dopamine responds to fluid balance-restoring stimuli in a state-dependent manner

Authors: *S. M. FORTIN, M. F. ROITMAN;
Univ. of Illinois At Chicago, Chicago, IL

Abstract: The consumption of nutritive stimuli is thought to result from homeostatic challenge or, in the absence of need, hedonic value. However, perturbations of homeostasis alter the hedonic value of a stimulus. This is perhaps best illustrated in sodium appetite, when a concentrated sodium solution is avidly consumed only after sodium depletion. We hypothesized that challenges to body fluid homeostasis by either sodium depletion or water restriction would recruit nucleus accumbens dopamine signaling - thought to participate in hedonic encoding - in response to fluid balance-restoring stimuli (e.g. sodium under sodium depletion; water under water restriction). We used fast-scan cyclic voltammetry to measure subsecond changes in dopamine concentration in the nucleus accumbens shell of both sodium deplete and replete and water restricted and unrestricted rats during intraoral delivery of either a hypertonic (0.45 M) NaCl solution or distilled water. A robust increase in dopamine concentration (41.0 ± 6.27 nM) from baseline (9.1 ± 0.21 nM; $p<0.05$) was evoked by intraoral infusions of NaCl in furosemide-induced sodium depleted rats. Conversely, in sodium replete animals, intraoral infusion of NaCl evoked a decrease in dopamine concentration (0.4 ± 2.97 nM) from baseline (15.9 ± 0.20 nM; $p<0.05$). The dopamine increase in sodium deplete rats was selective for a salt solution containing the sodium ion, as both potassium chloride and water infusions were without effect. Similar to the observed state-dependent specificity of dopamine signaling to a sodium stimulus, we found that water infusions evoked increases in dopamine concentration selectively in 24-hour water restricted animals (43.3 ± 9.40 vs 8.5 ± 0.40 nM for infusion vs baseline; $p<0.05$). Thus, dopamine neurons track fluid balance and respond to sodium and water stimuli in a state-dependent manner. The state-dependency of phasic dopamine signaling likely serves to provide a reinforcement signal only when the ingested stimulus satisfies the need state of the animal. Moreover, the data emphasize the participation of mesolimbic dopamine signaling in homeostatic-driven ingestive behavior.

Disclosures: **S.M. Fortin:** None. **M.F. Roitman:** None.

Poster

817. Thirst and Water Balance

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 817.12/UU3

Topic: F.09. Thirst and Water Balance

Support: Grant-in Aid from MEXT Japan (23580404)

Title: Intracerebroventricular administration of thyrotropin-releasing hormone suppresses water intake without affecting feed consumption in the neonatal chicks.

Authors: *S.-I. KAWAKAMI, Y. HAYASHI;
Hiroshima Univ. Grad. Sch. of Biosphere Sci., Hiroshima, Japan

Abstract: Exposure to high environmental temperature is known to negatively affect feeding behavior of animals, the brain mechanisms regulating heat stress-induced feeding suppression remain unknown. Thyrotropin-releasing hormone (TRH) is a neuroendocrine tripeptide which is mainly synthesized in the hypothalamus and regulates thermogenesis in the hypothalamus-pituitary-thyroid axis, but it has not been known whether TRH affect feed and/or water intake in the avian brain. Therefore, the aim of the present study was to examine the effect of intracerebroventricular (ICV) administration of TRH or its antagonist (chlordiazepoxide) on feed and water intake of neonatal chicks. The mail layer chicks (5-day-old) were fixed in a headholder that has a fitting pinhole for ICV injection and the solutions (10 µl) were administered free-hand through the pinhole using a microsyringe, according to the procedure of Davis *et al*. (1979). Feed and water intake were measured at 30, 60 and 120 min after the treatment. In the first trial, chicks with free access to feed and water were ICV injected with one of four doses (0, 12.5, 25 or 50 nmol) of TRH. In the second trial, with free access to water but being deprived of feed for 3 h, chicks were ICV injected with TRH and refed. In the third trial, after being deprived of both feed and water for 3 h, chicks were ICV injected with TRH and rehydrated. In the fourth trial, chicks with free access to feed and water were ICV injected with one of four doses (0, 0.15, 1.5 or 15 nmol) of chlordiazepoxide. In the first, second and third trials, ICV administration of TRH significantly inhibited cumulative water consumption at all doses in layer chicks when compared with vehicle ($P<0.05$). Cumulative feed consumption was unaffected by TRH administration in feed-deprived chicks, but significantly increased in chicks fed *ad libitum* only at the dose of 50 nmol after 120 min of TRH administration. In the fourth trial, TRH antagonist, chlordiazepoxide, increased cumulative water consumption at the dose of 15 nmol after 60 min of ICV administration, but did not affect cumulative feed consumption in layer chicks. These data suggest that TRH mainly plays an essential role in the control of water intake, not of feed intake, in the brain of neonatal chicks.

Disclosures: S. Kawakami: None. **Y. Hayashi:** None.

Poster

817. Thirst and Water Balance

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 817.13/UU4

Topic: F.09. Thirst and Water Balance

Support: FAPESP # 2014/15218-4

Title: Estradiol enhances vasopressin (AVP) secretion induced by dehydration through estrogen receptor beta without affecting transient receptor potential vanilloid subtype 1 (TRPV1) gene expression in the supraoptic nucleus

Authors: *T. VILHENA-FRANCO[1], G. ALMEIDA-PEREIRA[1], F. LUCIO-OLIVEIRA[1], A. S. MECAWI[2], L. L. K. ELIAS[1], J. ANTUNES-RODRIGUES[1];
[1]Univ. of Sao Paulo, Ribeirao Preto, Brazil; [2]Dept. of Physiological Sciences, Inst. of Biology, Federal Rural Univ. of Rio de Janeiro, Seropedica/Rio de Janeiro, Brazil

Abstract: Evidences show that estradiol could contribute to maintain hydromineral homeostasis increasing AVP secretion, but the mechanisms involved in this effect are unclear. Vasopressinergic neurons express estrogen receptor β (ER-β) and are innervated by osmossensitive neurons that express estrogen receptor α (ER-α). However, it has not yet been demonstrated *in vivo* which subtype of estrogen receptor mediates the estradiol effects on AVP secretion. Moreover, it is well known that AVP secretion induced by hyperosmolality involves activation of TRPV1 channel in magnocellular neurons, but it is unknown if estradiol could modulate this mechanism. **Objectives:** This study aimed to evaluate the effects of estrogen receptor agonists on plasma AVP concentrations and the effects of these agonists or estradiol treatment on TRPV1 mRNA expression in the supraoptic nucleus (SON) of the hypothalamus in response to water deprivation. **Methods and Results:** Female Wistar rats were submitted to bilateral ovariectomy and received subcutaneous injection of selective ER-β agonist (DPN: 300µg/Kg, 0.1 mL/rat, s.c.), selective ER-α agonist (PPT: 300µg/Kg, 0.1 mL/rat, s.c.), vehicle (sesame oil: 0.1 mL/rat) or estradiol (estradiol cypionate: 40µg/Kg) during seven consecutive days. On the seventh day, a group of animals was subjected to 24-h water deprivation and control animals remained with free access to water. After this period, all animals were decapitated and blood samples were collected for plasma AVP determination by specific radioimmunoassay. Brains were collected and SON punches were obtained for subsequent real-time PCR for TRPV1 mRNA expression analysis. In vehicle treated groups, water deprivation increased plasma AVP concentrations, compared to control hydrated group. Treatment with ER-α agonist did not alter AVP secretion induced by water deprivation. However, treatment with ER-β agonist potentiated plasma AVP concentration induced by water deprivation, compared to vehicle group. Regarding TRPV1 mRNA expression, this parameter was increased by water deprivation in the SON, but this response was not altered neither by estradiol, ER-α or ER-β agonist, compared to vehicle group. **Conclusions:** This study suggests that ER-β mediates the estradiol effects on AVP secretion in response to water deprivation, suggesting that estradiol effects occur directly in the AVP neurons. Dehydration increases TRPV1 gene expression and estradiol seems not to affect this response. These results contribute to clarify the mechanisms by which estradiol modulates AVP secretion induced by changes in plasma volume and osmolality.

Disclosures: **T. Vilhena-Franco:** None. **G. Almeida-Pereira:** None. **F. Lucio-Oliveira:** None. **A.S. Mecawi:** None. **L.L.K. Elias:** None. **J. Antunes-Rodrigues:** None.

Poster

818. Appetitive and Incentive Learning and Memory: Conditioning II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 818.01/UU5

Topic: H.01. Animal Cognition and Behavior

Support: RCMI Grant RR003037

NIH Grant 5R24DA012136-13

NIDA Grant SC1DA034995

Title: Cortico striato limbic circuits in pavlovian reward conditioning: a western blot analysis.

Authors: *R. ZANCA[1,2], R. CAAMANO-TUBIO[3], J. AVILA[1,2], P. SERRANO[1,2], A. DELAMATER[3,2];
[1]Hunter Col., New York, NY; [2]The Grad. Ctr., New York, NY; [3]Brooklyn Col., Brooklyn, NY

Abstract: A large number of studies with rodents have found that prefrontal and limbic structures participate in a cortico limbic circuit engaged by Pavlovian *fear conditioning*. Other research suggests that some of the key structures in this circuit (basolateral amygdala (BLA), central amygdala (CeA), hippocampus, prelimbic prefrontal cortex (PL), infralimbic prefrontal cortex (IL), orbitofrontal cortext (OFC)) also play a role in Pavlovian *reward learning*. In addition, the nucleus accumbens also plays a role in Pavlovian and instrumental paradigms. The present study analyzed synaptic fractions in these brain regions via Western blotting. Markers analyzed include: AMPA receptor subunit GluA2, Protein Kinase C ζ (PKCζ) and atypical Protein Kinase M ζ (PKMζ). These markers demonstrate synaptic plasticity changes that occur after Pavlovian conditioning or extinction. Rats were trained on a Pavlovian magazine approach-conditioning task in which a short duration auditory stimulus (15 s, 1500 Hz tone) was paired with delivery of a food pellet. Following 8 sessions of conditioning, rats either underwent 5 days of extinction training in which the tone CS occurred without food reward (Extinction), or were exposed to the experimental context without any scheduled events (No Extinction). On the following day, rats were given 4 non-reinforced *test* trials with the tone CS and then sacrificed 2 hours later. A third group of rats (Random) were trained on a truly random control contingency procedure in which an equal number of tone CS and food pellet US presentations occurred in each acquisition session; however, these two events occurred randomly in time. For the *test*-phase of the study, Random subjects were exposed to the experimental context without any events and were tested like the other two groups on the final day. The results from this study showed clear behavioral differences in the test day with the No Extinction group displaying more conditioned magazine approach responses to the tone CS than either of the other two groups. Western blotting has thus far revealed that in the BLA, No Extinction and Extinction groups both

displayed higher levels of synaptic GluA2 protein expression as compared to Random ($p < 0.01$). Similarly, this pattern was also seen in synaptic PKCζ ($p < 0.05$), but not in synaptic PKMζ expression in the BLA. Additional results will be reported for the different brain regions mentioned above, and we will also present data examining protein expression targeting NMDA, GluA1, and GABA receptors in these regions. Overall, the data will provide a more comprehensive view of plasticity in cortico-striato limbic circuits involved in Pavlovian reward learning.

Disclosures: R. Zanca: None. **R. Caamano-Tubio:** None. **J. Avila:** None. **P. Serrano:** None. **A. Delamater:** None.

Poster

818. Appetitive and Incentive Learning and Memory: Conditioning II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 818.02/UU6

Topic: H.01. Animal Cognition and Behavior

Support: Mitchell Center for Neurodegenerative Disease

UTMB Center for Addiction

Title: Aged dominant negative p38α mapk mice exhibit conserved adult-neurogenesis and context fear discrimination

Authors: *D. CORTEZ[1], K. T. DINELEY, 77550[2];
[1]UTMB, Galveston, TX; [2]Neurol., The Univ. of Texas Med. Br., Galveston, TX

Abstract: A major aspect of mammalian aging is the decline in functional competence of many self-renewing cell types, including adult-born neuronal precursors. Since age-related senescence of self-renewal occurs simultaneously with chronic up-regulation of the p38MAPKalpha (p38α) signaling pathway, we used the dominant negative mouse model for attenuated p38α activity (DN-p38$\alpha^{AF/+}$) in which Thr180 and Tyr182 are mutated (T→A/Y→F) to prevent phosphorylation activation (DN-p38$\alpha^{AF/+}$) and kinase activity. As a result, aged DN-p38$\alpha^{AF/+}$ mice are resistant to age-dependent decline in proliferation and regeneration of several peripheral tissue progenitors when compared to wild-type littermates.
Aging is the major risk factor for non-inherited forms of Alzheimer's disease (AD); environmental and genetic risk factors that accelerate the senescence phenotype are thought to contribute to an individual's relative risk. In the present study, we evaluated aged DN-p38$\alpha^{AF/+}$ and wildtype littermates in a series of behavioral paradigms to test if p38α mutant mice exhibit

altered baseline abnormalities in neurological reflexes, locomotion, anxiety-like behavior, and age-dependent cognitive decline. While aged DN-p38α$^{AF/+}$ and wildtype littermates appear equal in all tested baseline neurological and behavioral parameters, DN-p38α$^{AF/+}$ exhibit superior context discrimination fear conditioning. Context discrimination is a cognitive task that is supported by proliferation and differentiation of adult-born neurons in the dentate gyrus of the hippocampus. Consistent with enhanced context discrimination in aged DN-p38α$^{AF/+}$, we discovered enhanced production of adult-born neurons in the dentate gyrus of DN-p38α$^{AF/+}$ mice compared to wildtype littermates. Our findings support the notion
that p38α inhibition has therapeutic utility in aging diseases that affect cognition, such as AD.

Disclosures: D. Cortez: None. **K.T. Dineley:** None.

Poster

818. Appetitive and Incentive Learning and Memory: Conditioning II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 818.03/UU7

Topic: H.01. Animal Cognition and Behavior

Support: Cosmos Club Foundation

George Mason University OSCAR Program

Title: Dietary copper and zinc on fear extinction, NMDAR 2A and 2B, and Cu/Zn superoxide dismutase 1 expression: Implications for learning impairment

Authors: *C. NEELY, K. BOGGS, S. LIPPI, J. FLINN;
Dept. of Psychology, George Mason Univ., Fairfax, VA

Abstract: Copper (Cu) and zinc (Zn) play important roles in enzymatic activity and neuronal transmission, and both direct Cu deficiency and Zn-mediated Cu deficiency can evoke oxidative and behavioral impairment. For example, reduced Cu levels prevent Cu/Zn superoxide dismutase (SOD1) from detoxifying superoxide and hydroxyl radicals produced during oxygen metabolism, resulting in cellular damage. At the synaptic level, both Cu and Zn are concentrated at excitatory NMDAR receptors, often evoking inhibitory effects on the receptor itself or other excitatory synapses. This evidence suggests that Cu and Zn affect oxygen metabolism as well as NMDAR-driven fear extinction learning. To explore these biometal-protein-behavior interactions, we utilized diets to induce direct and indirect Cu deficiencies: a control 7012 diet [23ppm Cu], a 7012 diet reduced in Cu [7-12ppm], and Zn-supplemented 7012 diet [10ppm Zn via drinking water]. We included a “copper control” diet with 16ppm Cu (CC) used in past studies in our

laboratory. Sixty-six Sprague-Dawley rats were administered one of four diets for approximately 4.5 months before they underwent cued-conditioning and extinction. As expected, there were no significant freezing differences during conditioning, indicating that biometal manipulation did not impact acquisition of fear. There were significant freezing differences on the first day of extinction: Zn-supplemented and Cu-deficient animals unexpectedly extinguished faster compared to control animals which contradicted previous studies. There were no differences in freezing between Cu-deficient and Zn-supplemented animals, supporting that Zn-supplementation can lead to similar behavioral deficits seen in Cu deficiency. Western blot analyses showed marginally significantly decreased hepatic SOD1 levels in Cu-deficient and Zn-supplemented animals compared to control animals ($p=0.06$). NMDAR 2A and 2B expression will be examined to assess the effects of biometal manipulation. We will explore if glutamatergic-NMDAR signaling can explain unexpected behavioral results.

Disclosures: **C. Neely:** None. **K. Boggs:** None. **S. Lippi:** None. **J. Flinn:** None.

Poster

818. Appetitive and Incentive Learning and Memory: Conditioning II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 818.04/UU8

Topic: H.01. Animal Cognition and Behavior

Title: Chronic exercise restores contextual conditioning and reinstatement of conditioned fear in ageing mice

Authors: *J. H. KIM, V. BUI, H. MADSEN, A. HANNAN, A. SHORT;
Florey Neurosci. Inst., Parkville, Australia

Abstract: People born between 1946 and 1964 (‘‘baby boomers’’) are entering retirement in large numbers. This has major implications both for the individuals and the society. One serious consequence is the changes in the brain that accompany ageing, especially in the hippocampus, that is vulnerable to damage throughout life. It is also well-known that chronic exercise can maintain new neurons in the hippocampus. The hippocampus is critical for cognitive flexibility involved with extinction and reinstatement of conditioned fear. Therefore, we asked whether chronic exercise in middle-aged mice can improve extinction and/or reinstatement of conditioned fear compared to standard housing. Eight-months old C57Bl/6J mice either had access to a running wheel or remained in standard housing for three months, until 11 months of age. Then they received tone-footshock pairings, which was subsequently extinguished with tone-alone presentations the next day. Half of the mice then received a reminder treatment in the form of a single footshock, which has previously been shown in our laboratory to reinstate the

extinguished fear in 3-month-old young adult mice. Interestingly, 11-month-old mice housed in standard conditions exhibited impaired reinstatement. That is, the reminder treatment did not recover the extinguished fear compared to mice that did not receive any reminder. However, the reminder treatment was able to reinstate extinguished fear in 11-month-old mice that had access to a running wheel from 8 months of age. Similar results were found with contextual fear conditioning. These results show that while aged mice display decreased cognitive flexibility, positive changes in lifestyle even in well-past young adulthood is beneficial in reducing natural decline in cognitive abilities even when the change occurs late in life. We are currently investigating bdnf mRNA and protein levels in the hippocampus in these ages.

Disclosures: J.H. Kim: None. **V. Bui:** None. **H. Madsen:** None. **A. Hannan:** None. **A. Short:** None.

Poster

818. Appetitive and Incentive Learning and Memory: Conditioning II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 818.05/UU9

Topic: G.01. Appetitive and Aversive Learning

Support: NIDA; K08-DA037912-01

NARSAD; Grant no. 20829

Title: Individual differences in reward-related behaviors predict conditioned fear responses in rats

Authors: *A. GHEIDI[1], C. J. FITZPATRICK[1,2], R. L. ATKINSON[3], J. D. MORROW[1]; [1]Dept. of Psychiatry, [2]Neurosci. Grad. Program, [3]Col. of Literature, Science, and Arts, Univ. of Michigan, Ann Arbor, MI

Abstract: Pavlovian conditioned approach (PCA) behavior has been previously used to identify rats that attribute motivational salience to both reward- and fear-related cues (sign-trackers; STs) or whom do not (goal-trackers; GTs). Moreover, it is known that the attribution of motivational salience to reward- and drug-related cues in STs is associated with neural activity within a cortico-striatal-thalamic network; however, it is unknown whether the same brain regions are involved in the attribution of motivational salience in STs to fear-related cues. In the present study, rats underwent seven daily sessions of PCA training to categorize them as STs or GTs. Rats were then divided into three groups and underwent cued fear conditioning. The experimental group received five tone-shock pairings whereas the two control groups received

either shock alone (a control for arousal) or tone alone (a control for auditory stimulation). Next, the context was changed and rats underwent a cued fear expression test, during which all rats were exposed to the tone continuously for six minutes. Thirty minutes after exposure to the tone, brains were immediately perfused and flash frozen. Using a cryostat, 20 μm hemisections of the ventral hippocampus were collected and processed for c-Fos mRNA, a neural activity marker, using a modified version of fluorescent in situ hybridization. Following staining, slides were imaged with a Zeiss® epifluorescent microscope using an Apotome® to reduce scattered light. A single experimenter blind to the group conditions manually counted each image.We replicated previous findings and demonstrated that STs show greater cued fear expression than GTs. In addition, preliminary data shows that STs have comparable neural activity to GTs in the CA1, CA3 and dentate gyrus of the ventral hippocampus. These preliminary results suggest that the ventral hippocampus may not be involved with the attribution of motivational salience to fear-related cues in STs

Disclosures: A. Gheidi: None. **C.J. Fitzpatrick:** None. **R.L. Atkinson:** None. **J.D. Morrow:** None.

Poster

818. Appetitive and Incentive Learning and Memory: Conditioning II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 818.06/UU10

Topic: G.01. Appetitive and Aversive Learning

Support: NIH Grant 1R01MH096764

Title: Alpha-1 adrenergic blockade during sleep impairs fear memory consolidation in a mouse model of PTSD

Authors: *J. WALTON, J. HARTMANN, K. J. RESSLER;
McLean Hospital, Harvard Med. Sch., Belmont, MA

Abstract: Activation of the adrenergic system has been shown to increase fear memory consolidation, suggesting that its hyperactivation in the aftermath of trauma exposure may lead to fear memory 'over-consolidation'. While a role for beta adrenergic receptors is well established, the role of the alpha-1 adrenergic receptors during emotional memory consolidation (particularly during sleep-mediated consolidation) is relatively unclear. Prazosin, an alpha-1 adrenergic antagonist, has been shown to reduce PTSD symptom severity when administered to human participants prior to sleep. Given that sleep is known to promote both the consolidation of memory and the regulation of emotion, the present study aimed to identify whether inactivation

of the of the alpha-1 adrenergic system during the first night of sleep inhibited fear memory consolidation. Mice were initially exposed to immobilization stress, a paradigm which has been frequently used as a model for PTSD-like behavior. Seven days later, at the beginning of their sleep period, mice were fear conditioned using a tone-shock pairing. Two hours following fear acquisition, mice were injected intraperitoneally with either prazosin hydrochloride (1mg/kg) or vehicle and left undisturbed for the remainder of their sleep period. Fear expression, measured in terms of time spent freezing, to 30 tone-only presentations was tested over the next two days. On the first day of expression, mice that had been administered prazosin during the consolidation window showed significantly less freezing than controls ($p=0.05$). This difference was even more robust on the second day of expression ($p=0.005$). These data suggest that, in highly stressed mice, inactivation of the alpha-1 adrenergic system during sleep-mediated consolidation interferes with the formation of fear memory. If these results are replicated and further explored, they would suggest that administering prazosin before the first night of sleep following trauma exposure may decrease risk for development of subsequent PTSD.

Disclosures: J. Walton: None. **J. Hartmann:** None. **K.J. Ressler:** None.

Poster

818. Appetitive and Incentive Learning and Memory: Conditioning II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 818.07/UU11

Topic: G.01. Appetitive and Aversive Learning

Support: DFG FOR778

DAAD

WELLCOME TRUST

Title: Less reliable task state beliefs underpin an age-related decline in probabilistic reversal learning

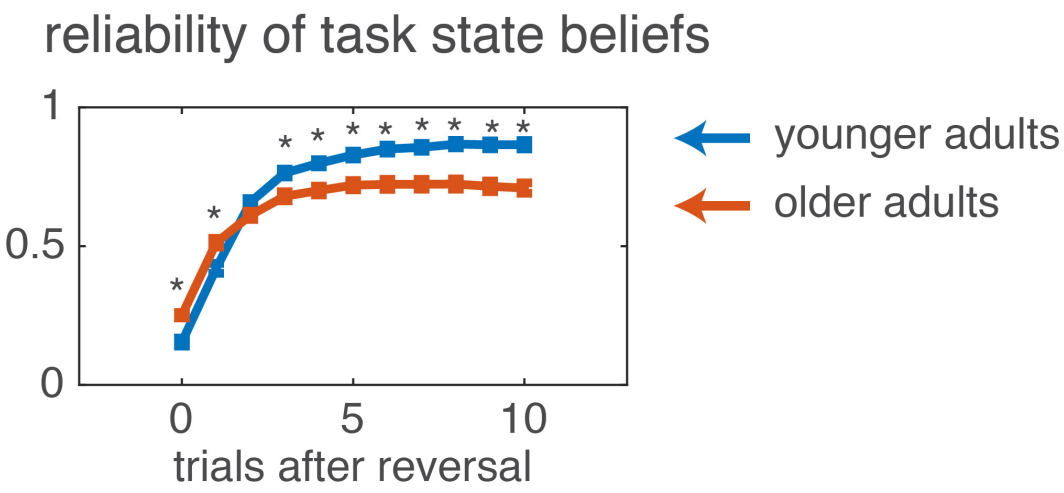
Authors: *D. HAEMMERER[1], T. H. B. FITZGERALD[2], S.-C. LI[3], E. DÜZEL[4], R. J. DOLAN[2];
[1]Inst. of Cognitive Neurosci., London, United Kingdom; [2]Max Planck–UCL Ctr. for Computat. Psychiatry and Ageing Res., London, United Kingdom; [3]Tech. Univ. Dresden, Dresden, Germany; [4]German Ctr. for Neurodegenerative Dis., Magdeburg, Germany

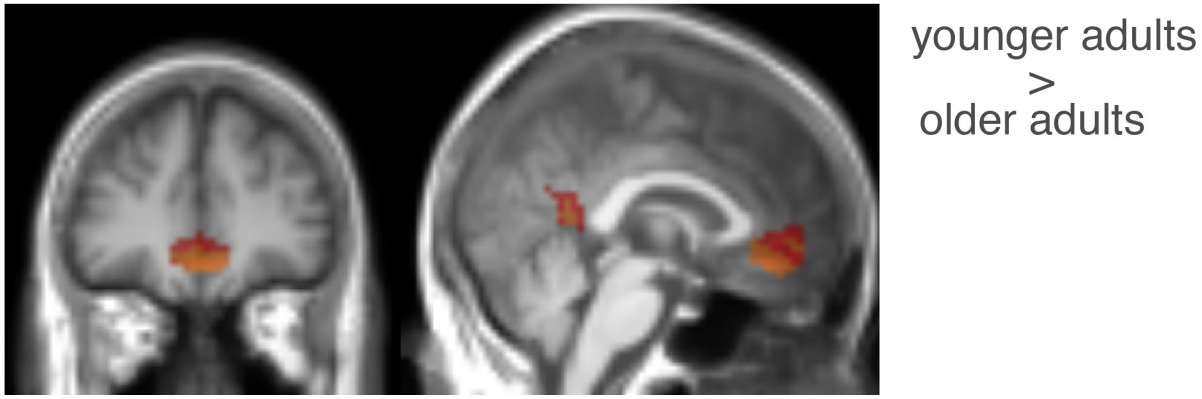
Abstract: Making correct choices in changeable and uncertain reward environments is challenging for older adults. This deficit is usually examined within a framework of an age-

related decrement in feedback processing. We asked whether an inability to form reliable task state beliefs affects older adults' feedback evaluation and decision making during uncertainty. Using two novel probabilistic reversal learning tasks, pupillometry and model-based fMRI, we find that older adults indeed decide based on less reliable task state beliefs.

At the brain level, older adults showed reduced encoding of changes in task state beliefs in vmPFC (see Figure) and reduced encoding of updating task state beliefs within caudate and putamen. Also, in support of our assumption that feedback processing is dependent on reliable task state beliefs, we find that areas encoding updating at feedback (SN/VTA) responded stronger when participants were more certain during choices, an effect weaker in older adults. Older adults furthermore showed reduced activations in locus coeruleus during feedback processing. This suggests that in addition to reduced dopaminergic modulation, a decline in noradrenergic modulation might underpin altered decision making during uncertainty in older adults. Complementary to our fMRI results, changes in pupil diameter when updating task state beliefs are blunted in older adults. This effect is less pronounced in older adults that are more certain regarding current task state beliefs.

In summary, our findings add to previous evidence of attenuated feedback processing in older adults and suggest additionally that underspecified representation of task state context affects feedback processing in older adults. We hope our findings help understand why older adults struggle when orienting their attention and actions especially in changeable and uncertain reward environments.





Disclosures: **D. Haemmerer:** None. **T.H.B. Fitzgerald:** None. **S. Li:** None. **E. Düzel:** None. **R.J. Dolan:** None.

Poster

818. Appetitive and Incentive Learning and Memory: Conditioning II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 818.08/UU12

Topic: G.01. Appetitive and Aversive Learning

Support: NIH Grant P20GM103643

UNE VPR mini-grant

Title: Neonatal pain and stress affect subsequent fear conditioning and sensory function in the rat

Authors: *M. A. BURMAN, C. SIMMONS, V. EATON, B. SASSO, E. HOLMQVIST, M. LEONARDO, J. GENTRY, T. KING;
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Abstract: Early life trauma is a contributing factor to a variety of negative outcomes later in life, including psychological disorders such as anxiety and depression, as well as sensory disorders such as chronic pain. One unfortunate source of neonatal trauma, especially for pre-mature infants, is procedures performed in the neonatal intensive care unit (NICU). In the NICU, neonates can experiences hundreds of skin-breaking painful events, which are often conducted without the benefit of analgesics. Moreover, these infants who spend time in the NICU are more likely to suffer later psychological and sensory disorders, in a manner correlated with the amount of pain and stress experienced in the NICU. However, with humans, it is difficult to disentangle the degree of original sickness with the later outcomes. Therefore, we have adopted a rodent model in which neonatal rats are exposed to non-painful neonatal handling or painful neonatal paw-pricks over postnatal days (PD) 1-7; modeling procedures that occur in the NICU. Rats are then exposed to a fear conditioning procedure in infancy (PD17), early childhood (PD 24), adolescence (PD 45) or adulthood (PD 66) followed by sensory testing. Our preliminary analysis shows clear age dependent changes in both contextual and auditory fear conditioning as well as sensory function. Neonatal pain and neonatal handling both create a tactile hypersensitivity, as measured by von Frey testing, which appears strongest at younger ages and declines over time. In contrast, neonatal pain impairs auditory fear conditioning; an effect that persists or increases during aging. Non-painful neonatal handling modestly enhances contextual fear conditioning; an effect not seen following neonatal pain. Together, these data indicate lasting affective and sensory consequences of neonatal pain and stress. Future work will begin to uncover the neuro-endocrine basis for these effects.

Disclosures: **M.A. Burman:** None. **C. Simmons:** None. **V. Eaton:** None. **B. Sasso:** None. **E. Holmqvist:** None. **M. Leonardo:** None. **J. Gentry:** None. **T. King:** None.

Poster

818. Appetitive and Incentive Learning and Memory: Conditioning II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 818.09/UU13

Topic: G.01. Appetitive and Aversive Learning

Support: NIH grant NINDS NS038890

Title: Factors influencing developmental differences in retention of Pavlovian fear conditioning

Authors: *K. L. BROWN, M. J. SODOMA, J. H. FREEMAN;
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Abstract: Pavlovian fear conditioning is a useful preparation for studying developmental changes in aversive learning and memory. The present study represents our efforts to identify factors influencing developmental differences in expression of fear memories. Postnatal day (P) 17 or 24 rats were trained with a white noise conditional stimulus (CS) and a floor shock unconditional stimulus (US) in context A. At test, the CS was presented in an environment (context B) that differed from the training context in visual, tactile, and olfactory features. Age differences in expression of fear memory at test - as indexed by freezing, the absence of movements except those required for respiration - were largely dependent on (1) the number of CS-US presentations at training, and (2) the interval between training and testing. With identical training (2 CS-US), freezing during the CS at test was robust and comparable across ages when the interval between training and testing was brief (20-30 minutes). However, at an intermediate train-test interval (2 days) freezing levels were significantly higher in P24s, replicating the pattern of findings reported by Richardson and colleagues (Kim et al., 2012, *Neurobiology of Learning and Memory*, 97, pp. 59-68). With 4 CS-US pairings at training, P17s overcame the 2 day retention deficit but displayed poor retention relative to P24s (2 CS-US) when testing occurred 14 days after training. Similarly, with an increase to 12 CS-US pairings at training P17s overcame the 14 day retention deficit. Baseline freezing at test was low, and in a separate experiment baseline freezing was further lowered in subjects receiving context B chamber exposure 1 day prior to testing. Additionally, neuronal activity in the prelimbic cortex was assessed during the 14 day test in a subset of subjects through use of tetrode recordings from a surgically implanted hyperdrive. Freezing levels were comparable to non-surgery counterparts, and long-latency CS-related unit activity characteristic of prelimbic recordings in adult rats were evident in P24s (2 CS-US) but not in P17s (4 CS-US). These findings provide the basis for novel investigations into the mechanisms underlying developmental changes in memory retention and retrieval.

Disclosures: K.L. Brown: None. **M.J. Sodoma:** None. **J.H. Freeman:** None.

Poster

818. Appetitive and Incentive Learning and Memory: Conditioning II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 818.10/UU14

Topic: G.01. Appetitive and Aversive Learning

Title: The role of infralimbic prefrontal cortex during behaviors guided by reward and punishment avoidance

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Abstract: The medial prefrontal cortex (mPFC) is thought to exhibit top-down control over dopaminergic prediction error signals and over Pavlovian fear responses from the central amygdala (CeA), thus influencing downstream behavior toward appetitive outcomes and away from aversive outcomes. However, in contexts where both appetitive and aversive outcomes are possible, current literature suggests conflicting roles for the ventral portion of mPFC, the infralimbic prefrontal cortex (ilPFC), implicating its activation during both approach and extinction behaviors, as well as the acquisition and expression of habit (Moorman et al. 2014; Peters et al. 2009; Gourley and Taylor 2016). However, no one has directly measured ilPFC single neuron activity during a task that looks at performance of both reward approach and punishment avoidance behaviors. By examining approach and avoidance aspects of reinforcement in the same task, we will determine the functional role of single neurons within the ilPFC as it relates to both motivators of behavior, reward and punishment avoidance. To address this issue, we recorded from single neurons (*N*= 347) within the ilPFC while rats performed our combined approach avoidance task. At the start of each trial, rats were presented with one of three pseudorandomly-interleaved auditory-visual stimuli for 5s, signaling whether the current trial would be a reward, shock or neutral trial. Five seconds after the cue initiation, a lever was extended into the chamber that could be pressed to produce one of three outcomes (dependent upon the auditory cue identity): delivery of a food reward (1 sucrose pellet; positive reinforcement behavior, *i.e.* reward trials), prevention of foot shock (negative reinforcement behavior, *i.e.* shock trials), or no consequence (*i.e.* neutral trials). If the animal failed to press the lever within the 10s lever period, no food reward was delivered on reward trials, foot shock (0.42 mV) commenced on shock trials, or there was no consequence on neutral trials. With this, we aim to characterize neural correlates in ilPFC and describe how ilPFC neurons respond to positive and negative reinforcement trial-types. This will be the first study to characterize neural correlates related to predicted positive and negative reinforcement in ilPFC.

Disclosures: R.N. Gentry: None. **M.R. Roesch:** None.

Poster

818. Appetitive and Incentive Learning and Memory: Conditioning II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 818.11/VV1

Topic: H.01. Animal Cognition and Behavior

Support: PAPIIT, DGAPA Proy. No. IN204014

CONACYT Scolarship to MT-C

Title: To eat or not to eat: Are conditioned taste aversion and attenuation of neophobia opposite learning?

Authors: M. TREJO-CASTILLO[1], *G. R. ROLDAN[2,1];
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[2]Natl. Autonomous Univ. of Mexico, Ciudad DE Mexico, Mexico

Abstract: Conditioned taste aversion (CTA) is a robust form of classical conditioning in which animals learn to avoid the consumption of a particular taste (conditioned stimulus, CS) that was previously paired with visceral discomfort (unconditioned stimulus, US). One of the most intriguing features of CTA is the ability of organisms to associate the CS with the US even when they are presented with a very long inter-stimulus interval (ISI) (up to 12 h). On the other hand, neophobia is an innate response of animals consisting in a cautious and moderate ingestion of an unknown taste, the consumption of which gradually increases as it becomes familiar (attenuation of neophobia, AN). It has been proposed that AN and CTA are opposed phenomena, because in the first, subjects learn that a taste is safe due to the absence of adverse effects after its intake, leading to preference for that taste, while in the second case the opposite is true. In order to reassess the effect of the ISI on acquisition and consolidation of CTA, we conducted a parametric study evaluating intervals of 30, 120, 180, 240 and 300 min, using an optimal design for training and testing that allow us detect very subtle aversions. We train male Wistar rats with a 0.1% saccharin solution followed by an ip injection of LiCl (0.15 M, 20 ml/kg) and test the retention of short and long term memory at 4 and 48 h, respectively. As expected, a gradual loss of taste aversion was found according to the longer ISIs, both at short and long term retrieval testing, being significant from 240 min; however, unlike the control (non-conditioned) group, rats trained with 240 or 300 min ISIs did not develop preference for saccharin after the second exposure (AN), suggesting some reminiscence of aversion learning. Because of this AN was analyzed under a free choice (water vs. saccharin) or forced consumption scheme with different concentrations of saccharin (0.1, 0.2, 0.3, 0.4 and 0.5%). Results showed free choice AN at low (0.1 and 0.2%), but not high (0.3% to 0.5%) saccharin concentrations, in which animals even reduced its consumption. Significant differences between the two AN methods for the two higher concentrations were observed. Our data indicate that: 1) the maximum ISI to induce a reliable CTA is 240 minutes, in contrast with prior reports; 2) this effect is due to an inability to associate the stimuli, as it occurs in short and long term memory; 3) the absence of AN in animals trained for taste aversion with long ISIs suggests a latent aversion learning, and 4) forced consumption models of AN using high saccharin concentrations are unsuitable to examine sure taste learning.

Disclosures: M. Trejo-Castillo: None. **G.R. Roldan:** None.

Poster

818. Appetitive and Incentive Learning and Memory: Conditioning II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 818.12/VV2

Topic: G.01. Appetitive and Aversive Learning

Support: DGAPA-PAPIIT IN204615

CONACyT 152208.

Technical assistants Gabriela Vera

Technical assistants Alejandro Rangel-Hernández

Title: Activation of NMDA receptors enhances aversive taste memory formation

Authors: *M. J. OLVERA-CALTZONTZIN[1], M. MIRANDA[2];
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Abstract: During conditioned taste aversion (CTA) a taste stimulus is recognized and associated with post-ingestional consequences; an aversive taste memory is formed if intoxication or malaise signals appear, inducing a significant decrease of consumption during the next encounter with that taste. Latent inhibition (LI) of CTA (e.g. decrement of taste association with aversive stimulus) could be observed when taste is pre-exposed. Previous findings suggest that the glutamatergic receptors (NMDAr) in the insular cortex (IC) have a differential function during taste aversive memory formation and during LI of CTA. These findings suggest that NMDA antagonism could be related with differential glutamate effects during incidental and aversive memory. Accordingly, the goal of this research was to evaluate the effects of NMDAr agonism during aversive memory formation and during IL of CTA. Thus, some rats were pre-exposed to a sweet solution (10% sugar) for 10 min. The next days, during CTA acquisition rats with or without pre-exposition were presented with sugar solution and 30 min before malaise-inducing agent (LiCl) were bilaterally injected in the IC with NMDA (6.8µM). 24 hrs later, aversive memory retrieval was tested and the aversive extinction was subsequently measured for 3 consecutive days. No pre-exposed animals injected with NMDA showed a significant decrease in liquid intake during the retrieval session, indicating that NMDAr activation enhanced aversive memory formation. On the other hand, pre-exposed animals only presented an intake reduction during extinction, suggesting that NMDAr has also an effect on taste re-learning. Globally these results give evidence about the differential role of NMDAr during CTA and the LI of CTA.

Disclosures: M.J. Olvera-Caltzontzin: None. **M. Miranda:** None.

Poster

818. Appetitive and Incentive Learning and Memory: Conditioning II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 818.13/VV3

Topic: G.01. Appetitive and Aversive Learning

Support: DGAPA-PAPIIT IN209911

CONACyT 152208

Technical assistants Gabriela Vera

Technical assistants Alejandro Rangel-Hernández

English review Shaun Harris

Title: Effects of long term Intermittent and withdrawal of sugar or high fructose corn syrup-55 consumption on taste preference and new aversive learning.

Authors: *D. BADILLO JUAREZ, M. I. MIRANDA;
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Abstract: Currently, consumption of sugar and high fructose corn syrup (HFCS-55, which is: 55 % fructose, 42 % glucose and 3 % higher saccharides) is increasing around the world. The increment availability of carbohydrates is having a significant impact on human eating behavior; for example, the Diagnostic and Statistical Manual of Mental Disorders IV and V (DSM) considers the binge eating and night eating syndrome as a disorder involving the escalated intake of carbohydrates is present. Recent works report that the chronic intermittent consumption of sugar or glucose elicits a high taste preference, because their consumption may activate the brain reward system in the same way as drugs. Thus the objective of this work was to evaluate in Wistar male rats the effect of the withdrawal of intermittent or chronic consumption sugar or HFCS-55 on anxiety, taste preference, and during a new aversive learning with the same taste. Thus, the intermittent group had access to food and sweet solution (10% sugar or 8% HFCS) only for 6 hours a day, during 21 days; the continuous group had permanent access to sweet solution and chow; and the control group had permanent access to chow. All groups had permanent access to water. After 21 days, rats were deprived of sweet solution during 1 or 3 days. Then their anxiety was measured, and subsequently the taste preference and ability to acquire conditioned taste aversion (CTA) were also evaluated. Rats subject to intermittent sugar consumption and 1 day of withdrawal, showed more taste preference compared to the control group, but not the continuous group; similarly, rats subject to continuous or intermittent HFCS-55 consumption and 1 or 3 days of withdrawal showed more preference compared with control group. Moreover, rats subject to intermittent sugar consumption and 1 day of withdrawal,

required more CTA training sessions compared with rats subject to intermittent sugar consumption and 3 days of withdrawal. Rats subject to continuous or intermittent sugar or HFCS55 consumption and their withdrawal showed a higher latent inhibition than control group. These results indicate that chronic intermittent exposition and withdrawal of HFCS-55 or sugar generate a significant preference and induced higher latent inhibition. The anxiety measures from the elevated plus maze and its correlation with consumption will be discussed. Altogether these results indicate that long-term sweet consumption induces higher consumption after withdrawal and also reduces the ability to learn negative consequences about the taste.

Disclosures: D. Badillo Juarez: None. **M.I. Miranda:** None.

Poster

818. Appetitive and Incentive Learning and Memory: Conditioning II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 818.14/VV4

Topic: G.01. Appetitive and Aversive Learning

Support: R01 DK094475

R01 DK075861

K 02HL112042

MH046001

MH042984

MH066122

MH001894

Title: Hypersensitivity and slower rate of habituation to pleasant food tastes in reward brain regions in obese compared to healthy weight children

Authors: *Z. L. MESTRE[1], A. BISCHOFF-GRETHE[2], C. E. WIERENGA[2], D. STRONG[3], K. N. BOUTELLE[4];
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Abstract: Introduction: Childhood obesity affects one-third of children in the United States. Childhood obesity is associated with poorer health outcomes, and premature death, and is highly correlated with adult obesity. A better understanding of the neural underpinnings of overeating and childhood obesity is critical to develop efficacious, evidence based treatments. Recent findings suggest that obesity may have a neurological basis. Obese (OB) adults, compared to healthy weight (HW) controls, exhibit increased activation and slower rates of habituation to food cues in brain regions associated with food reward and motivation, including the insula, amygdala, striatum and ventromedial prefrontal cortex. This hypersensitivity to food cues is related to increased food intake and weight gain. Our own data suggest that OB children, relative to HW, also show increased responses to food cues in similar brain regions. Yet, it is unclear whether OB children show alterations in habituation to food tastes. This knowledge could help explain why OB children eat past energy needs. Objective: We hypothesized that OB children, relative to HW, would show greater neural activation and decreased habituation to pleasant taste in the bilateral insula, bilateral amygdala, ventromedial prefrontal cortex, and striatum. Methods: Following a standardized breakfast, 23 age matched children (13 HW, BMI<85th; 10 OB, BMI>95th%; age 8-12) completed a taste paradigm during functional Magnetic Resonance Imaging, receiving 1 mL boluses of either 10% sucrose or ionic water delivered every 20 seconds. Neural responses to both solutions were later combined to examine the overall effect of taste by run (i.e., run 1 to run 3). Results: OB children were significantly more responsive to taste in the right ventromedial prefrontal cortex during the first run compared to HW children ($z=2.7$, $p=0.03$), suggesting a hypersensitivity to taste. OB children also had a significantly greater response to taste in the ventromedial prefrontal cortex in the first relative to the third task run ($z=3.4$, $p=0.002$). In the insula, results showed that OB children, compared to HW, were significantly more responsive to taste during the third run ($z=3.6$, $p=0.001$), suggesting decreased habituation to taste in this region. Conclusion: OB children, relative to HW, showed evidence of hypersensitivity and altered habituation to pleasant taste in reward brain regions. Our novel findings in a group of young children demonstrate that altered responses to food cues may develop in early childhood. Future research should examine this association longitudinally to try and establish the causal link between neurobiology and obesity.

Disclosures: Z.L. Mestre: None. **A. Bischoff-Grethe:** None. **C.E. Wierenga:** None. **D. Strong:** None. **K.N. Boutelle:** None.

Poster

818. Appetitive and Incentive Learning and Memory: Conditioning II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 818.15/VV5

Topic: H.01. Animal Cognition and Behavior

Support: MH 46904

MH 74006

Title: Medial auditory thalamus is necessary for expression of auditory trace eyelid conditioning

Authors: *L. C. HOFFMANN, S. J. ZARA, A. N. MANLEY, M. D. MAUK;
Ctr. for Learning and Memory, Univ. of Texas At Austin, Austin, TX

Abstract: Trace eyelid conditioning (ELC) requires a persistent input to the cerebellum from forebrain regions, such as prefrontal cortex, to bridge the temporal gap between stimuli. In order to identify the location(s) and computation(s) underlying this important stimulus transformation from a veridical representation of the conditioned stimulus (CS), and to understand forebrain contributions to trace ELC as a whole, it is imperative to identify and characterize the necessary pathway between CS-activated sensory neurons and sites of persistent activity for trace ELC. The medial auditory thalamic nuclei (MATN) are a necessary and sufficient subcortical input to the cerebellum for delay conditioning and represent the first site of plasticity in the CS pathway. MATN neurons display persistent responses during differential trace conditioning that signal stimulus salience. Thus, the MATN represent a sensible starting location in mapping the complete CS pathway for trace ELC. Here we test the necessity of the MATN for expression of auditory trace ELC using muscimol inactivation of MATN contralateral to the trained eye in rabbits. The results establish a foundation for a systematic mapping of the CS pathway to forebrain structures required for trace ELC to an auditory stimulus.

Disclosures: L.C. Hoffmann: None. **S.J. Zara:** None. **A.N. Manley:** None. **M.D. Mauk:** None.

Poster

819. Reward: Neuropharmacology

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 819.01/VV6

Topic: G.02. Motivation

Support: NRF 2012R1A6A3A03040362

PHS NIH grants AA020919 and DA035958

MSIP NRF-2015R1A5A7037508

NRF 2014R1A2A1A11053104

KIOM K16070

Title: Involvement of reactive oxygen species in methamphetamine-induced behavior changes and dopamine release in the nucleus accumbens

Authors: ***E. JANG**[1], D. M. HEDGES[3], A. C. NELSON[3], D. J. OBRAY[3], T. G. EKINS[3], B. T. GARCIA[3], S. P. KIM[1], J. Y. LEE[1], N. J. KIM[1], B. BITTER[3], K. M. SONG[2], S. J. JANG[2], H. Y. KIM[1], C. H. HEO[2], C. H. YANG[2], S. C. STEFFENSEN[3];
[1]Physiol., [2]Physiol. and Convergence Res. Ctr., Daegu Haany Univ., Daegu, Korea, Republic of; [3]Psychology and Ctr. for Neurosci., Brigham Young Univ., Provo, UT

Abstract: Methamphetamine (METH) markedly increases dopamine (DA) release in the mesolimbic DA system, which plays an important role in mediating the reinforcing effects of METH. Methamphetamine-induced DA release results in the formation of reactive oxygen species (ROS), leading to oxidative damage. We have recently reported that ROS are implicated in behavior changes and DA release in the nucleus accumbens (NAc) following cocaine administration. The aim of this study was to evaluate the involvement of ROS in acute and chronic METH-induced locomotor activity, self-administration, and enhancement of DA release in the NAc. Systemic administration of a non-specific ROS scavenger, N-tert-butyl-α-phenylnitrone (PBN; 0, 50 and 75 mg/kg, IP), or a superoxide ($O_2^{\bullet-}$) selective scavenger, 4-hydroxy-2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPOL; 0, 50 and 100 mg/kg, IP), attenuated METH-induced locomotor activity without affecting generalized behavior in METH naïve rats. PBN and TEMPOL significantly attenuated METH self-administration without affecting food intake. Increased oxidative stress was found in neurons, but not astrocytes, microglia or oligodendrocytes, in the NAc of METH self-administering rats. In addition, TEMPOL significantly decreased acute METH enhancement of DA release in the NAc. TEMPOL also decreased DA release in the NAc of METH-sensitized rats. Taken together, these results suggest that enhancement of ROS in the NAc contributes to the reinforcing effect of METH.

Disclosures: **E. Jang:** None. **D.M. Hedges:** None. **A.C. Nelson:** None. **D.J. Obray:** None. **T.G. Ekins:** None. **B.T. Garcia:** None. **S.P. Kim:** None. **J.Y. Lee:** None. **N.J. Kim:** None. **B. Bitter:** None. **K.M. Song:** None. **S.J. Jang:** None. **H.Y. Kim:** None. **C.H. Heo:** None. **C.H. Yang:** None. **S.C. Steffensen:** None.

Poster

819. Reward: Neuropharmacology

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 819.02/VV7

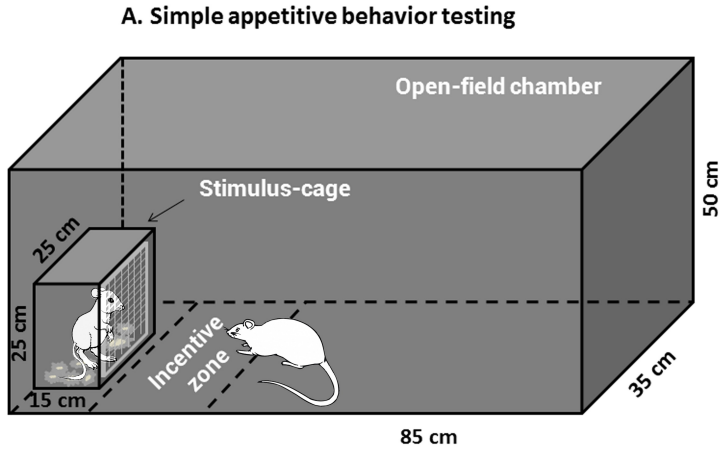
Topic: G.02. Motivation

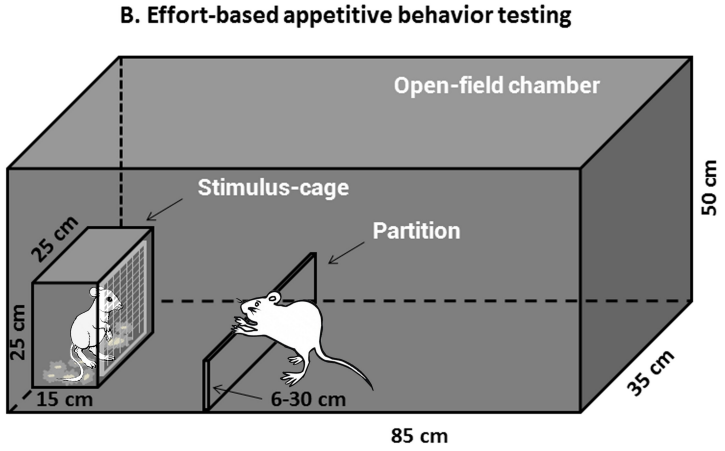
Support: National Natural Science Foundation of China 31000463

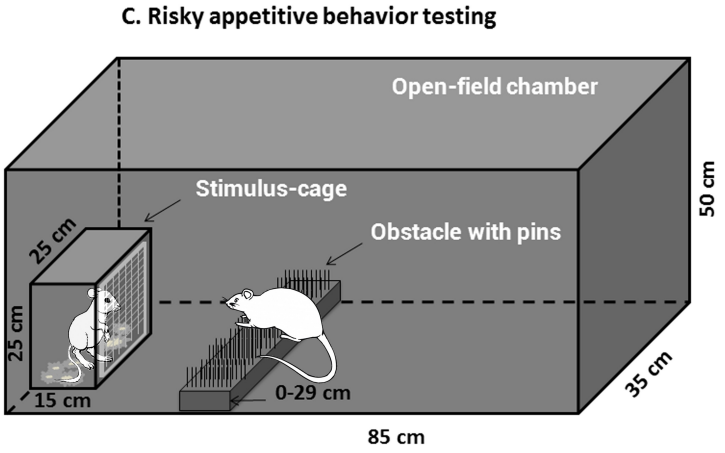
Title: The acute stress attenuated appetitive behaviors for social and sexual stimuli in long-term morphine-withdrawn rats

Authors: *Y. BAI[1], X. ZHENG[1], D. BELIN[2], Y. ZHANG[1], Z. LIU[1];
[1]Inst. of Psychology,Chinese Acad. of Sci., Beijing City, China; [2]Dept. of Pharmacol., Univ. of Cambridge, Cambridge, United Kingdom

Abstract: The anhedonia-like behaviors induced by an acute foot-shock stress following at least 14-days withdrawal from morphine were examined in the present study. Male rats were pretreated with either a binge-like morphine paradigm or daily saline injection for 5 days. Two types of natural rewarding stimulus were used, social stimulus (male rat) and sexual stimulus (estrous female rat). For each natural stimulus, appetitive motivational behaviors under three testing tasks, i.e., free, effort-based and risky approaching behavior tests were investigated. Before starting the tests, an intermittent foot shock at variable intervals was introduced within 10 minutes (0.5 mA*0.5 seconds*10min; mean intershock interval: 40 seconds, range: 10-70seconds). The results showed that the foot-shock stress decreased the appetitive motivations (sniffing time) to sexual stimulus during the 3-hour free-approach behavior test in male rats irrespective of pretreatment. In the effort-based appetitive behavior test, the stressed morphine-withdrawn rats demonstrated a diminished motivation to climb over the partition to approach social stimulus while the stressed saline-pretreated rats showed an increase in motivation to approach social stimulus, compared respectively with their stress control groups. When the aversive stimulus (needles) was involved, the risky approaching behaviors for sexual stimulus in both drug-withdrawn and drug-naïve groups exhibited a pattern of bi-polar distribution after the stress was introduced, i.e., the majority of the animals in each of the stressed groups had low risky appetitive behaviors but a minority of the animals showed rather highly risky behaviors. These results suggested that acute stress could induce motivational anhedonic behaviors for social and sexual rewards in protracted drug-abstinent animals. Notably, the acute foot-shock stress had a similar impact on the behavioral responses to sexual rewarding stimulus in drug-naïve and drug-withdrawn animals, but had contrary influences on their behavioral responses to social rewarding stimulus.







Disclosures: **Y. Bai:** None. **X. Zheng:** None. **D. Belin:** None. **Y. Zhang:** None. **Z. Liu:** None.

Poster

819. Reward: Neuropharmacology

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 819.03/VV8

Topic: G.02. Motivation

Support: R01AA024112

Title: Disulfiram inhibits approach behaviors during a Pavlovian conditioned approach paradigm.

Authors: K. Z. PASQUARIELLO, *D. DANIELS, P. J. MEYER;
Dept Psychol, Univ. at Buffalo Dept. of Psychology, Buffalo, NY

Abstract: Environmental rewards and Pavlovian reward cues can elicit motivational states that powerfully control behavior. In rats, the motivational value of food cues can be measured during a Pavlovian conditioned approach paradigm, in which rats engage in cue-directed approach (sign-tracking) or goal-directed approach (goal-tracking). While dopamine signaling is necessary for cue-directed approach, no studies have examined the role of noreprinephrine in these approach behaviors, although Tomie et al. (2004) reported an increase in norephinephrine in the prefrontal cortex during this paradigm. Thus, as a first step toward investigating the influence of norepinephrine in Pavlovian conditioned approach, we administered the dopamine beta-hydroxylase inhibitor disulfiram (0, 50, 100, or 200 mg/kg) to rats (n=48) as they learned that a food cue (an illuminated lever) preceded the delivery of banana-flavored food pellets into a food-cup. Rats received 25 lever-pellet pairings per day for three days, and sign- and goal-tracking were measured using lever contacts and food-cup entries, respectively. We found that disulfiram dose-dependently inhibits both lever contracts (sign-tracking) and food-cup entries (goal-tracking), $p < .05$. Thus, these findings show that disulfiram blocks both sign- and goal-tracking behaviors, and that this may be due to a general effect of disulfiram on learning. However, in addition to inhibiting dopamine beta-hydroxylase, disulfiram also inhibits aldehyde dehydrogenase peripherally and in the brain, and thus a role for this family of enzymes in the behavioral effects seen here remain to be ruled out. Supported by R01AA024112.

Disclosures: K.Z. Pasquariello: None. **D. Daniels:** None. **P.J. Meyer:** None.

Poster

819. Reward: Neuropharmacology

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 819.04/VV9

Topic: G.02. Motivation

Support: Cara Therapeutics Inc

Title: Investigation of the discriminative and reinforcing properties of the κ-opioid receptor agonist CR845 in rats

Authors: *D. J. HEAL[1], J. GOSDEN[1], N. SLATER[1], S. HOLLAND[1], J. SLADE[1], F. MENZAGHI[2], R. SPENCER[2], S. SMITH[1];
[1]RenaSci Ltd, Nottingham, United Kingdom; [2]Cara Therapeut. Inc, Shelton, CT

Abstract: CR845 is a peripherally-acting κ opioid agonist being developed to treat pain and pruritus. CR845 has no activity at μ or δ opioid receptors. These studies investigated whether CR845 generalised to the discriminative cue elicited by the centrally-acting mixed κ/σ agonist and μ partial agonist, (-)pentazocine, or substituted as a positive reinforcer in an intravenous self-administration (IVSA) experiment in heroin-maintained rats. Lister Hooded female rats were trained to discriminate (-)pentazocine (5mg/kg ip) from saline. Butorphanol, a κ/μ opioid agonist, was used as the reference comparator. Compounds were tested 15min after iv injection. Results are reported as mean±SD % generalisation to the (-)pentazocine cue. Sprague Dawley male rats were trained to self-administer heroin (0.015mg/kg/inj) on a FR5 schedule. After saline extinction, CR845 and (-)pentazocine were evaluated in separate groups of rats in 2 hr sessions. IVSA results are reported as mean±SEM. Drug discrimination was validated by the dose-dependent generalisation of (-)pentazocine (0.017-0.5 mg/kg iv) to the training cue (17.7±8.9% to 75.8±8.2%, n=6). Butorphanol (0.001-0.25 mg/kg iv), dose-dependently generalised to (-)pentazocine (17.1±11.7% to 76.6±17.5%, n=6/7). CR845 (0.05, 0.125, 0.25, 0.5 mg/kg iv) generalised to saline at the lowest dose, (23.6±10.5%, n=7) and partially generalised to (-)pentazocine at all other doses (35.4±20.2%, 31.0±17.9%, 34.5±10.1% respectively, n=7) with no evidence of dose-dependence. Heroin maintained IVSA in all rats (15.83±0.85 inj/session, n=13) that was significantly greater ($p<0.001$) than saline (3.65±0.37 inj/session, n=13). None of the CR845 doses (0.001, 0.005, 0.025, 0.125mg/kg/inj) maintained rates of IVSA at a level significantly greater than saline and all doses were significantly lower than heroin. (-)Pentazocine (0.03, 0.1, 0.245mg/kg/inj) maintained IVSA at significantly greater levels than saline. (-)Pentazocine and butorphanol both generalised fully to the cue elicited by ip (-)pentazocine validating the model for detecting drugs with μ and κ agonist properties. CR845 produced low level, non-dose-dependent, partial generalisation to (-)pentazocine, a result consistent with the fact that CR845 is a potent κ opioid agonist with poor brain penetration.

CR845 did not serve as a positive reinforcer in heroin-maintained rats. The reference comparator, (-)pentazocine, substituted for heroin in the model and served as a positive reinforcer across a range of doses. If these results translate into man, they predict that CR845 is unlikely to be recreationally abused.

Disclosures: **D.J. Heal:** B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution; CARA THERAPEUTICS. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); RENASCI LTD. **J. Gosden:** A. Employment/Salary (full or part-time): RENASCI LTD. **N. Slater:** A. Employment/Salary (full or part-time): RENASCI LTD. **S. Holland:** A. Employment/Salary (full or part-time): RENASCI LTD. **J. Slade:** A. Employment/Salary (full or part-time): RENASCI LTD. **F. Menzaghi:** A. Employment/Salary (full or part-time): CARA THERAPEUTICS. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); CARA THERAPEUTICS. **R. Spencer:** A. Employment/Salary (full or part-time): CARA THERAPEUTICS. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); CARA THERAPEUTICS. **S. Smith:** A. Employment/Salary (full or part-time): RENASCI LTD.

Poster

819. Reward: Neuropharmacology

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 819.05/VV10

Topic: G.02. Motivation

Support: nsF grant IOS1557755

nih grant R03DA038734

boettcher young investigator award

narsad young investigator award

Title: Benzodiazpines and their dual administration with ethanol increase accumbal transient dopamine release events

Authors: *D. R. RAKOWSKI, S. A. SCHELP, Z. BRODNIK, R. A. ESPAÑA, K. J. PULTORAK, E. B. OLESON;
Univ. of Colorado Denver, Denver, CO

Abstract: Drugs of abuse are commonly thought to increase the concentration of dopamine in the nucleus accumbens (NAc), although their effects on phasic dopamine release events remains to be fully characterized. Here, we are assessing the action of dual-administration of ethanol and benzodiazepines on accumbal dopamine release events. Using fast-scan cyclic voltammetry (FSCV) performed in the freely-moving rat, we first assessed the effects of benzodiazepines (0.3-1mg/kg IV) on accumbal dopamine release. We found that two distinct benzodiazepines, diazepam and zolpidem, increase the frequency of dopamine release events, but decrease the concentration of dopamine per release event. This effect was consistently observed in both the core and shell subregions. Previous FSCV studies from the Robinson' lab demonstrated that ethanol increases both the frequency and amplitude of accumbal dopamine release events. We then assessed for changes in dopamine concentration after treating animals with a range of ethanol doses (0.125-2g/kg IV) followed by 1.0mg/kg IV diazepam.

Disclosures: D.R. Rakowski: None. **S.A. Schelp:** None. **Z. Brodnik:** None. **R.A. España:** None. **K.J. Pultorak:** None. **E.B. Oleson:** None.

Poster

819. Reward: Neuropharmacology

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 819.06/VV11

Topic: G.02. Motivation

Support: DFG SO 952/6-1

Title: Oral estrogen administration alters neural activity associated to reversal learning in young healthy women

Authors: *J. BAYER, T. TUSCH, L. H. SCHULTE, J. GLÄSCHER, T. SOMMER;
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Abstract: One of the best known non-reproductive actions of the sex steroid 17-beta-estradiol (E2) is the maintenance and enhancement of hippocampal plasticity. In addition, human and animal research revealed hormonal modification of dopaminergic neurotransmission in the striatum. Both regions play a role in reversal learning, the adaptive learning of reversing stimulus-outcome contingencies. While the hippocampus is thought to mediate general

configural learning processes, the striatum rather mediates learning a new response after stimulus-outcome reversal. We applied 2, 4, 6, 12 mg of E2 or placebo to young naturally-cycling women (N = 125) within a randomized and double-blinded design. Different doses were chosen, because animal literature suggests linear but also inverted u-shape dose response functions of E2. Study participation was scheduled around the menstruation phase, where endogenous hormone levels are low. Levels of E2, progesterone and cortisol were assessed in saliva To characterize the effects of E2 on the reward-related neural activity, participants performed a probabilistic reversal learning task in the MR scanner. On average, drug administration resulted in salivary E2 levels of 2.6, 10.3, 16.3, 24.9 and 37 pg/ml. Experimental groups did not differ in behavior. Activity associated to positive relative to negative feedback was positively associated to E2-dose in the right hippocampus and the right nucleus accumbens. Activity associated to switching from one stimulus option to the other was positively associated to E2 dose in the left middle cingulum. Current results suggest that E2 modulates both hippocampus-mediated as well as striatum-mediated learning processes during reversal learning.

Disclosures: J. Bayer: None. **T. Tusch:** None. **L.H. Schulte:** None. **J. Gläscher:** None. **T. Sommer:** None.

Poster

819. Reward: Neuropharmacology

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 819.07/VV12

Topic: G.02. Motivation

Title: Phosphodiesterase 4 (PDE4) inhibition: A novel approach to treat deficits in motivation

Authors: *A. N. HANKS, Z. A. HUGHES;
Pfizer, Cambridge, MA

Abstract: While deficits in reward and motivation are hallmark symptoms of a broad range of psychiatric disorders, they also contribute to the 'neuropsychiatric' symptoms of neurodegenerative disorders and are significant co-morbidities in peripheral disorders of inflammation and autoimmunity. Dopamine signaling is strongly involved in reward processing with appetitive stimuli causing activation of the mesolimbic dopamine system and dopamine depletion or receptor antagonism resulting in motivational deficits. The aims of the present studies were to investigate whether the progressive ratio (PR) assay could be used in mice to detect pharmacologically-induced deficits in motivation. Due to the role of PDE4 in modulating DA signaling through controlling cAMP/PKA signaling, we investigated whether PR responding could be restored by the brain penetrant PDE4 inhibitor, ABI-4. A cohort of C57BL6/J male

mice were trained in the PR assay. Half of the mice were dosed once daily with vehicle, the other with ABI-4 (0.1 mg/kg; a dose resulting in 50% occupancy of PDE4). A range of pharmacological agents known to modulate dopaminergic signaling were evaluated: deficits in motivation were induced by acute administration of a D1 receptor antagonist, D2 antagonists, and a kappa opioid receptor (K) agonist. Finally the endotoxin, lipopolysaccharide (LPS) was used as an inflammatory challenge. On testing days ABI-4 was dosed four hours prior to PR testing and the 'disruptor' at 30 or 240 minutes prior to testing. Both the D2 antagonists, haloperidol (0.1 mg/kg) and risperidone (0.178 mg/kg) produced significant decreases in the number of rewards received compared to vehicle treated animals (both $p < 0.01$). Similarly when mice received the D1 antagonist, SCH23390 (0.056 mg/kg), LPS (0.32 mg/kg) or the K agonist, spiradoline (1.78 mg/kg) there were decreases in responding for rewards ($p < 0.01$). Chronic administration of ABI-4 (0.1 mg/kg) significantly attenuated each of these deficits in responding (all $p < 0.01$). These data suggest that PDE4 inhibition could represent an opportunity to attenuate deficits in motivation in patients regardless of the etiology (e.g. a dopaminergic deficit or an inflammatory burden) across different disorders.

Disclosures: A.N. Hanks: None. **Z.A. Hughes:** None.

Poster

819. Reward: Neuropharmacology

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 819.08/VV13

Topic: G.02. Motivation

Support: Funded by a grant from the Ontario Brain Institute - Integrated Discovery program: Canadian Biomarker Integration Network for Depression (CAN-BIND)

Title: Effect of chronic opioid exposure and spontaneous withdrawal on reactivity to palatable food in rats

Authors: *S. DANIELS[1], M. PRATT[2], F. LERI[2];
[1]Psychology and Neurosci., [2]Univ. of Guelph, Guelph, ON, Canada

Abstract: Administration of opiate agonists, as well as precipitated opioid withdrawal, significantly alter intake of highly palatable foods. It is not clear, however, how these acute effects relate to chronic opiate exposure and spontaneous withdrawal, and whether they represent changes in palatability and/or motor responses. These questions are relevant to patients on methadone who may experience alterations in dietary preferences as a direct effect of their maintenance treatment. Male Sprague-Dawley rats were implanted with subcutaneous osmotic

mini-pumps releasing 0, 10 or 30 mg/kg/day methadone and tested for consumption of, as well as taste reactivity to, a 50% high fructose corn syrup (HFCS) solution. Testing was repeated during spontaneous withdrawal induced by removal of the pumps. Locomotion was assessed in activity chambers during these periods. Methadone dose-dependently reduced total caloric intake, and this was associated with decreases in body-weight and locomotion. Importantly though, the percentage of caloric intake derived from HFCS was dose-dependently increased during the initial days of treatment. At later stages of treatment, there was a normalization of caloric intake from HFCS, and this was associated with motor hyperactivity. Interestingly, during spontaneous withdrawal, HFCS consumption was significantly reduced in both 10 and 30 mg/kg/day groups, while food intake was not significantly altered. Locomotor activity was also significantly reduced in the 30 mg/kg/day group. No significant effects on taste reactivity were observed in subjects tested up to date. These findings suggest that chronic methadone exposure and spontaneous withdrawal alter reactivity to palatable food. More specifically, preference for calories from HFCS is enhanced during maintenance, and consumption of HFCS is selectively suppressed by withdrawal. Interestingly, these effects are not related to changes in palatability or motor behavior. These observations in rats may explain why methadone maintained patients often report enhanced preferences for highly palatable foods, and highlight a possible nutritional outcome of anhedonic-like symptoms experienced during withdrawal.

Disclosures: **S. Daniels:** None. **M. Pratt:** None. **F. Leri:** None.

Poster

819. Reward: Neuropharmacology

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 819.09/VV14

Topic: G.02. Motivation

Support: Discovery Grant from the Natural Sciences and Engineering Research Council of Canada

Title: Dual self-administration of oxycodone and high fructose corn syrup in rats

Authors: *M. MINHAS, F. LERI;
Univ. of Guelph, Guelph, ON, Canada

Abstract: Introduction: The hypothesis of food addiction postulates that palatable rewards can lead to addictive behaviors because they act on systems of learning and reinforcement that are targeted by drugs of abuse. This leads to the prediction that “taking” and “seeking” behaviors reinforced by palatable rewards and addictive drugs should be comparable in a situation where

their availability, or availability of their conditioned stimuli, is similar. This study compared taking and seeking of oxycodone (OXY) and high fructose corn syrup (HFCS) by the same subjects.
Methods: Each male Sprague-Dawley rat was implanted with both intraoral (IO) and intravenous (IV) cannulas and trained to self-administer IO infusions of HFCS (50%) and IV infusions of oxycodone (0.2 mg/kg/inf), over 16 alternating days, 3 hours/day, on a continuous reinforcement schedule, by operating two different levers presented in the same context. After a 4-day abstinence period, all animals were tested in extinction conditions by simultaneously presenting both HFCS- and OXY-paired levers. Finally, rats received a test of cue-induced reinstatement during which lever presses activated the HFCS- or OXY-paired conditioned stimulus.
Results: It was found that, at the concentration and dose tested, there was greater operant responding for HFCS than for OXY. However, in the extinction tests, there was significantly more responding on the OXY-paired lever. Similarly, during tests of cue-induced reinstatement, responding on the lever that activated the OXY-paired stimulus was significantly higher than on the lever that activated the HFCS-paired stimulus.
Conclusion: These results suggest that HFCS and OXY differentially controlled motivated behaviors expressed by the same subjects. More specifically, although both reinforced lever pressing, responding on the OXY lever was more persistent than on the HFCS lever, both in the absence and in the presence of conditioned stimuli. Therefore, within these testing conditions, OXY appeared more reinforcing than HFCS.

Disclosures: **M. Minhas:** None. **F. Leri:** None.

Poster

819. Reward: Neuropharmacology

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 819.10/VV15

Topic: G.02. Motivation

Support: Ontario Brain Institute - Integrated Discovery program: Canadian Biomarker Integration Network for Depression (CAN-BIND)

Discovery Grant from the Natural Sciences and Engineering Research Council of Canada.

Title: Exploring the aversive effect of hypoglycemia in laboratory rats

Authors: *T. A. HORMAN, M. F. FERNANDES, F. LERI;
Psychology, Univ. of Guelph, Guelph, ON, Canada

Abstract: There is some evidence that hypoglycemia alters mood in humans and induces depressive-like behaviours in laboratory animals. Therefore, it is conceivable that a glycemic stressor could cause an aversive state and thus promote avoidance. To test this hypothesis, this study investigated whether the glucose antimetabolite 2-deoxy-D-glucose (2-DG) can serve as an unconditioned stimulus to produce a conditioned place avoidance (CPA), and whether this effect is modulated by food-induced glycemic states or altered by systemic suppression of norepinephrine (NE). In Experiment 1, male Sprague-Dawley rats were pre-fed, or food deprived, for three hours prior to place conditioning with 0, 300 or 500 mg/kg 2-DG (3/4 pairings in 6/8 days). In Experiment 2, blood glucose concentration was measured in pre-fed, or food deprived, rats after a single injection of 0, 300 or 500 mg/kg 2-DG. Experiment 3 examined relative intakes of laboratory chow and high fructose corn syrup (HFCS) in pre-fed, or food deprived, rats after injections of 0, 300 and 500 mg/kg 2-DG. To test the role of NE activity in 2-DG-induced CPA, rats in Experiment 4 with *ad libitum* access to chow received 0, 10, or 40 ug/kg clonidine, a noradrenergic alpha2 receptor agonist, concurrently with 500 mg/kg 2-DG during conditioning (4 pairings in 8 days). It was found that 2-DG produced a robust place avoidance and that this effect was significantly modulated by the pre-feeding state of the animal. Blood glucose concentration increased after 2-DG, and this was further enhanced by food deprivation. It was also found that 2-DG interacted with feeding state to alter consumption of food and HFCS. Finally, clonidine significantly reduced place avoidance induced by 2-DG. These results suggest that 2-DG is an effective glycemic stressor that can serve as an unconditioned stimulus to produce conditioned avoidance behaviour. It is conceivable that glycemic stressors can induce an aversive state that is dependent on acute NE hyperactivity. These results support the suggestion that metabolic stress can play a role in the psychopathology of mood disorders.

Disclosures: T.A. Horman: None. **M.F. Fernandes:** None. **F. Leri:** None.

Poster

819. Reward: Neuropharmacology

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 819.11/VV16

Topic: G.02. Motivation

Title: A comparison of the effects of peripheral or centrally-active CB1 receptor antagonists on palatable feeding and cue-induced reinstatement in the rat

Authors: *W. E. PRATT[1], S. GALLAGHER[1], R. YING[1], K. VEMURI[2], A. MAKRIYANNIS[2]; [1]Dept. Psychology, Wake Forest Univ., Winston Salem, NC; [2]Ctr. for Drug Discovery, Northeastern Univ., Boston, MA

Abstract: Central and peripheral cannabinoid (CB) signaling has been widely implicated in the regulation of ingestive behaviors. Antagonism of CB1 receptors suppresses food intake and enhances weight loss. Rimonabant (SR141716A) was briefly on the market in Europe, but was withdrawn due to symptoms of depressed mood and anxiety in some patients. It has been suggested that the adverse effects of SR141716A may be due to its inverse agonist properties, and there is hope that other strategies to inhibit the CB1 receptor may be effective at reducing body weight without causing adverse side effects. The goal of these experiments was to compare the efficacy of the brain-penetrating neutral CB1 antagonist AM4113 and the peripherally-restricted neutral CB1 antagonist AM6545 with that of SR141716A on the intake of a palatable diet, as well as cue-induced reinstatement of food-seeking. In the palatable feeding experiments, rats maintained on rat chow *ad libitum* were presented with a high fat/sucrose diet for daily 2-hr feeding sessions. Food intake and locomotor measures were monitored throughout the sessions. On multiple experimental days, rats (N= 8/group) received systemic injections of SR141716A (0-4.0 mg/kg), AM6545 (0-8.0 mg/kg) or AM4113 (0-8.0 mg/kg) prior to being placed into the feeding chambers. For the reinstatement experiments, food-restricted rats were trained to lever press on a conjoint FI20-VR5 schedule for sugar pellets and a concurrent light/tone cue (e.g., Lin & Pratt, 2014). Rats then underwent daily extinction sessions during which lever presses no longer presented the sugar or the cues. Once each rat reached 10% of their pre-extinction responding, they received two reinstatement test sessions (separated by 48h) in which they were tested upon renewed presentation of the light-tone cue on a VR5 schedule. Prior to each reinstatement test, rats received i.p. injections of vehicle or SR141716A, AM6545 or AM4113 (4.0 mg/kg; 3 groups of 11-12 rats). In the feeding experiments, injections of all three CB1 antagonists significantly reduced weight during the next 24-hr period, although only the centrally-active agents SR141716A and AM4113 acutely inhibited 2-hr intake of the sweetened fat diet. At 4.0 mg/kg, AM4113 (but not SR141716A or AM6545) significantly blocked cue-induced reinstatement of food-seeking. These data suggest that although peripheral CB1 receptor antagonism facilitates acute weight loss, central blockade of CB1 receptors is required to reduce feeding in response to palatable diets. Furthermore, in addition to enhancing satiety processes, some centrally-active CB1 antagonists also inhibit food-seeking in the presence of food-associated cues.

Disclosures: W.E. Pratt: None. **S. Gallagher:** None. **R. Ying:** None. **K. Vemuri:** None. **A. Makriyannis:** None.

Poster

819. Reward: Neuropharmacology

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 819.12/VV17

Topic: G.02. Motivation

Support: Commonwealth Universal Research Enhancement Program

Title: *In vivo* studies of the role of ERK1/2 phosphatase MKP3 in dopaminergic neurons on cocaine associated dopamine signaling and behaviors

Authors: *S. LEWANDOWSKI[1], D. L. BERNSTEIN[2], R. A. ESPAÑA[3], O. V. MORTENSEN[4];
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Abstract: Psychostimulant addiction is a destructive problem facing many societies and addicts typically undergo a vicious cycle of drug use, withdrawal, seeking and relapse. Approximately 2.5 million people abuse cocaine every year, with only 800,000 of them being treated. Cocaine exerts its addictive effects by blocking the dopamine transport (DAT), leading to excess dopamine (DA) in the synaptic cleft, resulting in the euphoric "high" that is often sought after during addiction. Currently, there are no FDA approved pharmacotherapies available for cocaine use disorders, and therefore it is imperative to develop more viable treatment options. The ERK1/2 Map kinase signaling pathway has been implicated in the locomotor-stimulant effects of psychostimulants such as cocaine, as well as the sensitization effects induced by repeated cocaine administration. However limitations exist in these previous studies as they were based on systemic or local administration of kinase inhibitors and as a consequence lack the anatomical resolution necessary for a more detailed examination of the role of ERK1/2 signaling in specific cell types. This is imperative to identify specific downstream targets of this pathway to reveal novel therapeutic targets for treating cocaine use disorders. In this study we describe the modulation of the ERK1/2 pathway *in vivo* by specifically expressing the ERK1/2 phosphatase MKP3 only in dopaminergic cells. We have generated adeno-associated viral (AAV) vectors with Cre recombinase (Cre)-dependent expression of MKP3 resulting in a decrease of the ERK1/2 signaling specifically in only DA cells of the ventral tegmental area (VTA). This construct was injected into the VTA of Long Evans rats expressing Cre in tyrosine hydroxylase positive cells (TH-Cre rats). We find that the overexpression of MKP3 in DA cells affects DA signaling and cocaine-induced psychomotor activation. In addition, we have examined the effects of MKP3 overexpression in DA neurons on cocaine-induced behavioral sensitization. Animals were injected with cocaine for three consecutive days and exposed to challenge injections on days 7 and 11 after their last injection and subjected to locomotor testing. Brain

tissue from the animals were analyzed by immunoblotting for changes in protein expression of dopaminergic proteins. Results from the present study identify specific relationships between ERK1/2 signaling in DA neurons and psychomotor behaviors that model human substance abuse. We believe these studies could have potential for identifying novel therapeutic targets for treating cocaine use disorders.

Disclosures: S. Lewandowski: None. **D.L. Bernstein:** None. **R.A. España:** None. **O.V. Mortensen:** None.

Poster

819. Reward: Neuropharmacology

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 819.13/VV18

Topic: G.02. Motivation

Title: Molecular mechanisms of action of M_5 muscarinic acetylcholine receptor allosteric modulators

Authors: *A. BERIZZI[1,1], P. RUEDA[2], A. J. LAWRENCE[3], C. J. LANGMEAD[2], A. CHRISTOPOULOS[2];
[1]Drug Discovery Biol., Monash Univ., Parkville, Australia; [2]Drug Discovery Biol., Monash Univ., PARKVILLE, Australia; [3]Melbourne Brain Ctr., The Florey Inst. of Neurosci. and Mental Hlth., Melbourne, Australia

Abstract: Recently, the first subtype selective allosteric modulators of the M_5 muscarinic acetylcholine receptor (mAChR) have been described, but their molecular mechanisms of action remain unknown. Using radioligand binding and IP accumulation in a recombinant cell line stably expressing the human M_5 mAChR, we investigated the effects of the positive allosteric modulator (PAM), ML380, and negative allosteric modulator (NAM), ML375. In functional assays, ML380 caused robust enhancements in the potency of the full agonists, acetylcholine (ACh), carbachol and oxotremorine-M, while significantly increasing the maximal response to the partial agonist, pilocarpine. ML380 also demonstrated direct allosteric agonist activity. In contrast, ML375, displayed negative cooperativity with each of the agonists in a manner that varied with the pathway investigated, and progressively reduced the maximal pilocarpine response. Radioligand binding affinity cooperativity estimates were consistent with values derived from functional assays in some instances but not others, suggesting additional allosteric effects on orthosteric ligand efficacy. This was confirmed in IP assays performed after reduction of receptor reserve by the alkylating agent, phenoxybenzamine, where ML375 inhibited the maximal ACh response. In contrast, identical experiments performed at the M_1 mAChR with the

prototypical PAM, BQZ12, revealed only enhancement in ACh potency with no effect on maximal response. Interaction studies between ML380 and ML375 also indicated that they likely utilized an overlapping allosteric site. Our findings indicate that novel small molecule modulators of the M_5 mAChR display different molecular mechanisms of action compared to previously characterized modulators of other mAChRs. Moving forward, these M_5 mAChR allosteric modulators lend themselves as useful tool compounds to probe M_5 mAChR activity in CNS disorders.

Disclosures: **A. Berizzi:** None. **P. Rueda:** A. Employment/Salary (full or part-time): Monash University. **A.J. Lawrence:** A. Employment/Salary (full or part-time): The Florey Institute of neuroscience and mental health. **C.J. Langmead:** A. Employment/Salary (full or part-time): Monash University. **A. Christopoulos:** A. Employment/Salary (full or part-time): Monash University.

Poster

819. Reward: Neuropharmacology

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 819.14/VV19

Topic: G.02. Motivation

Support: Simons Foundation 365029

NSERC PGSD Fellowship 471313

Teresa Seessel Postdoctoral Fellowship

Alfred P. Sloan Foundation

Title: Supralinear effects of combined oxytocin administration and opioid blockade on contingent social gaze dynamics

Authors: *M. R. PIVA[1], O. DAL MONTE[2], M. TRINGIDES[2], S. W. C. CHANG[3]; [1]Interdepartmental Neurosci. Program, [2]Psychology, [3]Psychology, Neurosci., Yale Univ., New Haven, CT

Abstract: Upon encountering other people in daily life, we initiate interactions, observe reactions, and respond using our own gaze behavior. This dynamic and contingent gaze interaction between individuals is a hallmark of social attention. However, there is a significant knowledge gap in our understanding of social attention with respect to contingent gaze dynamics. Moreover, the potential role of neuromodulation in social interaction remains unclear,

despite the known impact of certain neuromodulatory systems, including the oxytocin and opioid systems, on social cognition. Here, we utilized a live gaze interaction paradigm in pairs of rhesus macaques to explore how the oxytocinergic and opioidergic systems interact to modulate contingent gaze dynamics between two individuals. In this paradigm, two monkeys were placed in front of each other while eye positions were recorded from the two animals simultaneously. Monkeys freely explored the face of a conspecific following inhaled administration to one of the two monkeys of either oxytocin or naloxone, an opioid antagonist, or both. We found that oxytocin co-administered with naloxone more strongly promoted attention to the eyes of a conspecific's face compared to either drug administered alone. This increase was strongest approximately 1.0 to 1.5 hours following administration, indicating a time course for the behavioral effects. Preliminary analyses revealed that the effects of oxytocin and naloxone were simply additive for non-contingent looking behaviors, such that the added effects of oxytocin and naloxone alone mirrored the effect of oxytocin and naloxone administered together in a one-to-one positive linear correlation. As opposed to the linear additivity observed for non-contingent gaze, preliminary analyses indicated that the combination of oxytocin and naloxone invoked a supralinear enhancement of prolonged social attention following mutual eye contact compared to oxytocin or naloxone alone, such that administering the two agents together produced a significantly larger effect than the summation of the effects observed when the drugs were administered separately. Our findings are supported by the known regulatory relationship between the oxytocin and opioid systems, in which attenuated opioid processing is associated with stronger oxytocin release from the posterior pituitary. We provide the first preliminary evidence that the oxytocin and opioid systems interact to modulate social attention and exploration following contingent social interactions based on the observed supralinearly summed effect patterns.

Disclosures: **M.R. Piva:** None. **O. Dal Monte:** None. **M. Tringides:** None. **S.W.C. Chang:** None.

Poster

819. Reward: Neuropharmacology

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 819.15/VV20

Topic: G.02. Motivation

Support: Alfred P. Sloan Foundation

Title: Serotonin promotes sustained attention to viewer-directed social signals

Authors: *H. B. WEINBERG-WOLF[1], N. FAGAN[1], O. DAL MONTE[1], S. W. CHANG[1,2]; [1]Psychology, Yale Univ., New Haven, CT; [2]Neurobio., Yale Univ. Sch. of Med., New Haven, CT

Abstract: Rhesus macaques, live in large, complex, societies with strict dominance hierarchies (de Waal and Luttrell, 1985) and rely on highly stereotyped, species specific, social signals that help invididuals know when to engage in aggression, and when to submit (Partan, 2002). Navigating the social domain requires effectively attending to these these social signals, which are largely conveyed by a diverse array of viewer-directed facial expressions. Despite the stereotypy of these signals, individuals vary in their ability to competently interpret and deploy species typical social signals to achieve and maintain dominance status (Higley et. Al 1996). The serotenergic system is thought to be largely responsible for regulating these abilities. For example, non-human primates with low concentrations of cerebrospinal fluid (CSF) 5-hydroxyindoleacetic Acid (5-HIAA), a serotonin metabolite, are less likely to acquire and maintain social dominance than those with high CSF 5-HIAA concentrations (Higley & Linnoila, 1997). However, it remains unclear whether and how serotonin modulates attention to specific social signals communicated via facial expressions.

To address this, we investigated how rhesus macaques explore species typical social signals when their circulating levels of serotonin are increased. Following systemic administrations of serotonin precursor l-5-hydroxytryptophan (5-HTP), subjects were allowed to unconstrainedly explore social and non-social images for 5000 ms each. We tested the effects of a low (20 mg/kg), and high (40 mg/kg) 5-HTP dose, as well as a saline control, over strictly alternating days while their eye positions were tracked at high resolution.

We observed both an effect of 5-HTP on overall sustained attention as well as specific effects on viewing to particular facial expressions. High dose 5-HTP increased looking duration to facial expressions directed towards the subject but not away. Further more, this effect was specific to facial expressions which are used to convey dominance rank and evaluate fighting ability and intent. Together, these results support our hypothesis that serotonin promotes sustained attention to social signals that are relevant towards communicating dominance rank. Enhanced attention to viewer-directed social signals by way of serotonergic neuromodulation may improve social competency.

Disclosures: H.B. Weinberg-Wolf: None. **N. Fagan:** None. **O. Dal Monte:** None. **S.W. Chang:** None.

Poster

819. Reward: Neuropharmacology

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 819.16/VV21

Topic: G.02. Motivation

Support: NIH R01-MH099085

Title: Repeated low-dose ketamine elicits a sex-differential effect on behavioral sensitization and reward state

Authors: *K. J. SCHOEPFER, S. K. SALAND, K. N. WRIGHT, C. E. STRONG, M. KABBAJ;
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Abstract: Clinical studies have revealed rapid and robust antidepressant effects following treatment with a low subanesthetic dose of the noncompetitive NMDA receptor antagonist ketamine (KET) in treatment-resistant patients. Further, KET's therapeutic effects are maintained over a longer time course when delivered repeatedly. However, at higher doses, KET is a known recreational drug of abuse. As compared to males, females are at an elevated risk for both developing major depression and escalating from casual to compulsive drug use. Thus, investigating the long-term safety of repeated low-dose KET infusions in both sexes is crucial to its viability as a sound treatment option for depression. We recently reported that female rats are more sensitive than males to KET's antidepressant-like effects, responding to an acute dose 2.5 and 5 mg/kg (i.p.), respectively. Here, we aimed to determine whether there are also sex differences in addictive properties of repeated KET treatments in adult rats at these doses, as well as a higher concentration (10 mg/kg, i.p.) previously shown to elicit addictive behaviors in male rats. Using the conditioned place preference test to gauge pharmacological reward, we found that while all rats failed to develop a preference for 2.5 or 5 mg/kg KET, males formed a preference for 10 mg/kg KET. This suggests that repeated KET treatment at therapeutically relevant doses is not innately rewarding. Behavioral sensitization to KET's locomotor-activating effects was also assessed: Males and females both sensitized to repeated 5 or 10 mg/kg, but females' response to 5 mg/kg KET was amplified relative to males'. Sensitization to KET in both sexes was associated with increased ΔFosB expression in the nucleus accumbens (NAcc). However, unlike cocaine, viral-mediated ΔJunD overexpression in NAcc failed to block behavioral sensitization to repeated KET treatments. Taken together, these findings suggest that repeated low-dose KET induces behavioral and physiological changes similar to those of other drugs of abuse and high doses of KET, but that the transcriptional machinery underlying low-dose KET's behavioral phenotype may be unique. Therefore, more studies are needed to establish the safety of repeated KET treatment for treatment-resistant depression.

Disclosures: K.J. Schoepfer: None. **S.K. Saland:** None. **K.N. Wright:** None. **C.E. Strong:** None. **M. Kabbaj:** None.

Poster

819. Reward: Neuropharmacology

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 819.17/VV22

Topic: G.02. Motivation

Support: NIMH Grant R01 -MH087583

NIMH Grant R01 -MN099085

Title: Abuse potential of low dose intermittent ketamine exposure in male and female rats

Authors: *C. STRONG[1], K. J. SCHOEPFER[1], A. M. DOSSAT[1], S. K. SALAND[1], F. JOHNSON[2], M. KABBAJ[1];
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Abstract: Low-dose ketamine is gaining popularity as an alternative treatment for people suffering from major depressive disorder whose symptoms are not alleviated by typical SSRIs. Among this subpopulation with treatment resistant depression, a single infusion of low dose ketamine can alleviate suicidal ideation and other depressive symptoms within one hour, and can have long-lasting effects up to two weeks. However, ketamine in higher doses is a well-known club drug that is commonly abused. For this reason, and because addiction and depression are often comorbid, the abuse potential of ketamine at low doses needs to be investigated. Our lab previously showed that female rats respond to a lower dose than males, rescuing depressive-like behaviors at 2.5 mg/kg and 5 mg/kg (i.p.), respectively. In this study, we investigated the abuse potential of low doses of ketamine (2.5 and 5 mg/kg) administered once weekly in both males and females to mimic the treatment timeline used in the clinic. Locomotor activity and conditioned place preference (CPP) assays were used to assess measures of sensitization and drug-liking, and brains were collected to examine protein expression of molecular markers for addiction in the nucleus accumbens (NAc) as well as dendritic spine density in the core and shell of the NAc. While neither males nor females formed a place preference in the CPP paradigm, males treated with 5 mg/kg and females treated with both 2.5 and 5 mg/kg sensitized to ketamine. Additionally, dendritic spines were increased in the NAc shell in males and females at both doses. Expression of deltaFosB was increased in males, while GluA1 expression was increased in females, and significant changes were seen in BDNF and its downstream targets for both sexes. Taken together, we show that low dose ketamine, when administered intermittently, induces behavioral sensitization, accompanied by an increase in spine density and the NAc and protein expression changes in pathways commonly implicated in addiction.

Disclosures: C. Strong: None. **K.J. Schoepfer:** None. **A.M. Dossat:** None. **S.K. Saland:** None. **F. Johnson:** None. **M. Kabbaj:** None.

Poster

819. Reward: Neuropharmacology

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 819.18/VV23

Topic: G.02. Motivation

Support: R01MH087583

R01MH099085

Title: Reinforcing properties of intermittent, low-dose ketamine in males and female Sprague-Dawley rats

Authors: *K. N. WRIGHT, C. E. STRONG, K. J. SCHOEPFER, M. N. ADDONIZIO, M. KABBAJ;
Biomed. Sci., Florida State Univ., Tallahassee, FL

Abstract: Repeated intermittent exposure to ketamine has rapid and long-lasting antidepressant effects, but the abuse potential of ketamine has only been assessed at high doses. Furthermore, while females are more susceptible to depression and more sensitive to ketamine's antidepressant-like effects, its abuse potential in females is unknown. Therefore, the objective of this research is to determine the reinforcing properties of low-dose intermittent ketamine in both sexes and whether cycling gonadal hormones influence females' response to ketamine. In male rats, we also aimed to determine whether reinstatement to intermittent ketamine is comparable to intermittent cocaine. Male rats intravenously self-administered cocaine (0.75 mg/kg/infusion) or ketamine (0.05 and 0.1 mg/kg/infusion) once every fourth day, while intact cycling female rats self-administered ketamine only during stages of their four-day estrus cycle, when gonadal hormones are either high (proestrus) or low (diestrus). After acquiring self-administration, rats underwent daily extinction training followed by cue-primed and drug-primed reinstatement to assess drug-seeking behavior. Males and proestrus females reinstated to ketamine-paired cues, but diestrus females did not, due to lack of acquisition. Ketamine-primed reinstatement was dependent on simultaneous cue presentation. Male rats reinstated to cocaine priming independent of cue presentation. Additionally, progressive ratio was tested to assess the motivational salience of ketamine at different doses. Therefore, both females and males respond to ketamine's reinforcing effects under this treatment paradigm. Female's response was cycle-dependent.

Disclosures: K.N. Wright: None. **C.E. Strong:** None. **K.J. Schoepfer:** None. **M.N. Addonizio:** None. **M. Kabbaj:** None.

Poster

820. Neuroimaging and Behavioral Studies of Depression

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 820.01/VV24

Topic: G.04. Mood Disorders: Depression and Bipolar Disorders

Title: Activation of the ventral striatum during monetary incentive delay task and temperament, stress, and plasma homovanillic acid in mood disorder patients.

Authors: *Y. WAKATSUKI[1], N. HASHIMOTO[1], Y. OGURA[1], Y. NAKAI[1], T. MIYAMOTO[1], K. KITAGAWA[1], R. OKUBO[1], K. TOYOSHIMA[1], R. KAMEYAMA[1], H. NARITA[1], Y. FUJI[1], Y. NAKATO[2], K. ITO[1], Y. KAKO[1], S. ASAKURA[1], S. NAKAGAWA[1], T. INOUE[3], I. KUSUMI[1];
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Abstract: Background: Dysfunction of the dopaminergic reward system, predominantly in frontostriatal networks, has been pointed out in patients with mood disorder. On the other hand, Previous studies have suggested that affective temperaments, childhood abuse, and adult stressful life events influence pathogenesis of mood disorder. However, the relation of these factors and reward system in patients with mood disorder is unclear. In the present study, we investigated affective temperaments, childhood abuse, estimated intelligence score, adult stressful life events, anhedonia, and plasma homovanillic acid (HVA). Then we examined the relationship with the ventral striatum activation during monetary incentive delay task in the mood disorder patients. Methods: 66 mood disorder patients (age 19-50 years, major depressive disorder (MDD): bipolar disorder (BP) = 31: 35) participated in the functional magnetic resonance imaging scanning and worked with a modified version of the monetary incentive delay task. Temperaments, recent life events, childhood abuse were surveyed along with demographical background using the self-administered questionnaires: Life Experiences Survey (LES), Temperament Evaluation of the Memphis, Pisa, Paris, and San Diego auto-questionnaire (TEMPS-A), and Child Abuse and Trauma Scale (CATS), Snaith-Hamilton Pleasure Scale-Japanese version (SHAPS-J), and Japanese Adult Reading Test (JART). Blood samples were taken for the plasma HVA assay. Results: JART score and HVA concentrations significantly correlated (positive and negative, respectively) with beta value of \500(largest reward) minus \0(no reward) during the anticipation phase in the ventral striatum. In the 4 groups (MDD remission (rem), MDD non-rem, BP rem and BP non-rem), There are significant deference in response to \0, beta value of \100 minus \0, cyclothymic temperament, SHAPS-J and HVA. In the MDD rem group, activity in the ventral striatum for large incentive was larger compared to other groups. Conclusions: Our results suggest that the response to reward anticipation in the ventral striatum can be associated with dopamine dysfunction, in accordance with previous

findings. The activity in the ventral striatum was higher in MDD rem group than MDD non-rem or BP rem/non-rem group.

Disclosures: **Y. Wakatsuki:** None. **N. Hashimoto:** None. **Y. Ogura:** None. **Y. Nakai:** None. **T. Miyamoto:** None. **K. Kitagawa:** None. **R. Okubo:** None. **K. Toyoshima:** None. **R. Kameyama:** None. **H. Narita:** None. **Y. Fuji:** None. **Y. Nakato:** None. **K. Ito:** None. **Y. Kako:** None. **S. Asakura:** None. **S. Nakagawa:** None. **T. Inoue:** B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution; Otsuka Pharmaceutical, Eli Lilly, Eisai, Yoshitomiyakuhin, Mitsubishi Tanabe Pharma, AbbVie GK, Pfizer, Astellas, and Meiji Seika Pharma. D. Fees for Non-CME Services Received Directly from Commercial Interest or their Agents (e.g., speakers' bureaus); Otsuka Pharmaceutical, Pfizer, GlaxoSmithKline, Astellas, Eli Lilly, Mitsubishi Tanabe Pharma, Mochida Pharmaceutical, Meiji Seika Pharma, Asahi Kasei Pharma, Shionogi, Janssen Pharmaceutical, Takeda. **I. Kusumi:** None.

Poster

820. Neuroimaging and Behavioral Studies of Depression

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 820.02/VV25

Topic: G.04. Mood Disorders: Depression and Bipolar Disorders

Support: MNiSW Grant DI2013 012943

Title: Theta, alpha or beta - classification of major depression disorder using suport vector machines

Authors: *A. A. KOLODZIEJ[1], M. MAGNUSKI[2], A. BRZEZICKA[3];
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Abstract: Major Depressive Disorder (MDD) is one of the most prevalent psychiatric disorders. Previous EEG studies focused mostly on assymetry in the alpha band recorded from frontal channels as a potential biomarker of MDD. Most such studies measured frontal alpha assymetry (FAA) at rest and only for a selected subset of channels. However, it is still not clear whether FAA constitutes a reliable biomarker of MDD. Moreover, FFA is a univariate measure, while MDD may be potentially better characterized by the overall pattern of scalp oscillations in the relevant band (multivariate measure). In fact, alpha asymmetry can be more broadly considered as a subset of many potential multivariate patterns. We used support vector machine (SVM) with

linear kernel to test whether the pattern of theta (4 - 8 Hz), alpha (8 - 12 Hz) or beta (15 - 30 Hz) oscillations allows to classify participants as MDD patients (N=23) or controls (N=22). We avoided using extensive feature engineering and separatelly tested average power for each oscillatory band. Therefore for each frequency band the size of the feature space was equal to the number of channels used in the analysis (61). Standard procedures were used to select SVM hyperparameters and fit the classifier- 70% of the data was used as the training set and the remaining 30% was used for testing; 5-fold cross-validation was used to select SVM hyperparameters. Because classification on such small samples (N=55) can highly depend on the particular partitioning of the data into training and test sets we used the same partition for each frequency band and repeated the classification multiple times for different partitions. The results show that beta band was significantly better in classification than alpha or theta band. More specifically - only the pattern of beta band oscillations allowed to classify participants better than chance.

Disclosures: **A.A. Kolodziej:** None. **M. Magnuski:** None. **A. Brzezicka:** None.

Poster

820. Neuroimaging and Behavioral Studies of Depression

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 820.03/VV26

Topic: G.04. Mood Disorders: Depression and Bipolar Disorders

Support: Deutsche Forschungsgemeinschaft DFG ET 112/6-1

Title: Neurobiology of processing vocal emotions in unipolar depression

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[1]Gen. Dept. of Psychiatry, [2]Dept. of Biomed. Resonance, Univ. of Tuebingen, Tuebingen, Germany

Abstract: Correct interpretation of emotional signals is crucial for successful social interactions. In the auditory domain, such signals can be expressed verbally (semantic information) and nonverbally by modulation of speech melody (prosody). Behavioral experiments documented an impaired identification of vocal emotions in patients with MDD. These deficits occurred both during perception of positive and negative emotional prosody[1]. Furthermore, a mood congruent bias could be shown for patients with unipolar depression which resulted in altered evaluation of prosodic stimuli[2]. So far, no neuroimaging studies on processing of emotional acoustic information in major depressive disorder (MDD) are available.
Here, we investigated the neural correlates of disturbed perception of emotional information

expressed by prosody in patients with unipolar depression using functional neuroimaging magnetic resonance imaging (fMRI). We presented adjectives varying with respect to their emotional semantic content (positive, neutral, and negative) which were spoken in happy, neutral, or angry prosody. It was the task of the participants to either judge exclusively the valence (i.e., how positive or negative the emotional information was perceived) of the prosody or semantic content (control task) on a five-point scale. This design enabled us to localize stimulus-dependent networks (comparison of emotional and neutral prosody) as well as task-dependent brain areas (comparison of judgment of prosody versus judgment of semantic content).
We found depressed patients to make more errors in the identification of emotional prosody than matched healthy controls. Specifically, we found depressed patients to give less intense ratings for positive emotional prosody than healthy controls, whereas we did not find this difference in the evaluation of negative content, implying a reduced experience of positive information and a perceptual bias to positive emotions in depressed patients. Furthermore we found an altered neural response profile in depressed patients, supporting the behavioral results.
A mood congruent bias in patients with unipolar depression resulting in altered evaluation of prosodic stimuli was shown. Evaluation of emotional signals in the voice is of particular importance in modern society, where communication often occurs exclusively via the acoustic channel (e.g., telephone), adding furthermore to the relevance and application of the results in our day. Our results add importantly to the understanding of processing of emotional content in unipolar depression.
[1]Murphy & Cutting 1990; Peron et al. 2011
[2]Naranjo et al. 2011, Schlipf et al. 2013

Disclosures: **K. Koch:** None. **L. Schwarz:** None. **M. Reinl:** None. **M. Erb:** None. **T. Ethofer:** None.

Poster

820. Neuroimaging and Behavioral Studies of Depression

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 820.04/WW1

Topic: G.04. Mood Disorders: Depression and Bipolar Disorders

Support: Consortium grant (U54 EB020403) from the NIH Institutes contributing to the Big Data to Knowledge (BD2K) Initiative

Title: White matter abnormalities in major depression worldwide: meta-analytic findings of 1,538 cases and controls from the ENIGMA-MDD DTI working group

Authors: *S. M. KELLY[1], L. S. VAN VELZEN[2], S. HATTON[3], A. ALEMAN[4], B. BAUNE[5], U. DANNLOWSKI[6], M. DEPPE[7], B. COUVY DUCHESNE[8], T. FRODL[9], I. H. GOTLIB[10], N. GROENEWOLD[11], D. GROTEGERD[6], H. KUGEL[12], H. KUNUGI[13], J. LAGOPOULOS[14], T. A. LETT[15], K. L. MCMAHON[16], N. G. MARTIN[8], S. MEINERT[17], M. SACCHET[18], M. J. WRIGHT[19], M. J. PORTELLA[20], L. TOZZI[21], D. STEIN[22], H. WALTER[15], M. WALTER[23], I. B. HICKIE[24], P. M. THOMPSON[25], N. JAHANSHAD[25], L. SCHMAAL[26];
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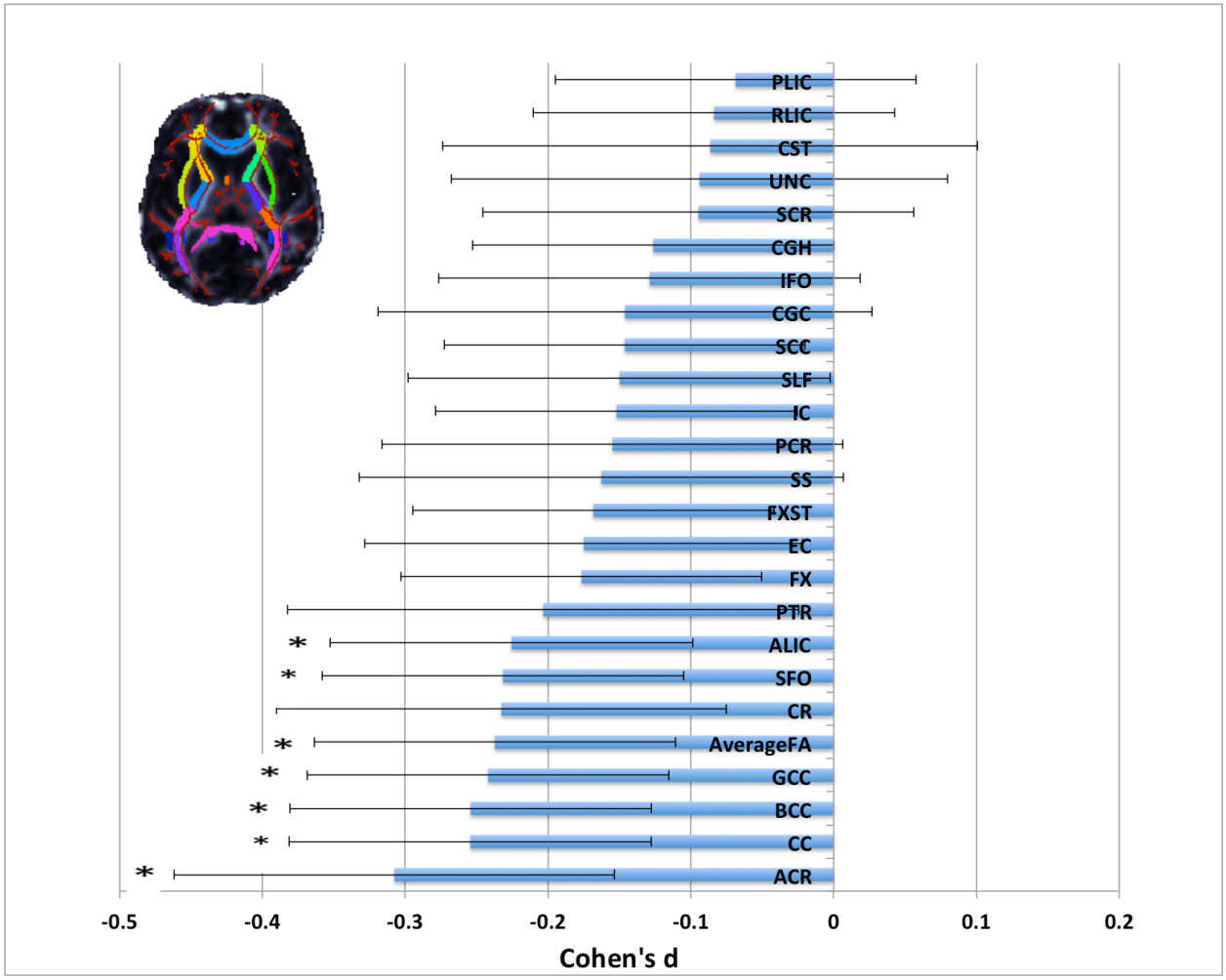
Abstract: Introduction Major depressive disorder (MDD) is a major public health concern affecting approximately 8-12% of the population. Disruption in the brain's white matter (WM) microstructure in patients with MDD has been reported, yet findings have been inconsistent. Large-scale collaborations in neuroimaging, such as ENIGMA, aim to increase statistical power and generate robust estimates of localized effect-sizes. Here, we applied the ENIGMA-DTI protocols to harmonize data from MDD patients and controls across 16 sites. **Methods:** We analyzed DTI data from 622 MDD patients and 916 healthy controls with a mean age of 33 years (SD=9.5) and 59% female. The ENIGMA-DTI protocols were run on the fractional anisotropy (FA) maps, as detailed online: http://enigma.ini.usc.edu/protocols/dti-protocols/. The average FA within each of 24 bilateral (left and right averaged) WM regions of interest (ROIs) were extracted. For each site, case control effect sizes were quantified with Cohen's d for all ROIs where age, sex, age by sex, age^2 and age^2 by sex effects were included as covariates. A random effects, inverse variance weighted meta-analysis was conducted to combine results across the 15 sites. **Results:** After Bonferroni correction, the largest effect size was observed for FA of MDD patients in the anterior *corona radiata* (ACR; d=-0.31, p=9.07x10^5), followed by the corpus callosum (BCC; d=-0.25; p = 8.27x10^5), the corpus callosum body (CC; d=-0.25; p=8.42x10^5), *genu* of CC (GCC; d=-0.24; p=0.0002), anterior limb of internal capsule (ALIC; d=-0.23, p=0.0005),superior fronto-occipital fasciculus (SFO; d=-0.23, p=0.0003) and average FA (d = -0.24, p=0.0003) (**Figure 1**).**Conclusions** In the largest meta-analysis of DTI in MDD, we

observed robust findings of decreased FA in cortico-thalamic, interhemispheric and fronto-parietal WM of MDD patients, suggesting that disruptions of connectivity between these regions may contribute to the pathophysiology of the disorder. Future meta-analyses will assess moderating effects of clinical covariates, including age of onset and symptom severity.



Disclosures: **S.M. Kelly:** None. **L.S. van Velzen:** None. **S. Hatton:** None. **A. Aleman:** None. **B. Baune:** None. **U. Dannlowski:** None. **M. Deppe:** None. **B. Couvy Duchesne:** None. **T. Frodl:** None. **I.H. Gotlib:** None. **N. Groenewold:** None. **D. Grotegerd:** None. **H. Kugel:** None. **H. Kunugi:** None. **J. Lagopoulos:** None. **T.A. Lett:** None. **K.L. McMahon:** None. **N.G. Martin:** None. **S. Meinert:** None. **M. Sacchet:** None. **M.J. Wright:** None. **M.J. Portella:** None. **L. Tozzi:** None. **D. Stein:** None. **H. Walter:** None. **M. Walter:** None. **I.B. Hickie:** None. **P.M. Thompson:** None. **N. Jahanshad:** None. **L. Schmaal:** None.

Poster

820. Neuroimaging and Behavioral Studies of Depression

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 820.05/WW2

Topic: G.04. Mood Disorders: Depression and Bipolar Disorders

Support: NIMH R01MH059282

NSF BCS-0746220

NIDA DA022582

NHLBI HL114092

NIMH MH091100-A1

Title: Resting-state functional connectivity similarity to clinical depression predicts self-reported mood scores in healthy individuals.

Authors: *J. F. HUCKINS[1], P. E. HOLTZHEIMER[3], E. M. GORDON[4], T. F. HEATHERTON[1], A. T. CAMPBELL[2], R. WANG[2], V. MISHRA[2], W. M. KELLEY[1]; [1]Psychological and Brain Sci., [2]Computer Sci., Dartmouth Col., Hanover, NH; [3]Psychiatry and Surgery, Dartmouth-Hitchcock Med. Ctr., Lebanon, NH; [4]VISN 17 Ctr. of Excellence for Res. on Returning War Veterans, Waco, TX

Abstract: Resting-state functional connectivity (RSFC) studies of clinical depression have previously identified aberrant RSFC across several regions of the default system (Grecius et al., 2007), and prior work has applied support vector classification to RSFC data to successfully distinguish healthy from clinically depressed individuals (Craddock et al., 2009). Here we show that an individual's RSFC similarity to a RSFC template of clinical depression predicts self-reported measures of depression. Two RSFC data sets were collected from a cohort of clinically depressed patients (N=49) and a cohort of college undergraduates (N=65). Standard RSFC preprocessing methods including motion censoring were applied to both data sets (Power et al., 2014). RSFC matrices were then created for each subject based on 264 standard whole-brain nodes (Power et al., 2011), modified to incorporate subcortical nodes within the amygdala, nucleus accumbens, and ventral tegmental area. A depression template was created based on mean connectivity across the clinical depression cohort. For each subject in the undergraduate sample, a similarity index was then computed to reflect the correlation between each subject's RSFC matrix and the clinical template. Results revealed that similarity to the clinical template predicted self-reported measures of depression using the Personal Health Questionnaire Scale. Subsequent parcellation analyses further revealed that subgenual cingulate parcels in the depression template are functionally connected to a different network (cingulo-opercular/salience

network) than is observed in healthy individuals (default network). These findings suggest that RSFC may be used as a biomarker for depression sensitivity and raise the intriguing possibility that advances in smart-phone technology may aide in the early identification of those most sensitive to mood disorders and life stressors.

Disclosures: **J.F. Huckins:** None. **P.E. Holtzheimer:** None. **E.M. Gordon:** None. **T.F. Heatherton:** None. **A.T. Campbell:** None. **R. Wang:** None. **V. Mishra:** None. **W.M. Kelley:** None.

Poster

820. Neuroimaging and Behavioral Studies of Depression

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 820.06/WW3

Topic: G.04. Mood Disorders: Depression and Bipolar Disorders

Support: National Institute of Mental Health of the National Institutes of Health under award numbers U01MH092221 and U01MH092250

Title: Resting-state functional connectivity classifies patients with major depressive disorder into clinically distinct sub-groups

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Abstract: There is significant variability in clinical presentations of Major Depressive Disorder (MDD). Any two individuals diagnosed with MDD may only share a single symptom among many. It is clear that specific dysfunctions in brain networks (e.g., due to atypical anatomy and/or structural and functional connectivity) may underlie the diverse clinical presentations of MDD. However, few studies have found evidence that brain network-based descriptions can distinguish patients into clinically meaningful sub-groups based on traditional analytic approaches. To explore this possibility we examined a subset of MRI brain measures collected from a large cohort of patients diagnosed with MDD and used an iterative clustering method to

classify patients into sub-groups. We focused on the patterns of resting-state functional correlation (RSFC) in their large-scale brain networks as inputs for this clustering approach. Data were analyzed from a large multi-site placebo-controlled trial of un-medicated patients (N=185, 18-65 yrs) with early-onset MDD (first episode < 30 years of age) from the Establishing Moderators and Biosignatures of Antidepressant Response for Clinical Care (EMBARC) study. For each participant, an RSFC matrix was built by measuring the pair-wise correlations in the blood oxygen level-dependent time-series of putative neocortical areas (Chan et al., 2014) and FreeSurfer-defined subcortical regions of interest. Patient-to-patient similarity in functional connectivity was quantified by comparing all patients' RSFC matrices to one another; then we established sub-groups by iteratively finding individuals with high RSFC similarity to many others and assigning each patient to a single cluster with which he/she exhibited high similarity. Patient clusters were identified across a variety of RSFC matrix thresholds and participant samples. Critically, the identified sub-groups exhibited multivariate clinical and anatomical variability that might otherwise be indiscernible by clinical ratings or brain anatomy alone. Sub-groups reliably differed in depressive symptoms as measured by several clinical scales and in FreeSurfer-based estimates of brain structure. This data-driven RSFC-clustering method identifies sub-groups of patients with multiple distinguishing clinical and anatomical features (e.g., symptoms of anhedonia, a reduced ability to experience pleasure, with reduced ventral striatum size) across MDD sub-groups and compared to non-MDD healthy controls. These findings suggest that RSFC network patterns may differentiate patients with MDD into clinically meaningful sub-groups that could assist with lab-based diagnoses.

Disclosures: The Disclosure Block has exceeded its maximum limit. Please call Tech support at (217) 398-1792 for more information.

Poster

820. Neuroimaging and Behavioral Studies of Depression

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 820.07/WW4

Topic: G.04. Mood Disorders: Depression and Bipolar Disorders

Support: NIH Grant R01 MH064821-04

Title: Cognitive behavior therapy (cbt) changes resting-state and task brain activity across mdd and ptsd

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Abstract: Introduction: Traditionally, MDD and PTSD were considered separate disorders with distinctive neuropsychopathology. With the advent of the Research Domain Criteria, there has been an emphasis on dimensions of psychopathology that extend across clinical diagnostic criteria to abnormalities in certain brain circuitry. CBT is an effective treatment for both MDD and PTSD. Here, we applied a Linear Mixed-Effects (LME) model to resting-state and task-based fMRI data to understand the neural substrates of CBT effects common across diagnostic categories (MDD and PTSD combined) and specific to each category (MDD or PTSD).
Methods: Patients were scanned (Siemens 3T Trio) at baseline and after 12 weeks of CBT using a 7-min resting-state scan followed by four runs of an emotional conflict task scan designed to probe emotional and cognitive control networks. Amygdala functional connectivity (n = 17 MDD, 21 PTSD) and task activation (n = 15 MDD, 16 PTSD) were computed at baseline and post-treatment and compared with 28 matched controls scanned at baseline. Patients were assessed using the MADRS, MASQ and PDS. Imaging data were analyzed using voxel-wise LME modeling to examine common and unique CBT effect on brain indices. Pearson's correlations were conducted to link brain function to symptom improvement. Imaging results were corrected for multiple comparisons using Gaussian Random Field theory ($Z>2.33$, $p<0.005$).
Results: Across patients, task-based activations of left DLPFC, bilateral IFG, bilateral dorsal ACC, left posterior insula, and left dorso-medial striatum were normalized following treatment. Dimensional brain-symptom associations revealed that left DLPFC baseline activation was significantly correlated with a treatment-related decrease in MADRS ($r=-0.39$, $p=0.03$, $n=31$). Resting-state results indicated that amygdala functional connectivity with bilateral dorsal ACC and left anterior insula increased with treatment to a level comparable to HCs.
Conclusions: Our results suggest that normalizing dysfunctions of cognitive control and emotional regulation networks may be a common biological mechanism of CBT efficacy in MDD and PTSD. The observed brain-symptom associations suggest that one effect of CBT is to improve depressive symptoms via normalizing the functional deficits in DLPFC. The dimensional brain-behavioral associations observed could potentially serve as an imaging marker to index inter-individual differences in treatment responses and provide empirical evidence to support dimensional approaches to understanding psychopathology.

Disclosures: Y.I. Sheline: None. **Z. Yang:** None. **D. Oathes:** None. **S.E. Bruce:** None. **T.D. Satterthwaite:** None. **P.A. Cook:** None. **E. Mikkelsen:** None. **E. Satchell:** None. **R.T. Shinohara:** None. **H. Shou:** None.

Poster

820. Neuroimaging and Behavioral Studies of Depression

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 820.08/WW5

Topic: G.04. Mood Disorders: Depression and Bipolar Disorders

Title: Altered dynamics of fMRI intrinsic connectivity relate to changed patterns of information integration in major depressive disorder

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Abstract: Interregional functional connectivity (FC) is viewed as a prerequisite of large-scale communication of neuronal assemblies. FC is calculated as a measure reflecting signal covariance, i.e. synchronous signal development over time. This can only occur when dominant frequencies of the time courses are identical, because otherwise signal would naturally diverge at significant periods of time. Information integration between distinct intrinsic connectivity networks (ICNs) is facilitated by the presence of highly connected nodes (functional hubs). We investigated the functional orchestration of ICNs in terms of frequency range covered by different ICNs in order to detect possible aberrant dynamics in major depressive disorder (MDD). We also examined the hub distribution in health and MDD. 10 min of rs-fMRI data was acquired from 25 MDD patients and 25 healthy controls (HC). 24 ICNs were identified using independent component analysis. Dynamic properties of ICNs were investigated by analyzing the centers of gravity of each single component spectrum. A repeated-measures ANOVA was performed on the weighted frequency values (wF) with group and ICN as main factors. In order to describe the hubs distribution, the degree centrality (DC) was calculated separately at 10 different frequency ranges of the signal (0:0.025:0.25 *Hz*). The ANOVA yielded a significant effect of ICN and a significant interaction between group and ICN. The interactions could be mainly attributed to the salience network (SAL) and visual network (VIS). SAL showed dynamics on a higher frequency range in MDD, whereas VIS had lower frequent dynamics. Shifts of wF could be attributed to a significant power loss at frequencies 0-0.025 *Hz* in SAL, and power loss at frequencies 0.075-0.15 *Hz* in VIS. DC analysis revealed unique hub localization for each frequency range. Alterations in DC were found between health and MDD, where the latter showed decreased DC in visual areas at frequencies 0.075-0.1 *Hz*, as well as decreased DC in frontal areas at frequencies 0.225-0.25 *Hz*.Our results demonstrate a stable and distinct temporal structuring between ICNs and also distinct frequency ranges in which differing aspects of information integration occur, which proof to be accessible via BOLD signal analysis. Aberrant brain functioning in MDD relates to changed dynamics in VIS and SAL and associated compromised information integration on the systems level.

Disclosures: **A. Ries:** None. **C. Meng:** None. **C. Sorg:** None. **A. Wohlschläger:** None.

Poster

820. Neuroimaging and Behavioral Studies of Depression

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 820.09/WW6

Topic: G.04. Mood Disorders: Depression and Bipolar Disorders

Support: Investigator initiated grant support to Dr. R. Ramasubbu from Astra Zeneca

Title: Thalamocortical connectivity is related to age of illness onset in major depressive disorder

Authors: ***E. C. BROWN**[1], D. L. CLARK[2], S. HASSEL[3], G. MACQUEEN[2], R. RAMASUBBU[2];
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Abstract: Background: Major Depressive Disorder (MDD) is a highly prevalent and heterogeneous disorder that has widespread aberrations across different brain regions, with one core network being the limbic-thalamo-cortical loop. Given the growing evidence that early-onset (EO) and adult-onset (AO) MDD may be distinct clinical phenotypes, we examined differences in the age of illness onset in the thalamocortical network, a network known to be disrupted in mood disorders, using resting state functional connectivity.
Methods: Resting-state functional magnetic resonance imaging (fMRI) data from 21 EO and 33 AO MDD patients, and 40 healthy controls (HC) were collected. The cortex was segmented into six regions of interest (ROIs) consisting of frontal, temporal, parietal, occipital, motor and somatosensory areas. BOLD signal time courses were extracted from each cortical seed and correlated with each voxel in the thalamus, while removing signals from every other cortical ROI.
Results: Our main findings firstly show that both EO and AO MDD patients had greater thalamocortical connectivity between temporal cortex and posterior parts of the thalamus. AO patients also showed some greater connectivity between temporal regions and medial thalamus compared to those with EO MDD. Secondly, frontal regions showed greater connectivity with medial thalamus only in AO MDD patients, but not EO. Furthermore, the topography of thalamocortical connectivity appeared different between EO and AO MDD patients, with EO MDD being more similar to HCs than AO. Notably, no significant correlations were found between illness burden (i.e. number of episodes and duration of illness) and thalamocortical connectivity.
Conclusion: Here we demonstrate both shared and differential abnormalities in thalamocortical

connectivity in EO and AO MDD. The observed thalamotemporal and thalamofrontal hyperconnectivity in AO MDD may be related to the abnormalities in temporo-frontal interactions via thalamus. The lack of thalamofrontal hyperconnectivity in EO MDD may be a marker for different disease pathologies dissociating EO and AO subtypes, whereas the thalamotemporal hyperconnectivity in both MDD groups appears less specific to age of onset, and more generally related to the underlying psychopathology of MDD. Elucidating the role of illness onset age in the biological basis of MDD could help to facilitate more targeted treatment for these subgroups.

Disclosures: E.C. Brown: None. **D.L. Clark:** None. **S. Hassel:** None. **G. MacQueen:** None. **R. Ramasubbu:** None.

Poster

820. Neuroimaging and Behavioral Studies of Depression

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 820.10/WW7

Topic: G.04. Mood Disorders: Depression and Bipolar Disorders

Support: NIHR PhD studentship to TW

Academy of Medical Sciences grant to DA

Title: Functional connectivity instability within the default mode network in major depression

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Abstract: Major depression is associated with changes in functional connectivity in many networks within the brain, most notably in the default mode network. However, so far no research has examined how connectivity between the medial prefrontal cortex and posterior cingulate cortex, key nodes in the default mode network, fluctuates over time in major depression. We calculated dynamic functional connectivity during a resting state fMRI scan between the medial prefrontal cortex and the posterior cingulate cortex. We examined the variability of connectivity strength between a group of 19 medication free patients with major depression and 19 healthy controls, and then assessed the reproducibility of this result in an independent sample of 19 medication free patients and 19 healthy controls. Connectivity

between the medial prefrontal cortex and posterior cingulate cortex, key nodes in the default mode network, was significantly less stable in patients with major depression than those of matched healthy control subjects. We were able to replicate these findings in an independent sample of individuals with depression, indicating that these results are robust. These findings show that alterations within the default mode network go beyond changes in connectivity strength, and suggest that individuals with major depression are unable to maintain consistent connectivity within important brain networks. We replicated this in an independent sample, indicating that this is a replicable finding. These results add another dimension to theories that suggest altered functional connectivity may underlie symptoms of mood disorders, particularly to rumination and negative self-directed thought.

Disclosures: **T. Wise:** None. **L. Marwood:** None. **A.M. Perkins:** B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution; Has received funding from Bionomics Inc. **A. Herane-Vives:** None. **R. Joules:** A. Employment/Salary (full or part-time): Employed by Ixico PLC. **D.J. Lythgoe:** F. Consulting Fees (e.g., advisory boards); Consulting for Ixico PLC. **W. Luh:** None. **S.C.R. Williams:** B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution; Has received support for investigator led studies from Takeda, Pfizer, Lundbeck, P1Vital, Roche and Eli Lilly. **A.H. Young:** B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution; lead investigator for the Embolden Study (AZ), BCI Neuroplasticity study, and Aripiprazole Mania Study and investigator initiated studies from AZ, Eli Lilly, Lundbeck, and Wyeth; and has received gran. F. Consulting Fees (e.g., advisory boards); sits on advisory boards for all major pharmaceutical companies with drugs used in affective and related disorders. **A.J. Cleare:** B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution; Has received honoraria for speaking from Astra Zeneca (AZ) and an educational organization supported by Pfizer, honoraria for consulting from Allergan and Livanova and r. **D. Arnone:** C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Has received travel grants from Janssen-Cilag and Servier.

Poster

820. Neuroimaging and Behavioral Studies of Depression

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 820.11/WW8

Topic: G.04. Mood Disorders: Depression and Bipolar Disorders

Title: Probabilistic tractography-guided analyses of connectivity in patients with severe major depression treated with electroconvulsive therapy

Authors: *E. TSOLAKI[1], K. NARR[2], R. ESPINOZA[3], N. POURATIAN[1];
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Abstract: ***Introduction***
Functional brain mapping studies have revealed increased activity in the subcallosal cingulate cortex (SCC) of subjects wth depression, while decreased activity in this region is associated with clinical improvement after treatment. Here, we test a new probabilistic tractography approach to identify subregions within SCC that have the highest probability of structural connectivity with critical brain areas involved in mood regulation. In a DBS pilot sample, preliminary results associate a targeted SCC area with good clinical outcome in patients with severe major depression. Our goal in this study is to apply and validate this new method in patients with major depression undergoing treatment with electroconvulsive therapy (ECT) and to investigate the structural connectivity of the tractography-guided optimal region within SCC over time.
Methods
MR diffusion data were aqcuired in 32 patients with major depression prior to, on completion of the acute index series, and 6 months after ECT. We use FSL to define the connectivity of an anatomically defined SCC seed within the whole brain in each subject. These results are used to define patient-specific regions of the bilateral medial prefrontal cortices and ipsilateral ventral striatum and anterior cingulate that were structurally connected to the SCC region. We apply probabilistic tractography to define the probability of connectivity of each voxel in the SCC seed with each of these 4 targets. These target-specific probability maps are subsequently integrated to define the region within SCC with the highest combined connectivity with all 4 targets. We evaluate whether patients who respond to ECT demonstrate different strengths and patterns of structural connectivity with the target regions than non-responders.
Results
We successfully applied our novel approach to identify a unique and potentially clinically relevant subregion of SCC in each subject. Preliminary results suggest that compared to ECT

non-responders, patients who responded to ECT demonstrate different structural connectivity between the tractography-guided optimal region within SCC and the target areas at baseline.
Conclusion
This report provides promising results about the effectiveness of the tractography guided methodology to define the best SCC subregion with clinical treatment implications. The functional relevance of the optimal SCC subregion as assessed by changes in rsfMRI remains under investigation.

Disclosures: **E. Tsolaki:** None. **K. Narr:** None. **R. Espinoza:** None. **N. Pouratian:** None.

Poster

820. Neuroimaging and Behavioral Studies of Depression

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 820.12/WW9

Topic: G.04. Mood Disorders: Depression and Bipolar Disorders

Support: Intramural Research Program at the National Institute of Mental Health, National Institutes of Health (IRP-NIMH-NIH).

Title: Changes in white matter microstructure in adults with treatment-resistant depression

Authors: ***S. SNIDER**, A. NUGENT, M. LENER, D. LUCKENBAUGH, C. ZARATE;
Natl. Inst. of Mental Hlth., Bethesda, MD

Abstract: Functional neuroimaging studies have identified the subgenual anterior cingulate cortex (sgACC) and its connections with the limbic system as key players in the pathophysiology of treatment-resistant depression (TRD). We hypothesize that communication between these two brain regions may not only be perturbed functionally, but also structurally, in TRD. We used diffusion tensor imaging (DTI) and probabilistic tractography to characterize the white matter (WM) microstructure of tracts connecting the sgACC and the left and right amygdala (LAmyg, RAmyg) in adults with TRD (n=26, 62% female, mean age=36.6), and healthy controls (n=14, 50% female, mean age=33.6). DTI and anatomical scans were obtained in a single session using a 3-T General Electric scanner (GE Signa) and an 8-channel phased-array head coil. Diffusion MRI data was processed with Tolerably Obsessive Registration and Tensor Optimization Indolent Software Ensemble (TORTOISE), as well as the Analysis of Functional Neuroimages (AFNI) FATCAT (Functional and Tractographic Connectivity Analysis Toolbox) package. Following motion and eddy current correction, the diffusion tensor was calculated using the FACTID algorithm. Amygdala ROIs were derived from the Eikhoff-Zilles atlas available in AFNI, and sgACC ROIs was manually drawn on a Talairach template image. These ROIs were transformed

to each subject's native anatomical space. The FATCAT toolbox was then used to calculate probabilistic tract maps for all possible tracts connecting our three ROIs. We found that the bundle of tracts connecting the sgACC to the RAmyg had a significantly lower mean fractional anisotropy (FA) in patients with TRD compared to healthy controls (p=.037). FA is a measure of the degree of directionality of the diffusion of water. Changes in FA are thought to reflect changes in white matter orientation and density, and reductions in FA have been observed following brain injury and in the biology of other neuropsychiatric disorders. The TRD group also appeared to have fewer tracts connecting sgACC to RAmyg when the number of tracts was normalized to the white matter surface area of each region, though this trend was not significant (p=.080). Interestingly, no differences in connectivity were found between sgACC and LAmyg between patients and healthy controls. The results of our study suggest that the structural connections between sgACC and RAmyg may be compromised in TRD. Future directions include boosting the number of subjects in our sample, conducting analyses with subject-specific regions of interest, and examining correlations between structural and functional imaging.

Disclosures: **S. Snider:** None. **A. Nugent:** A. Employment/Salary (full or part-time): National Institute of Mental Health. **M. Lener:** A. Employment/Salary (full or part-time): National Institute of Mental Health. **D. Luckenbaugh:** A. Employment/Salary (full or part-time): National Institute of Mental Health. **C. Zarate:** B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution; National Institute of Mental Health. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Patent application for the use of ketamine in depression.

Poster

820. Neuroimaging and Behavioral Studies of Depression

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 820.13/WW10

Topic: G.04. Mood Disorders: Depression and Bipolar Disorders

Support: Stanley Medical Research Institute

Ontario Mental Health Foundation

Title: Predicting outcome in patients with first-episode psychosis treated concurrently with antipsychotic and antidepressant medications

Authors: *S. RASMUSSEN, P. I. ROSEBUSH, M. F. MAZUREK;
McMaster Univ., Hamilton, ON, Canada

Abstract: Background: Many patients with first-episode psychosis experience prominent affective symptoms, and one strategy for treating these symptoms is to add antidepressant medications to ongoing antipsychotic treatment. Currently, there is limited evidence guiding the use of antidepressants in these patients. In particular, it is unclear whether early response after 2 weeks of antipsychotic/antidepressant treatment is a valuable predictor of treatment outcome.
Methods: In this observational study we investigated 115 antipsychotic-naive patients with first-episode psychosis throughout their initial hospitalization. All patients were treated with haloperidol. Within this sample, 34 patients received antidepressant medication, while 81 did not. Linear regression was used to determine whether early improvement on the Brief Psychiatric Rating Scale (BPRS) at week 2 or week 3 predicted improvement at hospital discharge, and whether this predictive value differed between treatment groups. In secondary analyses, we assessed whether early improvement on the Hamilton Depression Rating Scale (HAM-D) or Hamilton Anxiety Rating Scale (HAM-A) predicted improvement on these measures at hospital discharge.
Results: Most patients experienced dramatic improvement in psychiatric symptomatology, and the degree of improvement was not affected by the use of antidepressant medication. For patients who did not receive antidepressant medication, week 2 BPRS improvement was a significant predictor of BPRS improvement at hospital discharge ($p<.001$). However, for patients who were treated with an antidepressant, week 2 BPRS improvement did not predict improvement at hospital discharge ($p=.618$). BPRS improvement at week 3 predicted improvement at hospital discharge whether patients were treated with an antidepressant ($p=.004$) or not ($p<.001$). Week 2 HAM-D improvement predicted HAM-D improvement at hospital discharge in patients who did not receive antidepressant medication ($p<.001$), but it did not predict treatment outcome in patients who received antidepressant medication ($p=.247$). The predictive value of early HAM-A improvement did not significantly differ between treatment groups. Differences in baseline BPRS, HAM-D, or HAM-A scores did not significantly affect the predictive value of early response.
Conclusion: It may be difficult to predict treatment outcome based on week 2 response in patients treated concurrently with antipsychotic and antidepressant medications. This disadvantage must be weighed against the limited clinical benefits of antidepressant use in patients with first-episode psychosis.

Disclosures: S. Rasmussen: None. **P.I. Rosebush:** None. **M.F. Mazurek:** None.

Poster

820. Neuroimaging and Behavioral Studies of Depression

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 820.14/WW11

Topic: G.04. Mood Disorders: Depression and Bipolar Disorders

Title: Serum levels of autotaxin in major depressive disorders and schizophrenia: a pilot study

Authors: K. ITAGAKI[1,2,3], C. SHIBASAKI[4,1,2], K. OGA[1,3], W. OMORI[1,3], N. KAJITANI[1,2], H. ABE[1,2], M. OKADA-TSUCHIOKA[1,2], *M. TAKEBAYASHI[1,2,3];
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Abstract: [Background] Lysophospholipids such as lysophosphatidic acid (LPA) and sphingosine 1-phosphate are potent bioactive lipid mediators with diverse biological properties including involvement in neurodevelopmental processes, inflammation and the immune system. This suggests a possible association between lysophospholipids and the pathophysiology of psychiatric disorders, however, the association remains to be elucidated. Autotaxin (ATX) is major enzyme that is secreted to generate LPA and is strongly associated with LPA blood levels. Therefore, ATX is a candidate to act as a surrogate biomarker for LPA.
[Purpose] Serum levels of ATX were examined in patients with major depressive disorders (MDD), who had depressive episodes and were applicable for electroconvulsive therapy (ECT), and patients with schizophrenia (SCZ), who also had psychotic episodes and were also applicable for ECT, and compared with healthy controls. Serum levels of ATX were then compared before and after a course of ECT in patients with MDD and SCZ. An analysis was also done to determine whether there was an association between serum levels of ATX and clinical symptoms.
[Methods] This study was performed on MDD (N = 37; female: 22, male: 15) and SCZ (N = 25; female: 14, male: 11) following a course of ECT, and compared to the serum levels of healthy controls (N = 53; female: 30, male: 23). Serum ATX concentrations were measured by ELISA. Clinical severity was assessed using the 17-item Hamilton Depression Rating Score for MDD and the Positive and Negative Syndrome Scale for SCZ. The ethics committee of NHO Kure Medical Center approved the study protocol, and all participants provided written consent.
[Results] In healthy controls, serum ATX levels for females were significantly higher than those of males ($p < 0.001$), which indicates a gender difference for ATX. Prior to ECT, serum ATX levels in female patients with MDD, but not with SCZ, were significantly lower ($p < 0.01$) than those of female healthy controls. After ECT, serum ATX levels in female MDD were significantly increased. There was a significant negative correlation between depressive symptoms and serum ATX levels in female MDD ($Rho = -0.303$, $p < 0.05$). In contrast, there

were no significant differences in serum ATX levels between male psychiatric patients (both of MDD and SCZ) and male healthy controls either before or after ECT. Serum ATX levels in male psychiatric patients were not associated with symptom severity.
[Conclusion] Our findings suggest that alteration of lysophospholipids such as LPA could be related to female MDD. Serum ATX levels might be a gender-specific and state-dependent biomarker for depressive episodes in MDD.

Disclosures: **K. Itagaki:** None. **C. Shibasaki:** None. **K. Oga:** None. **W. Omori:** None. **N. Kajitani:** None. **H. Abe:** None. **M. Okada-Tsuchioka:** None. **M. Takebayashi:** None.

Poster

820. Neuroimaging and Behavioral Studies of Depression

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 820.15/WW12

Topic: G.04. Mood Disorders: Depression and Bipolar Disorders

Support: Fundação Carlos Chagas Filho de Amparo à Pesquisa do Estado do Rio de Janeiro (FAPERJ) (E-26/102.174/2013)

Title: Effect of physical exercise on cortical activity in elderly depressive patients: a randomized clinical trial

Authors: *A. C. DESLANDES[1], H. SILVEIRA, 22793395[2], J. LAKS, 22793395[3]; [1]IEFD, UERJ, Rio DE Janeiro, Brazil; [2]Neurosci. of Exercise Lab., [3]IPUB, UFRJ, Rio de Janeiro, Brazil

Abstract: Major depression (MD) is a highly prevalent disorder in both high- and low-income countries. The effectiveness of physical exercise in the treatment of depression is higher in patients older than 60 years and in subjects with mild symptoms. However, the central mechanisms are not well recognized. **Objective:** This study aimed to compare the effects of aerobic training (AT), strength training (ST) and low intensity exercise (control group/social contact) on cortical electrical activity. **Methods:** Older individuals clinically diagnosed with MD (n=27) were randomized into three groups: Aerobic Training (AT), Strength Training (ST) and a Control Group (CG; low-intensity exercise/social contact). All patients were evaluated prior to and following the 12 weeks of the intervention. EEG was used to assess cortical electrical activity through the Absolute Alpha Power (AAP). The examination was performed immediately after the assessment of depressive symptoms in all subjects before and after 12 weeks of intervention. The patients were seated in a comfortable sound- and light-attenuated room, while at least 8 minutes of eyes-closed alert/resting EEG data were collected from 20 monopolar

electrode sites (Fz, Fp1, Fp2, F3, F4, F7, F8, Cz, C3, C4, Pz, P3, P4, T3, T4, T5, T6, Oz, O1 and O2). **Results:** There was a decreased absolute alpha power (electrodes F4, F8, C4, T4, T6, T5, O2 and O1) in experimental groups (AT and ST) after 12 weeks; these results were not observed in the CG. **Conclusion:** Aerobic and strength training, controlled by the parameters of intensity, duration and frequency, promotes changes in cortical activity related to clinical responses in elderly depressive patients.

Disclosures: A.C. Deslandes: None. **H. Silveira:** None. **J. Laks:** None.

Poster

820. Neuroimaging and Behavioral Studies of Depression

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 820.16/WW13

Topic: G.04. Mood Disorders: Depression and Bipolar Disorders

Title: Serotonin-1A receptor polymorphism alters functional connectivity of default mode network

Authors: *H. ZHENG, K. ONODA, Y. WADA, S. MITAKI, S. YAMAGUCHI;
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Abstract: Serotonin 1A (5-HT1A) is a neurotransmitter that plays a critical role in emotional function. A recent study combining PET and fMRI has revealed that the binding potential of 5-HT1A receptor modulated the activity of the default mode network (DMN), which is a unique network showing increased activity at rest. Evidence showing that 5-HT1A polymorphism alters the binding potential in the raphe nuclei, suggests that genotype of 5-HT1A receptor might modulate the functional connectivity of resting-state networks including DMN. We conducted a resting-state functional MRI study to gain insights into mechanisms underlying the 5-HT1A receptor driving DMN, by investigating how functional connectivity is modulated via genetic variations of the 5-HT1A receptor. The C1019G polymorphism of 5-HT1A receptor was genotyped in 120 healthy participants (77 males, 43 females; age: 56.3 ± 14.0 years old). All participants underwent resting-state functional MRI and neuropsychological examinations. After standard preprocessing in Statistical Parametric Mapping 12, we extracted resting-state networks using independent component analysis, which identified 7 networks including anterior and posterior default mode, dorsal attention, salience, sensory-motor, visual and cerebellum networks. Since 5-HT1A receptor expression has been strongly implicated in gonadal steroid hormones, we performed a two-factor ANOVA (gender and genotype for CC/CG and GG). The result indicated significant gender-by-genotype interactions in the caudate nucleus included in anterior DMN, suggesting that functional connectivity between the medial prefrontal cortex and

caudate is modulated by a genotype of 5-HT1A and gender. The functional connectivity of C-allele carrier group was lower in females compared to males, but there was no gender effect in the GG group. Furthermore, only the C-allele carrier group showed a significant negative correlation between functional connectivity and apathy scores, which is indicative of a reduction in self-initiated goal-directed behaviors. These unique findings indicate that functional connectivity between anterior DMN and basal ganglia is affected by genetic variation of the 5-HT1A receptor and gender, which might be linked to the pathophysiology of apathetic syndrome.
Key words: 5-HT1A receptor polymorphism, default mode network, functional connectivity, apathy, sex

Disclosures: H. Zheng: None. **K. Onoda:** None. **Y. Wada:** None. **S. Mitaki:** None. **S. Yamaguchi:** None.

Poster

820. Neuroimaging and Behavioral Studies of Depression

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 820.17/WW14

Topic: G.04. Mood Disorders: Depression and Bipolar Disorders

Support: Indiana CTSI

Title: Decreased posterior cingulate cortex volume in early adulthood depression

Authors: *A. GUTIERREZ, M. MALARET, B. CARON, D. KELLAR, S. D. NEWMAN; Psychological and Brain Sci., Indiana Univ. Bloomington, Bloomington, IN

Abstract: Depression is one of the most prevalent diseases in the world, leading to global initiatives to treat and prevent it. In 2012, it was estimated that 350 million people worldwide suffered from depression (World Health Organization). According to the National Institute of Mental Health, depression is characterized by persistent sadness, decreased interest in typically pleasurable activities, restlessness, difficulty sleeping, and suicidal thoughts/attempts. Previous research has reported differences in brain morphology and volume in depression patients compared with non-depressed controls. Sheline et al. (1999) found that women with recurrent major depression who were otherwise physically healthy showed a decrease in bilateral hippocampal volume compared with matched controls. This literature suggests that there is a relationship between depressive symptoms and brain volume. In this study, 40 participants (male = 6; mean age = 19.5) completed a self-report depression scale (PHQ-9), then were brought in for a structural MRI scan. 20 participants self-reported as having depression while 20 were age-

matched controls. All participants were recruited through the Indiana University Hoosier Brain Project. Voxel-based morphometry was used to compare the differences in grey matter volume in the two groups. Individuals that scored as having major depressive symptoms had a significant increase in grey matter volume in the posterior cingulate cortex (PCC) compared with non-depressed participants. Leech and Sharp (2014) proposed that the PCC plays a role in self-directed cognition, such as recalling memories, and the region has abnormal morphology and functional connectivity in neurological diseases such as Alzheimer's (Zhang & Raichle, 2010). Our results suggest that the PCC may also be affected by major depressive disorder in young adults. Because the PCC may impact self-directed cognition, this decrease in volume may explain why the behavioral manifestations of depression often involve atypically sad or disinterested self-reflection. Future
research should work to further elucidate the relationship between PCC volume and function with depression.

Disclosures: **A. Gutierrez:** A. Employment/Salary (full or part-time): Part-Time. **M. Malaret:** None. **B. Caron:** A. Employment/Salary (full or part-time): Part-Time. **D. Kellar:** None. **S.D. Newman:** None.

Poster

820. Neuroimaging and Behavioral Studies of Depression

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 820.18/WW15

Topic: G.04. Mood Disorders: Depression and Bipolar Disorders

Support: Mental Health Services in the Capital Region of Denmark 2014

Title: Unaffected twins discordant for affective disorders show changes in anterior callosal white matter microstructure

Authors: ***J. MACOVEANU**[1,2], M. VINBERG[1], L. V. KESSING[1], K. MADSEN[2], H. R. SIEBNER[2], W. BAARÉ[2];
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Abstract: Healthy first-degree relatives to patients with major depression (MDD) or bipolar disorder (BD) bear an increased risk to develop affective disorders. Yet, the neurobiological mechanisms mediating this vulnerability remain poorly understood. Both MDD and BD seem associated with abnormalities in the function and structure of specific cortical and subcortical

brain regions. Here we investigated the microstructural properties of white matter fiber tracts facilitating the communication between brain regions implicated in affective disorders in individuals with a familial history of MDD or BD.

Eighty-nine healthy twins with a co-twin diagnosed with MDD or BD (high-risk group) and 57 healthy twins with a co-twin with no familial history of affective disorders (low-risk group) were included. Diffusion tensor imaging was used to measure water diffusivities in cingulum bundle, uncinate fasciculus, anterior limb of the internal capsule, and corpus callosum.

Within a priori hypothesized white matter tracts, the high-risk group showed decreased fractional anisotropy (FA), a directionality measure of water diffusion, and decreased radial diffusivity (RD) in the anterior region of corpus callosum compared to the low-risk group (Figure 1). This abnormality was not associated to zygosity and was independent of subclinical ratings predictive of increased vulnerability for affective disorders such as neuroticism and Hamilton depression scores.

In conclusion, the decreased anterior callosal fiber FA in the high-risk group suggests a deficient interhemispheric communication between left and right frontal cortices that may precede manifestation of clinical symptoms. This finding may act as a vulnerability marker for affective disorders in individuals at familial risk.

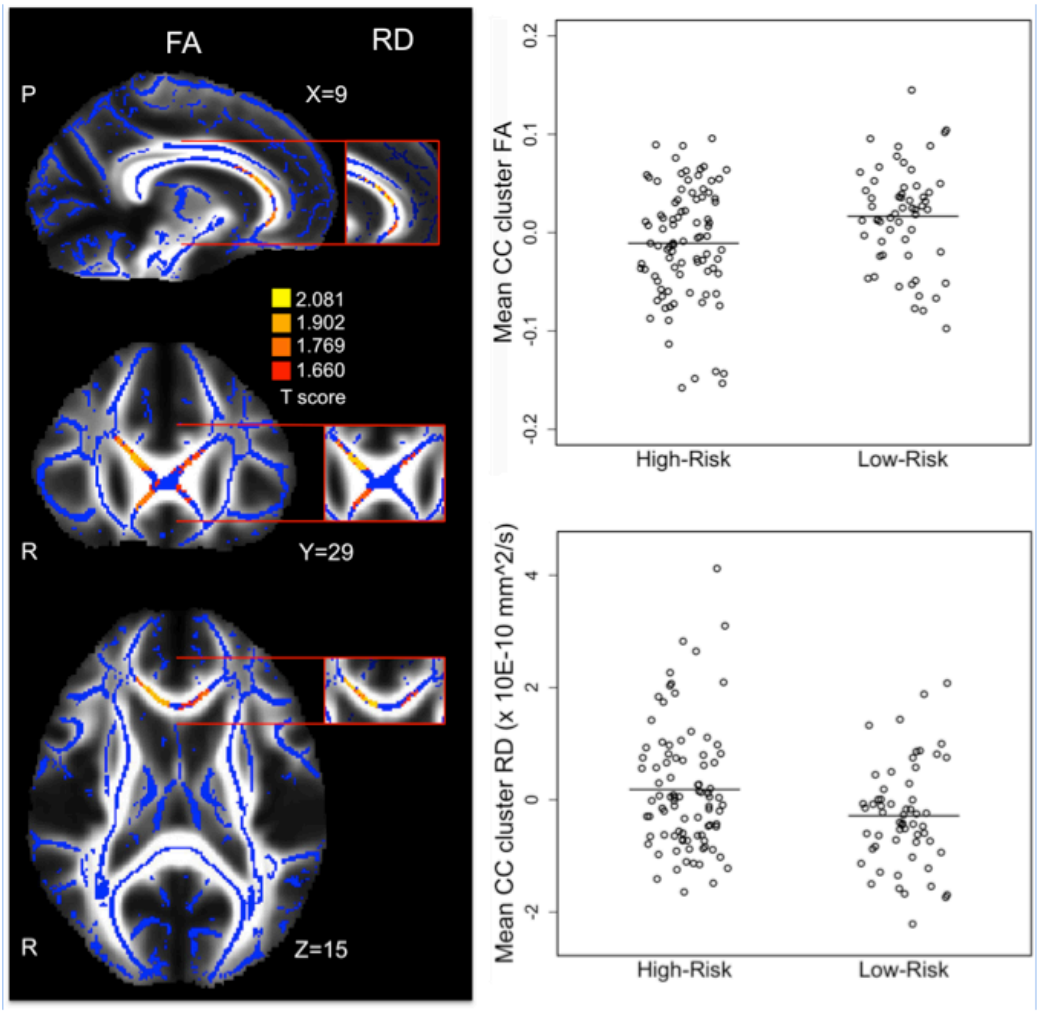

Figure 1. Left panels: Reduced fractional anisotropy (FA) in anterior corpus callosum (corrected $p<0.05$) in high-risk compared to low-risk (red-yellow). The T score corresponds to a p value ranging from 0.05 to 0.02. Insets enclosed in red borders show subregions with increased radial diffusivity (RD) at corrected $p<0.05$. Abbreviations: R – right, P – posterior. Right panels: partial plots of mean corpus callosum (CC) cluster FA and RD adjusted for sex and age.

Disclosures: **J. Macoveanu:** None. **M. Vinberg:** None. **L.V. Kessing:** None. **K. Madsen:** None. **H.R. Siebner:** None. **W. Baaré:** None.

Poster

820. Neuroimaging and Behavioral Studies of Depression

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 820.19/WW16

Topic: G.04. Mood Disorders: Depression and Bipolar Disorders

Support: KAKENHI(No.26350874)

Title: Examining the objectivity of using handwriting characteristics to evaluate the risk of mental health disorders using the clustering method

Authors: *Y. MASHIO[1], N. TANAKA[2], H. KAWAGUCHI[3];
[1]Toyo Univ., Gunma, Japan; [2]Grad. Sch. of Sci. and Engin., Toyo Univ., Saitama, Japan; [3]Grad. Sch. of Life Sci., Toyo Univ., Gunma, Japan

Abstract: Recently, the number of patients with mental health disorders has been increasing. Due to a high recurrence rate of these disorders, there is a pressing need for methods that predict the risk of mental health disorders. Therefore, we investigated handwriting characteristics as a predictor of mental health disorders. A total of 151 students were recruited for a longitudinal study conducted over 4 years. Participants voluntarily completed the Uchida-Kraepelin test and answered the mental health questionnaire GHQ-30. Their handwritings were analyzed using a digital pen that digitizes handwriting with a spatial resolution of 0.3 mm and a temporal resolution of 13 ms. Furthermore, the pen extracted the time intervals between the first and second stroke of a number (specifically the numbers 4, 5, and 7; the mean time interval was designated t1) and those between the completion of writing a number and the initiation of writing the next number (designated t2). We used the ratio of these time intervals to classify participants into high ($t2/t1 \geq 10$) and low mental health risk groups ($t2/t1 < 10$). We found that school absences and dropout rates significantly differed between the groups (odds ratio, 5.9). Thus, our results suggest that the ratio of stroke time intervals (t2/t1) is predictive of the risk of mental health disorders. To further test the utility of this classification method, we divided the participants into two groups using an automatic clustering method. There were significant differences between the two groups in three scales of GHQ-30, similar to that in the case of the ratio ($p < 0.05$). Moreover, the ratio value segregating the two groups calculated using the clustering method was nearly identical to the ratio determined using handwriting characteristics. Therefore, using the clustering method, we confirmed the objectivity of using handwriting characteristics to evaluate individuals for the risk of mental health disorders. The protocols used in this study were approved by the Ethics Committee at Toyo University. This work was supported by KAKENHI (No. 26350874).

Disclosures: **Y. Mashio:** None. **N. Tanaka:** None. **H. Kawaguchi:** None.

Poster

820. Neuroimaging and Behavioral Studies of Depression

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 820.20/WW17

Topic: G.04. Mood Disorders: Depression and Bipolar Disorders

Support: Iris and Junming Le Foundation

APIRE/Janssen Foundation

Mount Sinai Clinical Research Center

NIH Grant UL1TR000067

NARSAD Grant

Title: Habenula responses to reward prediction errors and losses in healthy and depressed individuals

Authors: *B. A. ELY[1], K. E. SIP[5], J. XU[2], D. L. ROSENTHAL[3], W. K. GOODMAN[4], V. GABBAY[4,6], K. A. B. LAPIDUS[7], E. R. STERN[4];
[1]Neurosci., [2]Radiology, Neurosci., [3]Psychiatry, [4]Psychiatry, Neurosci., Icahn Sch. of Med. At Mount Sinai, New York, NY; [5]New York Univ., New York, NY; [6]Nathan S. Kline Inst. for Psychiatric Res., Orangeburg, NY; [7]Northwell Hlth., Great Neck, NY

Abstract: Background: Recent studies suggest that the habenula (Hb), a small nucleus bordering the dorsomedial thalamus, plays an important role in reward processing and major depressive disorder (MDD). The Hb is thought to inhibit dopaminergic reward circuitry in response to reward prediction errors (RPEs, i.e. absence of expected rewards) and losses; elevated Hb activity is associated with depressive phenotypes in rodents and other organisms. Utilizing recent improvements in fMRI acquisition resolution and high spatial fidelity analysis techniques, we examined the Hb and other reward circuitry during RPEs in patients with MDD and healthy controls. **Methods:** Ten healthy controls and five MDD patients to date completed an RPE task (3 x 7min runs) during fMRI on a 3T Skyra with a 32-channel head-coil (2.1mm isotropic resolution, TR=1s). In Run 1 ("reward"), blue cues (2-6s) were always followed by a $0.50 reward (2s). In Runs 2 and 3, 67% of blue cues were followed by a reward while 33% were followed by no reward ("RPE") or a -$0.50 punishment ("loss"), respectively. In all runs, blue cue trials were intermixed with yellow cues that were always followed by no reward ("neutral"). Data were preprocessed via Human Connectome Project pipelines and lightly smoothed (FWHM=3mm). Left and right Hb ROIs were adapted from our recent manuscript (Ely et al, 2016, *HBM*). General linear models were constructed using SPM12 to contrast cues and outcomes within and between MDD and control groups, thresholded at $p<0.005$ (uncorr)

across the whole brain. **Results:** In healthy subjects, losses (Run 3) relative to rewards (Run 1) were associated with activation of the right Hb (small-volume corrected $p<0.001$ within the ROI), bilateral anterior insula, and dorsomedial prefrontal cortex, and deactivation of the ventromedial prefrontal cortex. MDD patients were not significantly different from controls for this comparison. However, MDD patients showed significantly increased activation of the right Hb compared to controls for blue cues in Runs 2 and 3 (small-volume corrected $p\leq0.05$), but not in Run 1. Hb activation for RPEs vs. rewards did not differ significantly in either group. **Conclusions:** Consistent with recent literature, we observed a strong Hb response to losses in healthy subjects. Preliminary group comparisons further revealed greater engagement of the Hb in MDD subjects relative to controls during blue cues only when these cues were occasionally followed by a punishment or lack of reward, but not for unambiguously rewarding cues. These findings appear consistent with the proposed role of the Hb in MDD, which entails negative biases when anticipating uncertain outcomes.

Disclosures: **B.A. Ely:** None. **K.E. Sip:** None. **J. Xu:** None. **D.L. Rosenthal:** None. **W.K. Goodman:** None. **V. Gabbay:** None. **K.A.B. Lapidus:** C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Medtronic. F. Consulting Fees (e.g., advisory boards); Halo Neuro, Inc. **E.R. Stern:** None.

Poster

820. Neuroimaging and Behavioral Studies of Depression

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 820.21/DP07 (Dynamic Poster)

Topic: G.04. Mood Disorders: Depression and Bipolar Disorders

Support: NSFC Grants 81371527, 81030027, 81227002, 81401398, and 81220108013

CPSF Grant 2013M530401

Title: Age effects on brain structural networks in major depressive disorder

Authors: ***T. CHEN**[1], J. WANG[2], X. HUANG[1], Q. GONG[1,3];
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Abstract: Major depressive disorder (MDD) has been associated with disruptions in the topological organization of brain structural and functional networks. However, it remains unclear whether such disruptions was modulated by aging and if so whether the influence of aging on

global or regional network characteristics differs between MDD patients and healthy controls. To address the question, we conducted a cross-sectional design in the present study. 101 patients with MDD (44 never-treated, first-episode patients and 57 treated patients; age range=18-60 years) and 101 age-, gender- and education-matched healthy controls (HCs) (age range=18-59 years) underwent structural magnetic resonance imaging (MRI) using a 3-Tesla scanner. To investigate age associations across an integrated brain network in MDD patients relative to healthy controls, and the relationships between such abnormalities and clinical parameters. We employed a recently developed method to construct single-subject grey matter morphological networks for each subject. Weighted graph-theory based network models were then used to characterize the topological organization of brain networks at global, nodal and connectional levels. Group differences and associations with age were explored. Finally, anomalous topological properties were correlated with Hamilton Depression Scale (HAMD) scores and illness durations in the patients. There were no significant group differences at global metrics. However, we found age-related global metrics in MDD. Specifically, global brain network efficiency measures correlated negatively with age in MDD patients but not in HC groups. In addition, the age-related global efficiency correlated negatively with illness durations in MDD. Age, gender, education level and medication were controlled for by treating them as nuisance covariates. We indicate that single subject grey matter morphological networks are often disrupted in clinically relevant ways in MDD patients. The present findings demonstrate widespread age-related changes in global network properties in MDD. Age-related alterations in brain anatomic network organization suggest alterations in the efficiency of information transfer within brain networks in MDD.

Disclosures: **T. Chen:** None. **J. Wang:** None. **X. Huang:** None. **Q. Gong:** None.

Poster

820. Neuroimaging and Behavioral Studies of Depression

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 820.22/WW18

Topic: G.03. Emotion

Support: National Centre for Mathematics and Interdisciplinary Sciences (NCMIS) of the Chinese Academy of Sciences

Title: The orbitofrontal cortex and depression

Authors: ***E. T. ROLLS**[1], W. CHENG[2], J. QIU[3], W. LIU[2], Y. TANG[2], C. HUANG[4], X. WANG[2], J. ZHANG[2], W. LIN[2], L. ZHENG[2], J. PU[2], S.-J. TSAI[4], A. C. YANG[4], C.-P. LIN[4], F. WANG[2], P. XIE[2], J. FENG[5];

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Abstract: We report the first brain-wide voxel-level resting state functional-connectivity neuroimaging analysis of depression with 421 patients with major depressive disorder and 488 controls. In this investigation, the analyses are described at the level of single voxels.
One major circuit with altered functional connectivity involved the medial orbitofrontal cortex BA 13, which is implicated in reward, and which had reduced functional connectivity in depression with memory systems in the parahippocampal gyrus and medial temporal lobe. The lateral orbitofrontal cortex BA 47/12, involved in non-reward and punishing events, did not have this reduced functional connectivity with memory systems, so that there is an imbalance in depression towards decreased reward-related memory system functionality.
A second major circuit involving the lateral orbitofrontal cortex BA 47/12 had increased functional connectivity with the precuneus, the angular gyrus, and the temporal visual cortex BA 21. This enhanced functional connectivity of the non-reward/punishment system (BA 47/12) with the precuneus (involved in the sense of self and agency), and the angular gyrus (involved in language) is thus related to the explicit affectively negative sense of the self, and of self-esteem, in depression.
The reduced functional connectivity of the medial orbitofrontal, implicated in reward, with memory systems provides a new way of understanding how memory systems may be biased away from pleasant events in depression. The increased functional connectivity of the lateral orbitofrontal cortex, implicated in non-reward and punishment, with areas of the brain implicated in representing the self, language, and inputs from perceptual systems provides a new way of understanding how unpleasant events, and lowered self-esteem, may be exacerbated in depression.
Relating the changes in cortical connectivity to our understanding of the functions of different parts of the orbitofrontal cortex in emotion helps to provide new insight into the brain changes related to depression. Understanding depression as including overactivity in attractor networks in the lateral orbitofrontal cortex provides new therapeutic approaches to the amelioration of depression.
Rolls,E.T. (2014) Emotion and Decision-Making Explained. Oxford University Press: Oxford.
Rolls,E.T. (2016a) Cerebral Cortex: Principles of Operation. Oxford University Press: Oxford.
Rolls, E. T. (2016b) A non-reward attractor theory of depression.
Rolls, E. T. and Deco, G. (2016) Non-reward neural mechanisms in the orbitofrontal cortex. Cortex.

Disclosures: **E.T. Rolls:** None. **W. Cheng:** None. **J. Qiu:** None. **W. Liu:** None. **Y. Tang:** None. **C. Huang:** None. **X. Wang:** None. **J. Zhang:** None. **W. Lin:** None. **L. Zheng:** None. **J. Pu:** None. **S. Tsai:** None. **A.C. Yang:** None. **C. Lin:** None. **F. Wang:** None. **P. Xie:** None. **J. Feng:** None.

Poster

820. Neuroimaging and Behavioral Studies of Depression

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 820.23/WW19

Topic: B.08. Synaptic Plasticity

Title: Cortical excitability responses to ketamine in patients with treatment-resistant bipolar disorder

Authors: *K. WILLS, A. NUGENT, D. A. LUCKENBAUGH, C. A. ZARATE, Jr;
Natl. Inst. of Mental Hlth., Bethesda, MD

Abstract: Background- Bipolar disorder (BP) has a high rate of treatment resistance (TR), increasing costs in health care treatment and chronic suffering. Clinical evidence shows that the drug ketamine, an N-methyl-D-aspartate receptor antagonist, has rapid anti-depressant effects in individuals with mood disorders. Ketamine increases synaptic glutamate levels, potentially increasing cortical excitability and causing synaptic potentiation. It has previously been shown that subjects with major depressive disorder (MDD) exhibited synaptic potentiation following ketamine if they demonstrated an antidepressant response.
Methods- Sixteen BP patients (age=24-62, 64% female) were enrolled in a double-blind placebo-controlled crossover trial of 0.5 mg/kg IV ketamine vs. saline infusion. Subjects were un-medicated except for lithium or valproate. Diagnoses were confirmed by a clinician using the Structured Clinical Interview for DSM Disorders (SCID). Magnetoencephalographic recordings were made on a 275 channel CTF system at baseline, as well as ~ 5 to 6 hours after both infusions, while patients received tactile stimulation on both index fingers 500 times. Antidepressant response was measured with the Montgomery-Asberg Depression Rating Scale (MADRS) at 60 minutes before and 230 minutes after infusions. MEG was localized to anatomical space using a SAM beamformer, utilizing a model of the head calculated from structural MRI images acquired at 3 Tesla. Localized signals in the 30-50Hz range were averaged across stimulus presentations to reveal stimulus locked gamma responses. Image maps were created for the cumulative power in a window 30-60s post-stimulus, and log-transformed to Talairach space. Mean images across subjects and sessions were created separately for left and right hand stimulation, and the peak voxel in each map was used to define 5mm spheres localized to the motor cortex. Mean power values from the contralateral hemisphere were analyzed using a linear mixed model in SPSS with factors for stimulation and drug session.
Results- Sixteen BP patients were included in the analyses. Stimulation on the left hand yielded significantly higher gamma power in the contralateral motor cortex than stimulation on the right hand ($F=5.048$, $p<.028$). There was no significant effect of scan session or response to ketamine.
Conclusion- Ketamine did not appear to increase cortical excitability in TR BP patients on mood-stabilizer monotherapy, in contrast to prior findings in un-medicated patients with MDD.

While this may be due to the small sample size, valproate has been shown to impact gamma power while lithium's effects on cortical excitability are unknown.

Disclosures: K. Wills: None. **A. Nugent:** A. Employment/Salary (full or part-time): NIMH. **D.A. Luckenbaugh:** A. Employment/Salary (full or part-time): NIMH. **C.A. Zarate:** B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution; NIMH. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Holds a joint patent with the government for ketamine.

Poster

820. Neuroimaging and Behavioral Studies of Depression

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 820.24/WW20

Topic: G.04. Mood Disorders: Depression and Bipolar Disorders

Support: NIH R01 MH094743

Title: Real-time fMRI neurofeedback motivates engagement of cognitive strategies for depression

Authors: *K. E. MACDUFFIE[1], K. C. DICKERSON[2], J. MACINNES[2], K. M. EDDINGTON[3], T. J. STRAUMAN[1], R. ADCOCK[2];
[1]Psychology and Neurosci., [2]Ctr. for Cognitive Neurosci., Duke Univ., Durham, NC; [3]Dept. of Psychology, Univ. of North Carolina at Greensboro, Greensboro, NC

Abstract: Advances in our understanding of neuroplasticity in adulthood have led to conceptualizations of psychotherapy as a learning experience, with the potential to alter brain function and even structure in the treatment of psychiatric disorders. This perspective has not yet been adequately communicated to patients served by psychotherapy, however, who tend to believe that a disorder framed biologically is amenable to medical, rather than psychological treatments. We sought to mend that gap by demonstrating to patients the power of psychotherapy strategies to affect brain activity. 13 patients with a previous diagnosis of depression and a standardized cognitive therapy experience were recruited for a micro-intervention using real-time functional magnetic resonance imaging (rt-fMRI). During the rt-fMRI imaging session, participants recalled negative autobiographical memories or worries to induce a negative mood state, and subsequently used cognitive strategies (learned in therapy or elsewhere) to regulate their mood. Across 20 trials, participants viewed a real-time fMRI signal from an ROI in the

anterior cingulate cortex (ACC). Unlike most rt-fMRI studies, participants here were not instructed to use the neurofeedback to alter their strategies; rather it was used as a salient demonstration of the correspondence between thoughts (negative memories, cognitive strategies) and brain activity. As predicted, ACC neurofeedback during the strategy phase predicted the frequency and efficacy of strategy use four weeks later. These results suggest that the experience of receiving rt-fMRI neurofeedback linking ACC activation to cognitive strategies was a powerful learning experience for participants—one that generalized outside of the experimental context to motivate strategy use weeks later. This study represents an initial attempt to demonstrate to participants a link between their thoughts, mood and neural activity. We argue that such interventions have the potential to shape how individuals relate to their biological systems—their *auto-biology*—with implications for identity, self-efficacy, and behavior.

Disclosures: K.E. Macduffie: None. **K.C. Dickerson:** None. **J. MacInnes:** None. **K.M. Eddington:** None. **T.J. Strauman:** None. **R. Adcock:** None.

Poster

821. Stress and Trauma: Therapeutics

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 821.01/DP08 (Dynamic Poster)

Topic: G.06. Post-traumatic Stress Disorder

Support: US Department of Defense - grant agreement no. W81XWH-11-2-0008.

Mafaat, IDF, I-Core cognitive-studies—Grant Agreement No. 693210

Ministry of Science, Technology and Space, Israel

Title: Amygdala NeuroFeedback reduces military stress vulnerability

Authors: J. N. KEYNAN[1,3], A. COHEN[1], A. DAVIDOV[6], N. GREEN[1,3], G. JACKONT[1], I. PODLIPSKY-KLOVATCH[1], K. GINAT[6], E. FRUCHTER[6], M. CAVAZZA[7], *T. HENDLER[2,3,4,5];
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Abstract: Hyper-activation of the amygdala among a priori healthy individuals prior to military traumatic exposure, has been previously found to predict more severe post-traumatic symptoms following exposure. Pharmacological and behavioral approaches however do not specifically

target the amygdala, possibly explaining the low efficacy of current treatment and preventive approaches. The current study tested whether neurofeedback (NF) training to volitionally down regulate amygdala activity prior to traumatic exposure may facilitate emotion regulation and reduce stress vulnerability among a-priori healthy Israeli soldiers. To enable mobile and accessible training at the soldier's home base we used a recently developed fMRI-Inspired EEG model of amygdala activity, termed the amygdala "electrical finger print" (amyg-EFP). 160 healthy soldiers of combative units were randomly assigned to one of three groups: (a) amyg-EFP (n=80), (b) A/T (n=40) and (c) no-treatment (n=40). The amyg-EFP group trained down regulation of the amyg-EFP, the A/T trained down regulation of alpha (8-12Hz) relative to theta (4-7Hz) and the no-treatment group continued military training as usual with no NF. The assignment to amyg-EFP and A/T was double blinded. Over a period of four weeks, participants underwent six NF session training down regulation of the relevant EEG signal (amyg-EFP or A/T). Before and after training, all participants underwent baseline and outcome measures of emotion regulation and stress vulnerability. Within a month following NF training 60 participants (30 amyg-EFP; 30 control) underwent post training fMRI. Results showed that following NF, only the amyg-EFP group exhibited improved emotion regulation as indicated by an emotional stroop task and lower difficulties in identifying and describing emotions as indicated by the Toronto alexithymia scale. Post training fMRI further demonstrated that relative to the control groups, the amyg-EFP group exhibited lower amygdala reactivity in response to threat cues (fearful facial expressions) and higher functional connectivity of the amygdala with the mPFC possibly indicating adaptive plasticity and reduced stress vulnerability. Together, these results demonstrate the promising potential of amygdala targeted NF as a preventive or early intervention of traumatic stress.

Disclosures: **J.N. Keynan:** None. **A. Cohen:** None. **A. Davidov:** None. **N. Green:** None. **G. Jackont:** None. **I. Podlipsky-Klovatch:** None. **K. Ginat:** None. **E. Fruchter:** None. **M. Cavazza:** None. **T. Hendler:** None.

Poster

821. Stress and Trauma: Therapeutics

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 821.02/WW21

Topic: G.06. Post-traumatic Stress Disorder

Title: Anxiolytic activity and enhancement of fear extinction demonstrated by BNC210 in rodent models translates directly to the clinic in a CCK4-challenge model of panic attack in healthy volunteers.

Authors: *S. M. O'CONNOR, C. J. COLES, J. D. MIKKELSEN;
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Abstract: BNC210 is a negative allosteric modulator of the a7 nicotinic acetylcholine receptor in development for the treatment of anxiety disorders. In the rat elevated plus maze, BNC210 (5-100 mg/kg; p.o.) fully reversed the anxiogenic effects of a CCK-4 injection (0.2 mg/kg; i.p.). To explore whether BNC210 (10, 30 and 100 mg/kg; p.o.) could enhance fear extinction and thus improve recovery from panic attack, a contextual fear conditioning extinction paradigm was used in C56BL6 mice. Freezing behaviour was measured and used as an endpoint for memory and/or the strength of the conditioned stimulus (CS; tone) - unconditioned stimulus (US; shock) association. Following a tone-shock conditioning session, the effect of daily doses of BNC210 on the extinction of freezing behaviour in response to a CS was measured for 6 days. On days 1-3, the CS was presented 10 times, on days 4-6 the CS was presented twice. On Day 1 of extinction, mice treated with 100mg/kg BNC210 froze significantly less to the CS as compared to vehicle-treated mice (70.12 ± 11.21 sec versus 119.10 ± 18.24 sec; $p<0.05$). On Day 2 of extinction, there was a non-significant trend to spend less time freezing to the CS in mice treated with 100 mg/kg BNC210 versus vehicle-treated mice (31.00 ± 7.97 sec versus 60.72 ± 13.22 sec). On day 3, the time spent freezing in response to the CS was similar for all groups; and by days 4, 5 and 6, all animals' freezing was extinguished.
In healthy volunteers, BNC210 has demonstrated anxiolytic activity in a CCK-4 challenge model of panic attack. Compared to placebo, subjects treated with a single dose of BNC210 (2000mg; p.o.) experienced a reduction in intensity (52.7%; $p=0.041$) and number (37.7%; $p=0.048$) of panic symptoms assessed on the panic symptoms scale. An emotional Visual Analogue Scale was used to subjectively assess recovery to emotional stability at 5, 10, 20, 30 and 60 minutes following the CCK-4 injection. Subjects treated with BNC210 returned to baseline emotional stability at 5 minutes post injection while the placebo treated subjects achieved baseline stability later at 60 minutes. The clinical effects of BNC210 on anxiety and enhanced recovery of emotional stability following a CCK-induced panic attack, represent direct translation of pre-clinical data to the clinic and indicate the BNC210 may be a useful therapeutic for anxiety disorders such as PTSD where deficits in fear extinction are thought to contribute to this disorder.

Disclosures: **S.M. O'Connor:** A. Employment/Salary (full or part-time): Bionomics. **C.J. Coles:** A. Employment/Salary (full or part-time): Bionomics. **J.D. Mikkelsen:** A. Employment/Salary (full or part-time): Bionomics.

Poster

821. Stress and Trauma: Therapeutics

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 821.03/WW22

Topic: G.06. Post-traumatic Stress Disorder

Support: State of Florida, Senate Education Appropriations

Title: The effect of Jiu Jitsu training on symptoms of PTSD

Authors: *A. E. WILLING[1], R. DEICHERT[3], R. WOOD[4], S. A. GIRLING[5], J. GONZALEZ[6], D. HERNANDEZ[6], E. FORAN[1], K. KIP[2];
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Abstract: Post-traumatic stress disorder (PTSD) is a disabling anxiety disorder that may occur after witnessing a traumatic event. Existing therapies are time-intensive and costly, with an overall success rate that remains relatively low. There is an urgent need for alternative therapies that can effectively help our veterans and service personnel overcome the effects of PTSD and lead fully productive lives as they reintegrate into society. Recent anecdotal evidence suggests that routine practice of Jiu Jitsu, a martial art that focuses on self-defense and control, can reduce psychological and physiological symptoms of PTSD. The purpose of this project was to examine whether Jiu Jitsu effectively reduces symptoms of PTSD among US service members and veterans. For this small pilot study, we screened 29 male U.S. active duty service members and veterans, enrolled 22 and had 9 of them complete a 5 month (40 session) Jiu Jitsu training program. Self-report measures were used to examine changes in PTSD and psychopathology symptoms over the course of the study. In addition, chronic stress was measured by analyzing cortisol concentration from forearm hair samples. Our study participants were predominantly veterans that ranged in age from 22 to 60 (mean = 34.5$\pm$13.1years). Most branches of the service were represented. Sixty-seven percent of the participants enrolled had previously been diagnosed with PTSD and been treated with multiple approaches. Our study participants demonstrated a substantial, clinically meaningful and statistically significant decrease in scores on the PCL-5, our primary instrument for measuring PTSD symptoms and the PTSD subscale of the Psychiatric Diagnostic Screening Questionnaire (PDSQ). In addition, there were significant decreases in global psychopathology, as measured by the PDSQ. Changes in cortisol concentrations were also observed. These preliminary data suggest that Jiu Jitsu training may be a beneficial, cost-effective and easily accessible therapy to assist service members and veterans manage their PTSD symptoms and reintegrate into civilian life.

Disclosures: **A.E. Willing:** None. **R. Deichert:** None. **R. Wood:** None. **S.A. Girling:** None. **J. Gonzalez:** None. **D. Hernandez:** None. **E. Foran:** None. **K. Kip:** None.

Poster

821. Stress and Trauma: Therapeutics

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 821.04/XX1

Topic: G.06. Post-traumatic Stress Disorder

Support: This study is supported by a NARSAD young investigator award to L.D.M.

Title: The effects of Gabapentin and Pregabalin in the consolidation and reconsolidation of auditory threat memory in rats

Authors: *L. DIAZ-MATAIX[1], S. A. SERKA[1], J. E. LEDOUX[1,2];
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Abstract: Exposure to traumatic events is a common experience. Post-Traumatic Stress Disorder (PTSD) symptoms are almost universal in the immediate aftermath of trauma, usually extinguished over time. For some individuals, however, the symptoms persist and cause impairment in functioning, leading to PTSD. Unfortunately, little progress has been made in identifying interventions to help clinicians provide a treatment strategy that can alleviate normal trauma reactions, decreases rates of PTSD or cures this incapacitating disorder.
In daily life, stimuli acquire significance as threats by their association with harmful events, in other words, through Pavlovian conditioning. These conditioned threats elicit automatic reactions called conditioned responses, such as freezing behavior and increased heart rate among others. Auditory Pavlovian Threat Conditioning (PTC) in rats is widely used to study the neurobiology of emotional learning and memory. Moreover, alterations of these processes seem to account for the appearance of PTSD. Actually, drugs that prevent the consolidation or reconsolidation of threat memories are potential targets to respectively prevent or treat PTSD.
Clinical epidemiologists have recently suggested expanding the notion of translational research to include bidirectional bedside to bench epidemiology to inform more tractable interventional approaches. These methods have determined that opioids show a strong evidence supporting a beneficial role in preventing PTSD in animal models. In fact, opiate and the non-opiate analgesics together with benzodiazepines are first-line treatment after acute trauma. Unfortunately, the use of narcotic analgesics may be very problematic (addiction), and it has been suggested that benzodiazepines increases the rate of PTSD development. The search of compounds with combined analgesic and anxiolytic properties but without the undesirable

effects of the opioids or the benzodiazepines, may hold promise as early PTSD-preventive agents.
Gabapentine (GBP) and Pregabalin (PGB) are two drugs that accomplish these properties but their effect in the consolidation and reconsolidation of threat memories is unknown and is the first step to elucidate their potential effect in preventing and/or treating PTSD. Rats treated with GBP or PGB exhibit an impairment in threat memory consolidation and reconsolidation. These preclinical results may represent the first step to acutely treat patients after a trauma with drugs that while inducing little acute side effect, might prevent the development of PTSD. GBP or PGB due to the observed effect in reconsolidating might be also agents to treat PTSD patients

Disclosures: **L. Diaz-Mataix:** None. **S.A. Serka:** None. **J.E. LeDoux:** None.

Poster

821. Stress and Trauma: Therapeutics

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 821.05/XX2

Topic: F.04. Stress and the Brain

Support: NIH Grant MH104603-01

NIH Fellowship F31NS093939

University of Kansas Strategic Initiatives Grant

Title: 5alpha-reductase mediates sensorimotor gating deficits induced by stress

Authors: ***L. J. MOSHER**[1,2], S. C. GODAR[2], M. BORTOLATO[2];
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Abstract: Tourette syndrome (TS) is a neurodevelopmental disorder characterized by repetitive motor and phonic tics. Research has shown that these manifestations are rooted in perceptual deficits, which are typically exacerbated by stress. The best-characterized perceptual deficit in TS affects sensorimotor gating, the function aimed at filtering relevant information. TS patients and animal models exhibit disruptions in the prepulse inhibition of the startle reflex (PPI), an operational index of sensorimotor gating.
The mechanisms whereby stress exacerbates TS symptoms remain incompletely understood. Our group has recently identified that the neurosteroid allopregnanolone (AP), a key mediator of stress response, potentiates tic-like phenomena and causes PPI deficits in animal models of TS. In line with this evidence, we documented that 5α-reductase (5αR), the key rate-limiting enzyme

in the biosynthetic pathway of AP, may be an attractive therapeutic target for TS. Indeed, clinical studies have shown that the prototypical 5αR inhibitor finasteride (FIN) markedly reduces tic severity in adult TS patients; furthermore, in mice, this drug counters the PPI deficits caused by the D1 dopamine agonist SKF 82958.
The synthesis of AP is posited to be mainly contributed by two different subtypes of 5αR, 1 and 2. To further characterize the separate roles of these isoforms with respect to PPI regulation, we tested the effects of SKF 82958 (0.3mg/kg, IP) on the PPI responses of 5αR1 and 5αR2 knockout (KO) mice. SKF induced PPI deficits in 5αR2 KO mice, but not 5αR1 KO mice. Furthermore, the sensitivity to the PPI-disrupting effects of SKF in 5αR1 KO mice was restored by a low dose of AP (3mg/kg, IP), which did not inherently reduce PPI in wild type (WT) mice.
Capitalizing on these findings, our current studies are evaluating whether stress-induced enhancements in AP levels can lead to PPI deficits. We found that following a 4-8 h long restraint, mice displayed significant PPI deficits, which were ablated by FIN (50mg/kg, IP). These data collectively suggest that stress exacerbates TS by increasing the synthesis of AP or other neurosteroids, which may interact with D1 receptor signaling. Future studies will be needed to evaluate the role of 5αR1 in the PPI deficits and tic-related phenomena triggered and/or exacerbated by stress.

Disclosures: **L.J. Mosher:** None. **S.C. Godar:** None. **M. Bortolato:** None.

Poster

821. Stress and Trauma: Therapeutics

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 821.06/XX3

Topic: F.04. Stress and the Brain

Support: CONACYT # 181334 G3

CONACYT # 264697

Title: Early social isolation disrupt neuronal plasticity: cerebrolysin ameliorate the morphological changes.

Authors: ***C. P. SANCHEZ**[1], M. FLORES-JIMÉNEZ[1], S. GUZMÁN-VELÁZQUEZ[2], G. SOLIS[1], M. MÁRQUEZ-PORTILLO[1], J. MENDOZA[1], S. ZAMUDIO[2], C. G. TORIZ[3], G. FLORES[4], I. CAMACHO-ABREGO[4], A. I. MELO[1], J. A. ARELLANO ALAMO[5], S. X. RODRÍGUEZ ROMERO[2];
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de México, Mexico; [4]Inst. de Fisiología, BUAP, Puebla, Mexico; [5]Inst. de Fisiología, BUAP, Puebla, Mexico

Abstract: In our laboratory we are founded that juvenile male rats that suffered partial maternal separation (PMS) or maternal deprivation by artificial rearing (AR) showed a decrease in total dendritic length, dendritic spine number and length of branch-order in medial prefrontal cortex (mPFC) and ventral hippocampus (VH) compared to control rats. However whether these effects are maintained until adulthood remain to be investigated. In order to assess the above possibility, male rat pups were reared in three conditions: 1) by their mother and littermates (MR group), 2) artificially reared (AR group) from postnatal day (pnd) 3 to 22, 3) removed from the nest by 2h/day from pnd 2-14 (PMS group). At pnd 70 brains were removed and stained with the Golgi-Cox procedure and neuronal morphological characteristics of dendrites were studied. The present study found that PMS decreases dendritic length in mPFC neurons and decreases total dendritic length and dendritic spine density in CA1 of VH pyramidal neurons, in comparison to MR. In clear contrast, we only found a decrease in the dendrite length of the neurons of the CA1 of VH in AR animals compared to MR rats. In order to revert the negative effects of early social isolation, rats of the three groups were treated by Cerebrolysin (a neurotrophic peptide mixture; 1.07 mg/kg), or vehicle, from pnd 30 to 58. We found that Cerebrolysin revert some of the negative effects of PMS in mPFC and the CA1 ventral hippocampus neurons. The results suggest that the effects of early social isolation remains until adulthood, and sub-chronic treatment with Cerebrolysin ameliorated some of the neuronal negative effects.

Disclosures: C.P. Sanchez: None. **M. Flores-Jiménez:** None. **S. Guzmán-Velázquez:** None. **G. Solis:** None. **M. Márquez-Portillo:** None. **J. Mendoza:** None. **S. Zamudio:** None. **C.G. Toriz:** None. **G. Flores:** None. **I. Camacho-Abrego:** None. **A.I. Melo:** None. **J.A. Arellano Alamo:** None. **S.X. Rodríguez Romero:** None.

Poster

821. Stress and Trauma: Therapeutics

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 821.07/XX4

Topic: F.04. Stress and the Brain

Title: Effect of modulated signaling by the endocannabinoid anandamide in stress-induced behavior

Authors: M. TEVOSIAN[1], K. RADYUSHKIN[1], N. UEDA[2], D. G. DEUTSCH[3], *B. LUTZ[1]; [1]Univ. Med. Ctr. Mainz, Mainz, Germany; [2]Kagawa Univ. Sch. of Med., Kagawa, Japan; [3]Stony Brook Univ., New York, NY

Abstract: Stress-related mental disorders, such as anxiety and depression, cause enormous personal suffering and large economic and societal costs. The endocannabinoid lipid signaling system is critical to keep the organism resistant to stress and high demands. The cannabinoid type 1 (CB1) receptor and the two major endocannabinoids (anandamide, AEA; and 2-arachidonoyl glycerol, 2-AG) have complex involvements in stress response regulatory processes, such as fear extinction and relief from anxiety. Genetic and pharmacological inhibition of the AEA degradation enzyme fatty acid amide hydrolase (FAAH) leads to enhanced extinction and anxiety reduction under normal conditions and reduces impairments in fear extinction under stressful conditions. AEA also appears to regulate the hypothalamus-pituitary adrenal (HPA) axis. Thus, there are various sources of evidence that AEA is critically involved in stress response regulation. We have generated mice with genetic deficiency of the AEA synthesizing enzyme NAPE-PLD specifically in the nervous system (NAPE-PLD$^{f/f;nestin\text{-}cre,wt}$; called NAPE-KO). The mutant mice showed decreased hippocampal levels of AEA, increased susceptibility to kainic acid-induced seizures, and a significant deficiency in spatial learning, as observed in the Morris Water Maze test. We further aimed at identifying and comparing phenotypes in transgenic mouse lines, where AEA levels are decreased (NAPE-KO) and increased (FAAH-KO; deficiency in the AEA degrading enzyme), respectively, using the social defeat stress paradigm and an established behavioral test battery to monitor consequences of the social defeat. Independent of the genotype, one of the observed stress-induced effects was an increase of body weight and food consumption during the social defeat stress. Furthermore, nesting behavior of the stressed mice showed improved nest building, when tested after 8-10 days after the last episode of stress and compared to unstressed littermates. We have found significant differences in other behaviors, in the social interaction test, light-dark test and in the elevated plus maze. Stressed animals generally show decreased social behavior and increased anxiety. In summary, we discovered that the lack of NAPE-PLD, resulting in decreased AEA signaling, can produce distinct biochemical and behavioral alterations, which under non-stressed conditions are memory impairment and seizure susceptibility. Furthermore, a strong influence of the social defeat stress paradigm on mice behavior was observed, but additional data will have to be acquired in order to understand the possible involvement of AEA signaling in stress resilience.

Disclosures: **M. Tevosian:** None. **K. Radyushkin:** None. **N. Ueda:** None. **D.G. Deutsch:** None. **B. Lutz:** None.

Poster

821. Stress and Trauma: Therapeutics

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 821.08/XX5

Topic: F.04. Stress and the Brain

Support: NIH K01NS079461

Title: Dietary reversal ameliorates high-fat diet induced working and spatial memory deficits early in life

Authors: *C. S. ROBINSON[1,2], E. BRUNO[2], S. JACKSON[2], J. BOGGS[1], E. L. FELDMAN[2]; [1]Neurol., Med. Univ. of South Carolina, Charleston, SC; [2]Neurol., Univ. of Michigan, Ann Arbor, MI

Abstract: Approximately 92 million children and adults are obese. Obesity is associated with a faster decline in cognitive function. A high-fat diet (HFD) is one of the major factors contributing to the current obesity epidemic. A HFD leads insulin resistance, one of the major features of obesity. Modifications to diet and/or weight loss can reverse peripheral insulin resistance and the obese phenotype; however, the reversibility of diet-induced changes in the brain are not known. Hence, the purpose of the following studies are to determine the long-term consequences of a juvenile onset of a HFD on both hippocampal insulin signaling and memory function in C57BL6 (B6) mice. In the current study, at four weeks of age, B6 mice were placed into one three groups based on the diet: a standard diet (control), a HFD, or a HFD for 16 weeks then switched to the standard diet for the remainder of the study (HF_{16}). Hippocampal insulin signaling was evaluated using *ex vivo* insulin stimulation studies. Furthermore, working memory and spatial memory were evaluated using the novel object recognition task and the Morris Water Maze, respectively. Our data demonstrates that HFD-induced peripheral and hippocampal insulin resistance occurs concurrently with deficits in both working and spatial memory. We observed a decrease in downstream hippocampal insulin signaling and insulin receptor expression. The decrease in hippocampal insulin signaling and memory deficits were reversible in the HF_{16} mice with dietary intervention. Interestingly, the HFD-induced decrease in insulin receptor expression in the hippocampus was not reversible. In summary, our results demonstrate that while memory deficits due to the consumption of a HFD at an early age are reversible, the decrease in insulin receptor expression is not. Given that insulin receptor expression decreases with age, it is possible that this phenomenon may be the link between obesity and the increased risk of neurodegenerative disorders. Future studies will evaluate this possibility as well as explore whether memory deficits are reversible with a HFD later in life.
This work was funded by the NIH NINDS K01NS079461.

Disclosures: C.S. Robinson: None. **E. Bruno:** None. **S. Jackson:** None. **J. Boggs:** None. **E.L. Feldman:** None.

Poster

821. Stress and Trauma: Therapeutics

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 821.09/XX6

Topic: F.04. Stress and the Brain

Support: Bezmialem Vakif University Scientific Research Council grant 3.2015/22

Title: Behavioral and molecular effects of perinatal music on rat pups

Authors: *H. YANIK[1], M. BEKER[2], I. KIRPINAR[3], B. ELIBOL[2];
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Abstract: Previous studies on music both on human and non-human animals showed that prenatal music have behavioral, cognitive, and molecular effects on newborn. In this study, effects of music on anxiety, motor coordination, learning and memory, and depression were examined in Wistar albino rats in perinatal period. Wistar albino rat pups were divided into four music groups; control (no music exposure, n=8), classical (Canon in d major/ Johann Pachelbel, n=8), Sufi (Whirling dervish/ Omar Faruk Tekbilek, n=5), and rock (In your face/ Children of Bodom, n=6) music. Mother dams were exposed to music types of their own groups for one hour/day during pregnancy. After giving birth, dams and their pups (male n=13, female n=14) together were exposed to music for one hour/day, till weaning period. After that, dams were discarded from the study and pups were allowed to grow up until their 60th day. On the 63rd day, anxiety, motor coordination, learning & memory, and depression tests were applied on rats, respectively. Data of behavior tests were statistically analyzed. Total oxidative stress, total antioxidant capacity, oxidative stress index, and corticosterone levels were analyzed in the blood serum. This study concludes that rock music group had decreased level of anxiety and depression, and low level of learning and long term memory abilities. Rock music had increased level of corticosterone level compared to Sufi music, as well. Classical music group had increased level of oxidative stress compared to rock music group. Classical and Sufi music groups had increased level of anxiety-like behaviors and depression, however they had increased level of learning and long term memory compared to control group. Sufi music group had high level of anxiety and depression, while having high performance in short term memory ability. It was found that being subjected to different types of music was not related with motor coordination skills in rats. In the side of molecular analysis, no significant difference was found in the total antioxidant capacity and total oxidative stress among experiment groups. This study concluded that exposure to different types of music during perinatal development affects the levels of behavioral parameters differently in rats.

Disclosures: **H. Yanik:** None. **M. Beker:** None. **I. Kirpinar:** None. **B. Elibol:** None.

Poster

821. Stress and Trauma: Therapeutics

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 821.10/XX7

Topic: F.04. Stress and the Brain

Title: Enhanced effect of anti-influenza virus drug on drug-induced abnormal jumping behavior in mice

Authors: *N. ONO;
Res. Unit, Miki Hlth. Sci. Res. Inst., Fukuoka-shi, Japan

Abstract: The relationship of anti-influenza virus drug, oseltamivir phosphate to self-injury and delirium in humans remains unsolved for therapy. We studied drug-induced jumping behavior using mice as a model of abnormality. Mice were placed onto a circular jumping platform that was 28 cm in diameter and 35 cm in height. When a mouse jumped off, it was immediately returned to the platform. The number of jumps was counted for 40 min and the time when a mouse first jumped was recorded. A combined treatment with haloperidol (0.5 mg/kg) and clonidine (10 mg/kg) induced jumping behaviors to some extent. Oseltamivir (50-150 mg/kg) administered orally before the combined haloperidol-clonidine treatments dose-dependently enhanced jumping behavior significantly, although oseltamivir alone did not induce in the jumping behavior. Pretreatment with acetazolamide, diazepam, valprolate, fluoxetine carbamazepine or phentolamine before oseltamivir completely abolished the oseltamivir-stimulated jumping behavior. Oseltamivir may be contributing to jumping behavior under a certain conditions in the central nervous system. Treatment with some drugs may reduce against the risk or other adverse reactions of oseltamivir.

Disclosures: N. Ono: None.

Poster

821. Stress and Trauma: Therapeutics

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 821.11/XX8

Topic: G.06. Post-traumatic Stress Disorder

Support: The Canadian institute of Health Research MOP-42411

Israel academy of science 203622

Title: DNA methylation landscapes of post traumatic stress disorder susceptibility and resilient point to novel therapeutics

Authors: *G. WARHAFTIG[1], N. ZIFMAN[1], C. SOKOLIK[1], O. GABAY[1], R. MASSART[3], T. BARELI[1], H. AHDOOT[1], M. SZYF[3,4], G. YADID[1,2];
[1]The Mina and Everard Goodman Fac. of Life Sci., [2]The Leslie and Susan Gonda (Goldschmied) Multidisciplinary Brain Res. Ctr., Bar-Ilan Univ., Ramat Gan, Israel; [3]Dept. of Pharmacol. & Therapeut., [4]Sackler Program for Epigenetics and Psychobiology, McGill Univ., Montreal, QC, Canada

Abstract: Post-traumatic stress disorder (PTSD) is a trauma- and stress-related disorder that may develop in survivors of a traumatic event, such as a military combat. PTSD can cause intense fear, feeling of helplessness and anhedonia (the inability to experience pleasure or reward). We decided to look into the nucleus accumbens (NAc), a dominant brain region that is related to motivation and hedonia, which is known to be related for reduced reward responsivity in PTSD patients. In addition, since PTSD is characterized as a memory disorder, we were looking to elucidate long-lasting changes in gene expression regulation. One of the mechanisms that control the regulation of genes is an epigenetic mechanism called DNA methylation that was approved in relation to memory formation in the adult hippocampus and in the NAc of addicted rats. In this study we mapped the DNA methylation landscapes in the NAc of susceptibility and resilience using an established rat model for PTSD and a state-of-the-art genome-wide DNA methylation detection technic. Based on the detected DNA methylation patterns of susceptibility and resilience to PTSD and their correlations with PTSD-like symptoms, we have treated susceptible rats with a 'cocktail' of the ubiquitous methyl donor S-adenosylmethionine (SAM) and other food supplements (the formula is in patent application) that attenuated all tested PTSD-like symptoms. These data support the involvement of epigenetic mechanisms in PTSD susceptibility and resilience. In addition, the study suggests a novel approach for therapeutic treatment for PTSD, using a combination of drugs that are directed to distinct pathways that are epigenetically reprogrammed, with the goal of altering expression of genes that will result in attenuating susceptibility to the trauma reminder.

Disclosures: G. Warhaftig: None. **N. Zifman:** None. **C. Sokolik:** None. **O. Gabay:** None. **R. Massart:** None. **T. Bareli:** None. **H. Ahdoot:** None. **M. Szyf:** None. **G. Yadid:** None.

Poster

821. Stress and Trauma: Therapeutics

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 821.12/XX9

Topic: G.06. Post-traumatic Stress Disorder

Support: NRF Korea Grant 2014R1A1A2055960

NRF Korea Grant 2015M3C7A1031395

Title: Characterization of serum derived exosomal RNAs by RNAseq analysis

Authors: *H. KANG, K. CHOI, S. LEE, S. SEOL, E. KIM;
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Abstract: Exosomes are cell derived small vesicles that secreted into biological fluid. As they contain biologically active molecules including small RNAs, exosomes has been suggested that they mediate intracellular communication and provide a microenvironment for the morbidity of disease. Thus, analyzing the altered composition of exosomes may give us critical information for conditions of disease. Posttraumatic Stress Disorder (PTSD) is the most common mental health state in the aftermath of traumatic stress. Hypothalamus pituitary adrenal (HPA) axis regulation has been implicated in the etiology of stress related disorders such as PTSD. The release of glucocorticoids promotes the response for a fight or a flight and binding of glucocorticoid to their receptor (GR) is crucial to terminate the stress reaction via negative feedback. FK506-binding protein 51 (FKBP5) is demonstrated that can lead extended stress response by impaired negative feedback regulation of the HPA axis after binding to the GR. In this study, we investigated the altered exosomal RNAs in the blood of FKBP5 KO mice compared to the WT by employing small RNA sequencing. Further characterization of the responsible small RNA in the serum derived exosomes will provide insight into the GR associated mechanism under the stress and profile for blood based diagnostic biomarkers of human psychiatric disease.

Disclosures: **H. Kang:** None. **K. Choi:** None. **S. Lee:** None. **S. Seol:** None. **E. Kim:** None.

Poster

821. Stress and Trauma: Therapeutics

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 821.13/XX10

Topic: F.04. Stress and the Brain

Support: UCLA Graduate Summer Research Fellowship

Title: Hepatic regulation of homeostatic recovery with glucose intervention following traumatic stress.

Authors: *M. A. CONOSCENTI[1], N. J. SMITH[1], T. R. MINOR[1,2,3,4];
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Abstract: Ingesting a concentrated glucose solution following uncontrollable traumatic stress eliminates the PTSD-like and depression-like behavior that normally develops in rats as a result of the insult. Here we report three experiments that examined the physiological effects of the glucose treatment. Corticosterone (CORT) is the primary glucocorticoid in the rat. The hormone occurs in three forms in blood: 1) free, which is generally considered to be the active form of the steroid; 2) bound to corticosteroid binding globulin (CBG), a high affinity, low-capacity binding molecule that is primarily synthesized in the liver; and 3) bound to albumin, a high-capacity, low-affinity molecule. CORT's primary function is to maintain blood glucose levels in the face of depleted liver glycogen stores by facilitating hepatic gluconeogenesis. Rats were exposed to 100 inescapable tail shock or simple restraint in tubes in three experiments. Each of these stress conditions received free access to water or a concentrated glucose solution for 18 hours immediately following stress to complete a 2 x 2 factorial design. All rats were then exposed to 5 fixed-duration reinstating shocks in a shuttle box before being killed by decapitation. Experiment 1 determined that liver glycogen stores are significantly depleted in rats exposed to traumatic uncontrollable stress relative to control levels. Post-stress glucose replenished liver glycogen stores. Experiment 2 determined that free and total plasma CORT concentrations are significantly elevated relative to control levels in rat exposed to traumatic stress. Post-stress glucose decreased free CORT, without changing the total, suggesting that glucose increased liver synthesis of CBG. A final experiment is in progress, which is accessing activation of the serpinA6 gene in liver in the four groups, which codes for CBG synthesis.

Disclosures: **M.A. Conoscenti:** None. **N.J. Smith:** None. **T.R. Minor:** None.

Poster

821. Stress and Trauma: Therapeutics

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 821.14/XX11

Topic: F.04. Stress and the Brain

Support: PROFOCIE 2015-2017

Title: Anxiolytic effect of Brosimum Alicastrum and its relationship with c-Fos and synaptophysin expression on Wistar rat hippocampus

Authors: *C. R. VUELVAS-OLMOS[1], J. E. MUÑOZ-ALATORRE[1], R. M. GONZÁLEZ-GONZÁLEZ[2], H. PARRA-DELGADO[2], A. L. PERAZA-CAMPOS[2], J. L. COLLÁS-AGUILAR[1], O. GONZÁLEZ-PÉREZ[1], J. GUZMÁN-MUÑIZ[1], N. A. MOY-LÓPEZ[1];
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Abstract: Pathological anxiety is one of the most common mental disorders, and are widely treated with anxiolytics drugs. However, use of ancient traditional medicine and herbal extracts has become a common practice in some Mexican regions, due to empirical knowledge that suggest anxiolytic effects of some plants, for which they are being traditionally used as complementary treatment for disorders associated with anxiety. One of the plants usually consumed for its alleged anxiolytic effects is Brosimum alicastrum (Mojo), which is an arboreal species that is distributed throughout Mexico, and is often taken as an infusion made from the leaves. Because of this, we aimed to analyze the effects of the Brosimum alicastrum aqueous extract on anxiety rate, in relation with c-fos and synaptophysin expression in the hippocampus of Wistar rats. In order to accomplish this, we used 16 male Wistar rats, 8 from control group (CG) and 8 from the experimental group (EG). CG had an oral administration of (1ml/kg) of saline solution, while EG had an oral dose of aqueous extract from the leaf of B. alicastrum (25.63 mg/kg). Both groups were administrated from postnatal 60 (P60) to P66. In P67, anxiety rate was evaluated using the Elevated Plus Maze (EPM), considering the number of open arms entries, total of entries in both arms and time spend in open arms and total. Also Open Field Test (OF) was used to discard any sedative effect. Once behavioral tests ended, brain tissue was obtained to perform synaptophysin and c-Fos immunohistochemistry. Data analysis of EPM showed no significant difference in anxiety rate between groups ($U=21.00$, $p = 0.248$), although EG showed a lower rate in comparison with CG. On the other hand, expression of synaptophysin was significantly lower EG in CA3 ($U=4.00$, $p = 0.028$) and GD ($U=1.00$, $p = 0.004$) hipocampal regions. Similar results were found on c-Fos expression, where EG also had a lower staining in CA3 ($U=0.00$, $p = 0.021$) and GD ($U=0.00$, $p = 0.021$) areas. Considering our results, we found that there is a tendency toward an anxiolytic effect in the group that received the extract. These results indicate that extract from Brosimum alicastrum modifies the neural activity in regions

responsible for regulating anxiety processes, even if this is not directly reflected on behavioral tests. Although, there is a chance for an anxiolytic effect in rats that received the extract, more population and dose-response studies are needed. Finally, presented data partially supports use and traditional beliefs that infusion of Brosimum alicastrum has an effect on anxiety reduction.

Disclosures: **C.R. Vuelvas-Olmos:** None. **J.E. Muñoz-Alatorre:** None. **R.M. González-González:** None. **H. Parra-Delgado:** None. **A.L. Peraza-Campos:** None. **J.L. Collás-Aguilar:** None. **O. González-Pérez:** None. **J. Guzmán-Muñiz:** None. **N.A. Moy-López:** None.

Poster

822. Psychostimulants and Other Drugs of Abuse

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 822.01/XX12

Topic: G.08. Drugs of Abuse and Addiction

Support: NIH Grant P50DA037844

Title: Sensory reinforcement is related to the reinforcing efficacy of food cues, and to locomotor activity during a cocaine conditioned cue preference paradigm.

Authors: *P. MEYER[1], A. M. GEORGE[2], J. A. TRIPI[3], C. D. MARTIN[2], K. ISHIWARI[2], C. P. KING[3], A. A. PALMER[4], J. B. RICHARDS[2];
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Abstract: Drug addiction is associated with a number of traits related to behavioral regulation, including the response to novelty, sensation seeking, and incentive salience attribution to cues. Understanding the relationship between these traits may be important for determining common behavioral and genetic processes involved in predisposition to addiction. As part of an ongoing genome-wide association study of these traits, we tested 500 rats during six behavioral tests. Here, we focus on the light reinforcement task, and characterize how rats with high and low levels of responding behave during Pavlovian conditioned approach (in which a food cue predicts delivery of a food pellet), conditioned reinforcement (in which rats respond for food cue presentations), and cocaine-induced cue preference (in which cocaine is paired with a tactile floor cue). While correlations between tasks were weak (less than $r = 0.2$ in most cases), the top 5% and bottom 5% of responders during the light reinforcement task differed among several measures. For example, high-responders tended to sign-track the food cue and respond more for the food cue during the conditioned reinforcement test, compared to low-responders. In addition, high-responders were more active during the cocaine-induced cue-preference test, including

during trials in which they received saline or cocaine injections. However, there were no consistent differences between high- and low-responders in measures of preference for the cocaine cue. These results suggest that while light reinforcement, conditioned reinforcement, and locomotor activity are only weakly correlated, strong relationships between these tasks are observed when the extreme phenotypes are considered. This raises the possibility that these individuals harbor genetic variants that pleiotropically lead to multiple addiction-related phenotypes. This also highlights the need for characterization of individual differences when determining the relationship between behavioral tasks. Supported by P50DA037844

Disclosures: **P. Meyer:** None. **A.M. George:** None. **J.A. Tripi:** None. **C.D. Martin:** None. **K. Ishiwari:** None. **C.P. King:** None. **A.A. Palmer:** None. **J.B. Richards:** None.

Poster

822. Psychostimulants and Other Drugs of Abuse

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 822.02/XX13

Topic: F.02. Behavioral Neuroendocrinology

Support: NIDA Grant R01-DA032789

Title: Estradiol microinjections to the mPOA increase cocaine-induced conditioned place preference

Authors: *C. L. ROBISON[1], J. R. MARTZ[1], R. G. WILL[1], C. C. RAY[1], J. M. DOMINGUEZ[2]; [2]Psychology, [1]Univ. of Texas at Austin, Austin, TX

Abstract: The medial preoptic area (mPOA) has long been recognized as an integrative site for reproductive behaviors such as copulation and parental care. However, a growing body of research implicates the MPOA in a broader array of reward-associated behaviors, including behavioral and physiological responses to drugs of abuse. Previous studies have shown that bilateral lesions of the mPOA exacerbate conditioned place-prerference (CPP) to cocaine. Furthermore, the microinjection of estradiol into the mPOA increases cocaine-induced release of dopamine in the nucleus accumbens. Here, we demonstrate that the microinjection of estradiol in the mPOA of previously estradiol-primed, ovariectomized female rats results in robust cocaine-induced CPP, greater than that observed in aCSF-injected controls. This further implicates the mPOA as an integrative site for the estrogenic regulation of reward response and in the response to drugs of abuse such as cocaine.

Disclosures: **C.L. Robison:** None. **J.R. Martz:** None. **R.G. Will:** None. **C.C. Ray:** None. **J.M. Dominguez:** B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution; NIDA R01-DA032789.

Poster

822. Psychostimulants and Other Drugs of Abuse

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 822.03/XX14

Topic: G.08. Drugs of Abuse and Addiction

Support: NIH Grant GM083883

NIH Grant DA033877

NIH Grant GM100829

Title: Ontogeny of cocaine pharmacokinetics

Authors: ***M. A. MOHD-YUSOF**, D. E. HUMPHREY, A. T. QUIROZ, C. P. PLANT, C. A. CRAWFORD, S. A. MCDOUGALL;
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Abstract: Cocaine differentially affects the behavior of rats across ontogeny. For example, multiple authors have reported that preweanling rats are more sensitive to the locomotor activating effects of cocaine than adult rats, while adolescent rats are often hypoactive. These behavioral differences are typically ascribed to age-dependent maturational changes in the neural mechanisms (e.g., receptor numbers, transporter efficacy, etc.) mediating behavior. Seldom do researchers consider drug pharmacokinetic factors when explaining age-dependent differences in drug responsiveness. The purpose of this project was to measure cocaine half-life and peak cocaine levels in the dorsal striatum of preweanling, adolescent, and adult rats. To this end, male and female rats were injected intraperitoneally with 15 mg/kg cocaine on postnatal day (PD) 5, 10, 15, 20, 35, or 70. To examine the impact of route of administration, separate groups of PD 20 rats received subcutaneous injections of 15 mg/kg cocaine. Rats were killed at ten different time points (0-210 min) after cocaine treatment, and the dorsal striatum was dissected bilaterally on an ice-cold dissection plate and stored at -80 °C. Dorsal striatal cocaine levels were later quantified using HPLC-UV. Results showed that peak cocaine concentrations in the dorsal striatum increased linearly according to age, with peak cocaine values being significantly greater at PD 70 (4.18 µg/g wet wgt tissue) than at PD 5 (2.02 µg/g wet wgt tissue). The one exception

involved adolescent rats, as peak cocaine concentrations at PD 35 (1.75 µg/g wet wgt tissue) were significantly lower than in younger (PD 20) or older (PD 70) age groups. Cocaine half-life values declined in a progressive manner as age increased. Among rats injected intraperitoneally with 15 mg/kg cocaine, drug half-life was significantly greater at PD 5 (80.7 min) and PD 10 (71.3 min) than at PD 70 (36.5 min). Not surprisingly, the intraperitoneal route of administration produced greater peak cocaine values and a shorter half-life than subcutaneous injections. Drug injection volume (2 vs. 5 ml/kg) did not affect half-life or peak cocaine values. In conclusion, cocaine pharmacokinetics differs substantially across early ontogeny. It is likely that maturational changes in drug pharmacokinetics (e.g., peak values in brain and half-life) are at least partially responsible for some of the age-dependent differences in the behavioral response to cocaine.

Disclosures: **M.A. Mohd-Yusof:** None. **D.E. Humphrey:** None. **A.T. Quiroz:** None. **C.P. Plant:** None. **C.A. Crawford:** None. **S.A. McDougall:** None.

Poster

822. Psychostimulants and Other Drugs of Abuse

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 822.04/XX15

Topic: G.08. Drugs of Abuse and Addiction

Support: PICT 2012-0924, Foncyt, Argentina

PICT-2012-1769, Foncyt, Argentina

UBACYT 2014-2017 #20120130101305BA , Argentina

NIH award P20 GM103425

Title: Central and peripheral inflammatory responses associated with caffeine and cocaine administration in mice.

Authors: J. MUNIZ[1], B. GONZALEZ[1], J.-L. CADET[3], E. GARCIA-RILL[4], F. J. URBANO[5], *V. BISAGNO[2];
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Abstract: Cocaine is often used in combination with other psychostimulants like caffeine. Caffeine is also a common adulterant of seized regular cocaine samples or samples of “coca

paste" (an inexpensive by-product of processing raw coca leaf into cocaine). Thus, this study was aimed to investigate potential toxic effects of combined intake of caffeine and cocaine in mice. Male C57/BL-6 mice were treated with Cocaine-Coc- (10 mg/kg), Caffeine -Caf- (5mg/kg), their combination (Caf-Coc) (10 mg/kg Coc + 5 mg/kg Caf) or vehicle (Veh), in an intermittent binge protocol (3 i.p. injections, 1 h apart, one day on/off for 13 days). We investigated astroglial activation (by GFAP immunostaining) in some areas of the CNS (Ventral and Dorsal Striatum and Motor Cortex, M1) that are involved in reward and motor functions. In addition, we performed histopathological analysis on several organs: lung, heart, liver and kidney tissues (by H&E stain). Histopathological examinations (from tissue extracted 24 hours after chronic treatments) showed increased liver inflammation (hepatitis and/or hepatosis) in all psychostimulant-treated groups, however the group that received the combination of Caf-Coc was the only group that presented severe hepatitis and necrosis. Caf or Coc treatments used in this study did not induce signs of histopathology or inflammation in any of the other organs tested.Astrocytes are major contributors to synaptic plasticity induced by drugs of abuse and can react to various insults rapidly, leading to astrogliosis. In the present study, Coc, Caf and Caf-Coc groups showed significantly higher count of GFAP-positive astrocytes in the Dorsal Striatum (compared to Veh values) and the group that received both psychostimulants combined showed significantly higher number of GFAP-astrocytes compared to any other group. This effect decreased after a withdrawal period of seven days. We are currently measuring astrogliosis on the Ventral Striatum or M1 to clarify if increments in activated astroglia mediated by psychostimulants are area-dependent or part of a generalized inflammatory response.While caffeine have shown neuroprotective properties in neurotoxin models of Parkinson's Disease, we did not find any protective effect induced by caffeine on cocaine-mediated alterations either at the CNS or peripherally. Moreover, our findings involving low intermittent caffeine doses suggest additive inflammatory responses of cocaine and caffeine on CNS and peripheral organs.

Disclosures: **J. Muniz:** None. **B. Gonzalez:** None. **J. Cadet:** None. **E. Garcia-Rill:** None. **F.J. Urbano:** None. **V. Bisagno:** None.

Poster

822. Psychostimulants and Other Drugs of Abuse

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 822.05/XX16

Topic: G.08. Drugs of Abuse and Addiction

Support: The Jackson Laboratory

NIDA R01 DA037927

NIDA Drug Supply Program

Cancer Center Core Grant CA034196

NIGMS P50 GM076468

Title: Assessing genetic mechanisms of intravenous cocaine self-administration and novelty-related behaviors using the Diversity Outbred mouse population

Authors: *P. E. DICKSON, T. WILCOX, T. A. ROY, E. J. CHESLER;
The Jackson Lab., Bar Harbor, ME

Abstract: Preference for and reaction to novelty are associated with substance use disorders in humans. However, the genetic variants and molecular mechanisms underlying these phenomena are largely unknown. Although the relationship between novelty- and addiction-related traits has been observed in mice and rats, the majority of these studies have been conducted in populations with limited genetic variation and precision. Thus, the extent to which novelty-related traits predict addiction-related traits through a common biological mechanism is largely unknown. We examined the relationship between intravenous cocaine self-administration and multiple novelty-related traits in Diversity Outbred (DO) mice, a recently developed high-resolution genetic mapping population possessing high allelic and phenotypic diversity. The DO was derived from an intercross of eight mouse strains consisting of five commonly used strains derived from the earliest laboratory strains (A/J, C57BL/6J, 129S1/SvImJ, NOD/LtJ, and NZO/HILtJ) and three wild-derived strains (CAST/EiJ, PWK/PhJ, and WSB/EiJ). The DO offers advantages over commonly used experimental populations such as (1) substantially increased genetic diversity compared to classical laboratory mouse strains, (2) high behavioral diversity, (3) high-precision quantitative trait locus (QTL) mapping of behaviors, and (4) reduced linkage disequilibrium enabling dissociation of relationships caused by true pleiotropic effects from those secondary to genetic linkage. Moreover, DO mice are outbred, providing a tremendous source of novel allelic combinations, the potential for high sample size mapping studies, and restoration of the broad and continuous range of behavioral phenotypes which were constrained in the derivation of common mouse resources. This expanded range of variation enables detection of variation and covariation not typically observed in laboratory mice. DO mice of both sexes were tested on open field exploration, hole board exploration, and novelty preference followed by cocaine IVSA. These data were examined for behavioral QTL, behavioral covariation, and sex effects. The high genetic precision and phenotypic diversity in the DO will facilitate discovery of the biological mechanisms driving addiction disorders.

Disclosures: **P.E. Dickson:** None. **T. Wilcox:** None. **T.A. Roy:** None. **E.J. Chesler:** None.

Poster

822. Psychostimulants and Other Drugs of Abuse

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 822.06/XX17

Topic: G.08. Drugs of Abuse and Addiction

Support: PICT 2012-0924 - Argentina

PICT-2014-2499 - Argentina

NIH award P20 GM103425 to UAMS, USA

Title: Epigenetic alterations in the mouse testis after chronic cocaine administration: potential involvement in transgenerational cocaine-induced phenotypes

Authors: *B. GONZALEZ[1], J. A. MUÑIZ[1], J. CADET[2], E. GARCIA-RILL[3], F. J. URBANO[4], A. VITULLO[5], V. BISAGNO[1], C. GONZALEZ[5];
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Abstract: There is growing evidence of epigenetic mechanisms contributing to the transgenerational transmission of stress and psychiatric diseases. Regarding paternal transmission, it has been proposed that environmental factors like chronic stress, nutritional status, toxins and drugs of abuse trigger epigenetic mechanisms in the testicular germ line that can lead to variations in offspring's development and behavior. Chronic psychostimulant intake also causes epigenetic changes and toxic consequences not only in dopaminergic brain areas but in peripheral organs as well, including the testis. The mechanisms by which the parental experience influences their offspring are poorly understood, but a reprogramming of testicular germ cells seems to be central to this process. In the present study, we measured epigenetic and functional markers in testis of adult mice treated with cocaine (Coc - 10 mg/kg) compared to vehicle (Veh), in an intermittent binge protocol (3 i.p. injections, 1 h apart, one day on/off for 13 days). Mice were euthanized on day 14. We have previously shown that this Coc administration protocol induced testicular germ cell loss together with increased ROS species (González et al., PLoS One. 2015 doi: 10.1371/journal.pone.0142713). Importantly, toxicity occurred in parallel with testicular dopaminergic system dysregulation: Coc induced increased tyrosine hydroxilase expression and dopamine receptors Drd1 and Drd2 downregulation, similarly to Coc effects in CNS. In the present study, we found that Coc treatment caused a decreased in histone deacethylases HDAC1 and HDAC2 mRNA and protein expression and a concomitant increase in

global histone 3 acetylation (H3ac), and no changes in global histone 4 acetylation (H4ac). We also found decreased Hdac3, Hdac8, Tet1 and Tet3, and increased Tet2 and Dnmt3a mRNA expression after Coc. We found no changes in Dnmt1 and Mecp2 among treatments. This data indicates that chronic Coc induce changes in markers associated with H3 acetylation and DNA methylation/hydroximetylation events in testicular cells. Our results further support that cocaine abuse can induce epigenetic changes in different cell types of the testis, that could lead to germ cells reprogramming affecting individuals from next generation.

Disclosures: **B. Gonzalez:** None. **J.A. Muñiz:** None. **J. Cadet:** None. **E. Garcia-Rill:** None. **F.J. Urbano:** None. **A. Vitullo:** None. **V. Bisagno:** None. **C. Gonzalez:** None.

Poster

822. Psychostimulants and Other Drugs of Abuse

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 822.07/XX18

Topic: G.08. Drugs of Abuse and Addiction

Support: 1R01DA037327

Title: Heritability of cocaine-conditioned avoidance behavior

Authors: M. EID[1], D. PULLMANN[1], P. VENTO[1], *T. C. JHOU[2];
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Abstract: Although cocaine is powerfully rewarding, only a fraction of drug exposed individuals actually transition to become drug-dependent users. The effects of cocaine result from an interplay between a rewarding component and an aversive component. Indeed, several studies have demonstrated that single infusions of cocaine produce aversive effects starting 15 minutes after infusion, when the rewarding effects have dissipated. While cocaine's rewarding effects have been studied for decades, its aversive component has been investigated to a lesser extent. The crash that results from aversion can, however, be extremely powerful; it is sufficient to condition a net aversion to cocaine that can overcome the drug's rewarding effects. Thus the factors that drive progression into drug dependence are numerous and still not clearly understood. There is growing evidence that vulnerability to addiction is partly influenced by heritable factors. Because animal models are crucial tools in elucidating these factors, we investigated behavioral responses to cocaine in rats performing a runway operant task that is particularly suited for assessing the combined rewarding and aversive properties of cocaine. In this task, developed by Ettenberg and colleagues, rats traverse a 5-foot long corridor to obtain a single daily dose of cocaine. After 4-7 trials, we found wide individual variation in cocaine

avoidance behavior in several groups of rats, including large significant differences between two inbred rat strains (Brown Norway vs Buffalo), suggesting a heritable component. To further test whether this behavior is heritable, we also examined an outbred strain (Sprague-Dawley), in which we had also noted wide individual variation in cocaine avoidance behavior. We selected breeding pairs having the highest and lowest latencies to obtain cocaine on the runway task. We bred two lines: a "low cocaine-avoidance" (LA) line, and a high avoidance (HA) line. In performing our selection, we also controlled for other behaviors known to influence cocaine seeking and taking such as locomotor response to novelty. We observed that the offspring Sprague-Dawley show a strong response to selective pressure, resulting in narrow-sense heritability. We seek to replicate and extend this result with NIH Heterogeneous Stock (HS) rats, which will allow further characterization of this trait both behaviorally and genetically.

Disclosures: M. Eid: None. **D. Pullmann:** None. **P. Vento:** None. **T.C. Jhou:** None.

Poster

822. Psychostimulants and Other Drugs of Abuse

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 822.08/XX19

Topic: G.08. Drugs of Abuse and Addiction

Support: EPS0814442

P20 GM104360

Title: Transgenerational effects of embryonic cocaine exposure in zebrafish.

Authors: C. A. BOYLE[1], A. SCHEIDEGGER[2], *T. DARLAND[1];
[1]Biol., Univ. of North Dakota, Grand Forks, ND; [2]Univ. of North Dakota Sch. of Med. and Hlth. Sci., Grand Forks, ND

Abstract: Cocaine addiction has both genetic and environmentally driven components. Relatively recently several groups have suggested that epigenetic regulation of gene expression might be the mechanism linking environmental influence and inheritance in drug addiction. We have shown previously that embryonic cocaine exposure increases physiological and behavioral sensitivity to the drug in longitudinal adults. In this study, we provide evidence that the effects of embryonic pre-exposure to cocaine are transgenerational in zebrafish. In addition, we show how gene expression in the zebrafish telencephalon, which includes the teleost equivalent of the nucleus accumbens, changes during acute cocaine treatment during behavioral testing. These experiments outline gene expression pathways not extensively studied in the context of cocaine

response. We show how embryonic exposure to cocaine affects these gene expression pathways when the longitudinal animals are acutely exposed. Finally, we show how chronic embryonic exposure affects these same gene expression pathways in 5-day old embryos.

Disclosures: C.A. Boyle: None. **A. Scheidegger:** None. **T. Darland:** None.

Poster

822. Psychostimulants and Other Drugs of Abuse

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 822.09/XX20

Topic: G.08. Drugs of Abuse and Addiction

Support: P50DA037844

Title: Cadherin 13 (Cdh13) gene deletion alters reinstatement and instrumental responding for intravenous cocaine.

Authors: *C. P. KING[1], N. P. ROBERSON[1], C. L. VERSAGGI[1], A. A. PALMER[2], P. J. MEYER[1];
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Abstract: Human genome-wide association studies have suggested that variation at the Cadherin-13 (*CDH13*) gene locus can alter susceptibility to a variety of behavioral disorders including substance use disorder and attention-deficit hyperactivity disorder. To examine whether *Cdh13* can produce similar behavioral effects in rodent models of substance use disorder, we examined whether *Cdh13* knockout rats would show differences in operant self-administration of cocaine when compared to heterozygous and wild-type subjects.
A *Cdh13* knockout line (n =37) of Dahl salt-sensitive rats were implanted with jugular catheters and then trained to self-administer a 0.2mg/kg/infusion dose of cocaine across 10 sessions with increasing infusion criteria (10, 20, and 40 infusions per session). Each infusion of cocaine was paired with presentation of a visual light stimulus. Following acquisition, rats were then tested for responding during 2 sessions of a progressive ratio task at two doses (0.2 mg/kg/infusion; 0.5 mg/kg/infusion), in which within-session requirements for cocaine reinforcement were gradually escalated following each reinforcement. Subjects were then re-established at an FR1 schedule over 4 sessions, and then extinguished over 8 sessions in which cocaine and cocaine cues were removed. Subjects were lastly tested for cue-induced reinstatement of responding for cocaine to ascertain relapse behavior.
Knockout and heterozygous subjects showed greater responding during the cue-induced

reinstatement and progressive-ratio tests compared to wild-type and saline controls. However, there were no differences in rate of drug-taking when self-administering on an FR1 schedule, nor were there differences in rate of extinction following removal of the drug. These data suggest that rodents with either reduced or absent *Cdh13* function will show increased drug-directed behaviors in an experimental setting. In humans, this suggests that the association between *CDH13* and substance use disorder may be influenced by alterations the motivational effects of self-administered psychomotor stimulant drugs between individuals, thus increasing the risk of relapse in the face of drug cues.

Disclosures: C.P. King: None. **N.P. Roberson:** None. **C.L. Versaggi:** None. **A.A. Palmer:** None. **P.J. Meyer:** None.

Poster

822. Psychostimulants and Other Drugs of Abuse

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 822.10/XX21

Topic: G.08. Drugs of Abuse and Addiction

Title: The impact of abstinence from methamphetamine on brain metabolites

Authors: *A. BURGER, S. BROOKS, D. J. STEIN, F. M. HOWELLS;
Univ. of Cape Town, Cape Town, South Africa

Abstract: *Background:* Methamphetamine (MA) use has become a global health concern. ^{1}H-MRS studies on MA use have reported decreased *n*-acetyl-aspartate metabolites, and choline metabolites, indicating decreased neuronal integrity and viability as well as decreased synthesis and degradation of cellular membranes. To the authors' knowledge, there are no studies investigating the change in metabolites from acute (<2 weeks) to short-term (<6 weeks) abstinence in MA abusers using ^{1}H-MRS. This study aimed to evaluate the relationship between MA use and neurometabolites to further understand the impact of MA and MA abstinence on cortical brain metabolites. *Methods:* Adult participants with a history of MA dependence (n = 31) and healthy controls (n = 22) were recruited and underwent 2D-chemical shift ^{1}H-MRS imaging (TR 2000ms, TE 30ms). The 2D-chemical shift imaging slice included voxels from bilateral anterior cingulate (ACC), frontal white matter (FWM), and dorsolateral prefrontal cortices (DLPFC). Control participants were scanned once. The MA dependence group was scanned twice, i) after acute MA abstinence (1.5±0.6 weeks, n=31) and ii) after short-term MA abstinence (5.1±0.8 weeks, n=22). The change in metabolites over time in MA abstinence was also investigated (n = 19). Metabolite concentrations, relative to Cr+PCr, of interest were *n*-acetyl-aspartate (NAA), *n*-acetyl-aspartate with *n*-acetyl-aspartyl-glutamate (NAA+NAAG),

glutamate (Glu), glutamate with glutamine (Glu+Gln), *myo*-inositol (Ins), and glycerophosphocholine with phosphocholine (GPC+PCh). *Results:* The results from this study show that MA abstinence results in decreased neuronal integrity, i.e. decreased NAA and NAA+NAAG, in cortical tissues in the left DLPFC, FWM and right ACC, as well as decreased synthesis and degradation of cellular membranes, i.e. decreased GPC+PCh in the left FWM. Further, in short-term abstinence there was evidence of neuroinflammation, i.e. decreased NAA and NAA+NAAG and increased Ins, within the right ACC. *Conclusion:* The present study shows damage to neuronal integrity in acute abstinence, persisting into short-term abstinence - and is accompanied by neuroinflammation. This is the first ^{1}H-MRS study to report the development of neuroinflammation with MA abstinence, and provides insight for the development of early intervention strategies. *Conflict of interest declaration:* The authors declare no conflict of interest.

Disclosures: **A. Burger:** None. **S. Brooks:** None. **D.J. Stein:** None. **F.M. Howells:** None.

Poster

822. Psychostimulants and Other Drugs of Abuse

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 822.11/XX22

Topic: G.08. Drugs of Abuse and Addiction

Support: NIDA/IRP

Title: Monitoring methamphetamine-induced calcium dysregulation in the endoplasmic reticulum in rat brain

Authors: *S. BÄCK, P. KOIVULA, J. NECARSULMER, B. K. HARVEY;
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Abstract: The endoplasmic reticulum (ER) is essential not only for proper protein folding and protein homeostasis, but it serves as an important regulator of intracellular calcium. Dysregulation of ER calcium can result in ER stress and activation of the unfolded protein response which works to restore ER homeostasis. However, in conditions of prolonged and severe ER stress, these actions may not be sufficient to reverse the stress, and the cell will die. We have developed a *Gaussia* luciferase-linked secreted ER calcium modulated protein (GLuc-SERCaMP) that is retained within the ER under physiological conditions, but is secreted in response to a decrease in ER calcium. By monitoring the GLuc activity in the extracellular fluid, we are able to track ER calcium dysregulation. Here we provide evidence that GLuc-SERCaMP can be monitored in cerebral spinal fluid (CSF) to detect ER calcium dysregulation in the rat

brain.
Long-Evans rats received bilateral intracerebral injections of AAV1 vectors expressing GLuc-SERCaMP. Starting from two weeks post-injection, CSF was withdrawn from the rat cisterna magna at three time points and a baseline of GLuc-SERCaMP activity was determined. Four weeks after AAV transduction, rats were challenged with four injections of methamphetamine given with 2 hour intervals. At various time points after methamphetamine treatment, CSF was again withdrawn and GLuc-SERCaMP was measured to assess neuronal ER calcium homeostasis.
Our results show that 1) we are able to detect GLuc-SERCaMP in the CSF after intracerebral AAV vector delivery, and that 2) methamphetamine causes a significant increase in GLuc-SERCaMP in the CSF, indicating ER calcium dysregulation. The methamphetamine-induced dysregulation of ER calcium can be a contributing factor to the well documented neurotoxic changes seen after methamphetamine use. Since dysregulation of ER calcium and ER stress are common features in a wide variety of disorders, we believe that our SERCaMP model, allowing longitudinal monitoring of ER calcium levels, will be a valuable tool in studies of basic pathological mechanisms as well as in the development of novel protective treatments.

Disclosures: S. Bäck: None. **P. Koivula:** None. **J. Necarsulmer:** None. **B.K. Harvey:** None.

Poster

822. Psychostimulants and Other Drugs of Abuse

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 822.12/YY1

Topic: G.08. Drugs of Abuse and Addiction

Support: NIH Grant P50DA037844

Title: Identification of Individual differences in novelty seeking in heterogeneous stock rats.

Authors: *A. M. GEORGE[1], C. D. MARTIN[1], K. ISHIWARI[1], P. J. MEYER[2], A. A. PALMER[3], J. B. RICHARDS[1];
[1]Res. Inst. On Addictions, Buffalo, NY; [2]Psychology, The State Univ. of New York at Buffalo, Buffalo, NY; [3]Psychiatry, UCSD, San Diego, CA

Abstract: Six-hundred and twelve male and female heterogeneous stock (HS) rats were tested on light reinforcement and locomotor procedures. Both of these procedures have been hypothesized to measure individual differences in novelty seeking. We have previously shown that the effectiveness of the light as a reinforcer is related to novelty. The reinforcing effectiveness of the light rapidly habituates with repetition[1]. On average HS rats demonstrated an

initial increase in responding to novel light stimulus reinforcer followed by monotonic decrease in responding as the reinforcing effects of the novel response contingent light habituate. Responding for the novel light reinforcer was associated with locomotor activity in a novel test environment. Linear regression analysis (n = 612) produced small but significant positive correlations between novel light reinforced responding and locomotion [Activity r= 0.083 p=0.039433, Ambulation r=0.150 p=0.000202, rearing r=0.118 p= 0.003459, time in center time r=0.040 p=0.318070].
To further evaluate the individual differences in responding for the novel light reinforcer, the rats were sorted into high and low responders on the light reinforcement task. The 5% of the rats (n=31) that responded at the highest rate for the novel light reinforcer had an accelerating pattern of responding and showed large increases (167%) in responding in comparison to baseline levels. The 5 % of rats (n=31) that responded at the lowest rate for the novel light reinforcer had a decreasing pattern of responding and had a much smaller increase in responding (37%). These differences in the pattern and magnitude of responding indicated that there are large individual differences in the reinforcing effectiveness of the novel response contingent light stimulus. Novel Light onset was stronger reinforcer for female than male rats. There were 8 male and 23 female rats in the high light reinforcer group and 25 males and 6 females in the low light reinforcer group. Comparisons of locomotor activity measures between high and low 5% light reinforcing groups produced highly significant differences in [Ambulation (p = 0.000173) and rearing (p= .00007)] but not activity [(p= 0.107684) or center time (p= 0.105099)]. These results indicate that the light reinforcement procedure may identify extreme high and low novelty seekers in the HS rat population.
1. Lloyd, D.R., Medina, D.J., Hawk, L.W., Fosco, W.D., Richards, J.B., Habituation of Reinforcer Effectiveness. Front Integr Neurosci. 2014 Jan 9;7:107. doi: 10.3389/fnint.2013.00107

Disclosures: **A.M. George:** None. **C.D. Martin:** None. **K. Ishiwari:** None. **P.J. Meyer:** None. **A.A. Palmer:** None. **J.B. Richards:** None.

Poster

822. Psychostimulants and Other Drugs of Abuse

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 822.13/YY2

Topic: G.08. Drugs of Abuse and Addiction

Support: JSPS (KAKENHI) 16K21364

Title: Concurrent development of conditioned place preference and object aversion in place-object compound conditioning with methamphetamine US: Implications for opponent-process theories of drug conditioning

Authors: *Y. KOSAKI;
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Abstract: Current theories on the development of drug addiction emphasise the importance of both instrumental and Pavlovian learning processes. In the current study, I investigated how drug conditioning develops towards different parts of environmental stimuli, in a compound conditioning paradigm.
In Experiment 1, I examined whether drug conditioning with methamphetamine (METH; *i.p.*, 2.0 mg/kg) US reveals overshadowing, a representative cue competition effect. Three groups of C57BL6/J strain mice (n=12 each) were subjected to a modified version of conditioned place preference (CPP) task in which a place cue and a scented object cue formed a compound CS. For Group Overshadow, the drug US was always associated with the same place-object compound CS, whereas a different place-object compound CS was associated with saline injections. For Group Place and Group Object, the US was correlated only with the presence of a particular place and object element, respectively, while the other element was present but uncorrelated with the US. The effect of drug conditioning was assessed separately for place and object elements, in post-conditioning elemental choice tests (i.e., place test and object test) after eight days (4 x CS+ and 4 x CS- trials) and 16 days (8 trials each) of conditioning. In both the first and the second tests, CPP was observed in Group Overshadow and Group Place with the extent of preference being not different between groups, indicating a lack of overshadowing. By contrast, neither Group Object nor Group Overshadow revealed any sign of conditioning accrued to the object in the first test. During the second test, however, both groups revealed a significant conditioned aversion developed to the object from the CS+ compound.
In two subsequent experiments, I sought to identify a condition which supported the development of delayed conditioned aversion to the scented object. In Experiment 2, pairing METH with the scented object alone, in the absence of differential place cues, did not result in the conditioned aversion to the scented object. In Experiment 3, the object and odour cues were separated, and presented in compound with place cues in Group Object and Group Odour, respectively. Pairing the odour-place compound CS with METH US resulted in the delayed acquisition of conditioned aversion to the odour, whereas METH failed to induce conditioned aversion to the unscented object.
The current results suggest that Pavlovian drug conditioning may be mediated by different associative mechanisms from those applicable for conditioning with phasic CSs and natural USs. Implications for opponent-process theories of conditioning and drug addiction are also discussed.

Disclosures: Y. Kosaki: None.

Poster

822. Psychostimulants and Other Drugs of Abuse

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 822.14/YY3

Topic: G.08. Drugs of Abuse and Addiction

Support: University of Toledo

Bath Salts Grant

National Institution on Drug Abuse (NIDA)

Title: Lethal and hyperthermic effects of Synthetic Psychoactive Cathinones

Authors: *O. N. ISSA[1], D. MUSKIEWICZ[1], N. HALL[1], T. OSTING[1], F. RESENDIZ GUTIERREZ[1], F. S. HALL[1], Y.-S. PIAO[2], I. SORA[3];
[1]Pharmacol. and Exptl. Therapeut., Univ. of Toledo, Col. of Pharm. and Phar, Toledo, OH; [2]Geriatrics, Capital Med. Univ., Beijing, China; [3]Psychiatry, Kobe Univ., Kobe, Japan

Abstract: Synthetic psychoactive cathinones (SPCs) are synthetic drugs similar to methamphetamine (METH) and methylenedioxymethamphetamine (MDMA). Increased abuse of SPCs has been reported to be associated with increased risk of overdose and death. SPCs have powerful psychostimulant and hallucinogenic effects, like METH and MDMA, which are thought to underlie their potential for abuse and addiction. Most SPCs are monoamine releasers (amphetamine-like), although some, e.g. 3,4-methylenedioxypyrovalerone (MDPV), are monoamine reuptake blockers (cocaine-like), in both cases acting on dopamine (DA), norepinephrine (NE), and serotonin (5-HT), although the ratio of action differs across SPCs. Most research into the actions of SPCS has examined monoaminergic mechanisms related to the behavioral effects that may underlie their abuse potential. Much less is known about the mechanisms underlying their potential lethal and toxic effects. Our previous study with methylone suggested that DAT may be an important mediator of its lethal effects, which were observed at lower doses than METH or MDMA, and that mechanisms underlying lethality were separate from those mediating hyperthermia. These studies investigated the lethal, toxic and hyperthermic effects of SPCs. The LD_{50} for a single administration of MDPV, METH, and MDMA were determined in C57BL6/J mice. The LD_{50} for MA and MDMA were 84.5 mg/kg IP and 95.7 mg/kg IP, respectively. MDPV did not induce any lethality at does up to 140 mg/kg IP. Preliminary studies of the lethal effects of another SPC, methcathinone, also did not demonstrate any lethal effects at doses up to 140 mg/kg IP. MA, MDMA and MDPV were hyperthermic at most doses, although hypothermia was observed at the highest doses. Moreover, hyperthermia was not associated with
lethality, consistent with previous observations with methylone in which lethality was

substantially reduced in dopamine transporter knockout mice, but not hyperthermia. Importantly, in contrast to the results with MDPV and methcathinone, methylone induced lethality at lower doses than METH or MDMA. Thus, SPCs do not appear to be universally more lethal (at least under the conditions studied here), in contrast to popular representation in the media, and many clinical reports. However, these reports often lack confirming blood toxicology, and use of other drugs that complicate interpretations. The mechanisms underlying these effects are still unknown, and are a subject of current investigations, but these results have implications for the regulation of SPCs as illicit substances, as well as their possible use therapeutically.

Disclosures: O.N. Issa: None. **D. Muskiewicz:** None. **N. Hall:** None. **T. Osting:** None. **F. Resendiz Gutierrez:** None. **F.S. Hall:** None. **Y. Piao:** None. **I. Sora:** None.

Poster

822. Psychostimulants and Other Drugs of Abuse

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 822.15/YY4

Topic: G.08. Drugs of Abuse and Addiction

Support: KAKENHI (20375489, 20659177, 23591671 and 26461716)

Title: NrCAM regulating neural systems in addiction vulnerability

Authors: *H. ISHIGURO[1], T. SAKURAI[2], N. MOTOHASHI[1], E. S. ONAIVI[3];
[1]Univ. of Yamanashi, Chuo, Yamanashi, Japan; [2]Kyoto Univ., Kyoto, Kyoto, Japan; [3]William Paterson Univ., Wayne, NJ

Abstract: We have previously shown that genetic variations associated with decreased NrCAM expression in brain was protective against addiction vulnerability in humans and that *Nrcam* knockout mice did not develop conditioned place preferences for illegal drugs or alcohol. NrCAM was involved in addiction vulnerability, which may involve specific neural circuits underlying behavioral characteristics relevant to addiction, such as novelty seeking, obsessive compulsion and responses to aversive or anxiety-provoking stimuli. We analyzed expression patterns of neural molecules including glutamate and GABAergic regulated by Nrcam and methamphetamine (MAP) treatment in midbrain of *Nrcam* knockout mice, using micro-array gene expression analysis in comparison between wild and heterozygote genotypes, and between treatment with saline and MAP. In our previous study presented in Sfn 2014 conference, glutaminase (GLS) and metabotropic glutamate receptor 2 appeared to be reduced in MAP treated *Nrcam* heterozygote mice, although any difference of its expression was found between genotypes with saline treatment. Also GABAergic molecules were also detected differences in

their expression. The agonists and antagonists were examined for their effects on addiction-related behavior in this study. Slc17a7 was also detected its expression change by treatment of methamphetamine, which had been reported its possible role in neural circuit underlying cocaine and alcohol addiction. We therefore examine the expression change of the gene using TaqMan gene expression analysis in *Nrcam* knockout mice treated with cocaine, alcohol and also morphine in order to demonstrate Nrcam's role in common addiction pathway. In conclusion, NrCAM could affect addiction-related behaviors via at least partially modulation of some glutamatergic and GABAergic pathways and neural function in brain.

Disclosures: H. Ishiguro: None. **T. Sakurai:** None. **N. Motohashi:** None. **E.S. Onaivi:** None.

Poster

822. Psychostimulants and Other Drugs of Abuse

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 822.16/YY5

Topic: G.08. Drugs of Abuse and Addiction

Support: PhRMA Foundation Research Starter Grant

NIDA: DA037426

NIH: T32 NS044928

Title: Drugs of abuse alter SGK1 phosphorylation and activity in the ventral tegmental area

Authors: *M. A. DOYLE[1], V. BALI[2], S. KASKA[3], S. E. COOPER[1], M. S. MAZEI-ROBISON[2];
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Abstract: Drugs of abuse are known to regulate activity of the mesolimbic dopamine system. Specifically, within the ventral tegmental area (VTA) changes in cellular activity and gene regulation caused by drugs of abuse contribute to behavioral outputs that characterize drug seeking and abuse. Previous work from our lab has shown that serum- and glucocorticoid-inducible kinase 1 (SGK1) phosphorylation and catalytic activity are increased by chronic but not acute administration of cocaine and morphine. Increased phosphorylation of SGK1 and its substrate N-myc downstream regulated gene (NDRG) are observed 1 hour, but not at 24 hours, post-injection. However, the functional significance of these changes in drug-related behaviors remains unclear. Our lab has created viral constructs that will be used to mimic or prevent phosphorylation at specific SGK1 residues, and the behavioral relevance of these changes will be

assessed. Specifically, we are investigating the role of phosphorylation at Ser78, which is increased by drugs of abuse, as well as the canonical S422 and T256 sites. We will evaluate voluntary drug intake using a morphine two-bottle choice task, and drug reward via conditioned place preference for both cocaine and morphine. In addition to looking at the effect of SGK1 activity modulation while cocaine and morphine are on board, we are also interested in how VTA SGK1 activity is altered following abstinence and drug re-exposure. To address this question, we injected mice with saline, cocaine, or morphine for 7 days and mice were subjected to 6 days of abstinence before receiving a challenge dose of saline or drug. VTA was microdissected from these animals and processed for western blot analysis. Surprisingly, significant increases in SGK1 phosphorylation were observed in mice with previous drug experience that received saline, but not drug, on challenge day. Future studies will assess whether this change is dependent on drug context and will utilize viral vectors to determine whether changes in VTA SGK1 signaling influence drug seeking or craving. Thus, the goal of these studies is to characterize the role of VTA SGK1 activity in drug-related behaviors to better understand the neuroadaptations that contribute to drug addiction.

Disclosures: M.A. Doyle: None. **V. Bali:** None. **S. Kaska:** None. **S.E. Cooper:** None. **M.S. Mazei-Robison:** None.

Poster

822. Psychostimulants and Other Drugs of Abuse

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 822.17/YY6

Topic: G.08. Drugs of Abuse and Addiction

Support: Dreyfus Health Foundation

Title: Impulsivity and frontal asymmetry in substance-dependent individuals

Authors: *I. BERRIOS-TORRES[1], B. K. RUNDLE[1], M. STANFORD[2], J. H. PATTON[1]; [1]Psychology & Neurosci., Baylor Univ., Waco, TX; [2]Hope & Healing Ctr., Houston, TX

Abstract: Right-frontal cortical activity at rest has been associated with impulsive and aggressive behaviors. Impulsivity has also been shown to play an important role in substance dependence as both an antecedent and consequence of drug use. Past research has suggested that impulsivity is a multi-dimensional construct, with characteristic factors observed throughout different stages of a drug abuse trajectory. The present study sought to investigate frontal asymmetry in impulsive versus not-impulsive substance-dependent individuals receiving rehabilitation treatment. Eighteen male substance-dependent individuals (impulsive = 10)

receiving treatment for at least 21 days were recruited to participate in a resting EEG paradigm to assess frontal cortical activity. Results from a mixed-design ANOVA analysis showed a trend for impulsive individuals towards increased right relative to left frontal cortical activity compared to non-impulsive individuals. This effect was only observed at mid-frontal electrode sites. Results suggest that increased right frontal cortical activity could be associated to impulsivity manifested during the abstinent/rehabilitation stage of drug abuse.

Disclosures: I. Berrios-Torres: None. **B.K. Rundle:** None. **M. Stanford:** B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution; Dreyfus Health Foundation. **J.H. Patton:** None.

Poster

822. Psychostimulants and Other Drugs of Abuse

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 822.18/YY7

Topic: G.08. Drugs of Abuse and Addiction

Support: DA06227

Title: Dysregulated dopamine transporter function associated with alpha-PVP “flakka” abuse and delirium

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Abstract: Synthetic cathinones are derivatives of the designer drugs known as “bath salts”. Alpha-pyrrolidinovalerophenone (alpha-PVP) has become a top-seller cathinone very popular in South Florida. Alpha-PVP or street name “flakka” inhibits dopamine (DAT) and norepinephrine transporters (NET) similar to cocaine, but with a higher potency. Excited delirium syndrome (ExDS) is a controversial disorder that manifests as a combination of delirium, psychomotor agitation, anxiety, hallucinations, speech disturbances, disorientation, violent and bizarre behavior, insensitivity to pain, elevated body temperature, and superhuman strength. It is typically associated with the use of drugs that alter dopamine processing, hyperthermia, and deaths in the custody of law enforcement. Subjects typically die from cardiopulmonary arrest, although the cause is debated. We report here a study of 7 fatal alpha-PVP intoxications in people who presented in a state of excited delirium before death. We measured striatal DAT density in postmortem brain using the cocaine analog [^{3}H]WIN35,428. Saturation analysis of the total radioactivity confirmed significantly lower numbers of DAT binding sites in the

anteroventral striatum of alpha-PVP intoxications compared to age-matched controls (N=7; $p<0.05$). Core body temperatures where reported were markedly elevated in these cases (~ 40.1^{o}C). We measured the expression of heat shock protein 70 (HSP70) in brain as a biomarker of hyperthermia. Heat shock protein gene expression was elevated approximately 3-fold in all cases examined. This case series suggests an association of hyperthermia and striatal DAT dysregulation in alpha-PVP intoxications associated with ExDS. Drug-related excited delirium is most often associated with cocaine abuse and we have previously reported altered dopamine transporter levels in ExDS fatalities (Mash et al., 2002; Mash et al., 2009). The potent dopaminergic actions of alpha-PVP may increase risk for excited delirium and other toxic physiologic effects with recreational use. Supported by DA06227.

Disclosures: **P. Illiano:** None. **S. Garamszegi:** None. **D. Mash:** None.

Poster

822. Psychostimulants and Other Drugs of Abuse

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 822.19/YY8

Topic: G.08. Drugs of Abuse and Addiction

Support: 5 G12 RR 003035-27 (PS)

SC1GM084854-06 (CAJR)

(NSF) OISE-1545803 (CAJR)

Title: The effect of xylazine on the intrinsic excitability of rat prefrontal cortex pyramidal cells

Authors: *P. SANABRIA-RAMIREZ[1], K. COLON[1], N. MOREIRA[2], S. ALEGRE[1], A. FRET[2], J. ROJAS[1], N. BETANCOURT[1], C. A. JIMENEZ-RIVERA[3];
[1]Physiol., Univ. Central Del Caribe, Bayamon, PR; [2]Univ. of Puerto Rico-Bayamon Campus, Bayamon, PR; [3]Physiol., Univ. of Puerto Rico-Medical Sci. Campus, Rio Piedras, PR

Abstract: Xylazine is a veterinary non-opiate sedative that has been used as an adulterant to drugs of abuse in Puerto Rico since early 2000. The potential addiction profile of xylazine is unknown but users have described increased withdrawal symptoms after intravenous use of heroin and xylazine preparations. Currently, little is known of how xylazine acts in the CNS in humans and in particular the prefrontal cortex (PFC). The PFC is an important brain area for decision and working memory, and is also part of the neuronal circuits implicated in the initiation and development of addiction. Evidence in recent years has pointed to significant alterations of intrinsic properties of neurons upon exposure to drugs of abuse. In this study we

tested, using whole-cell recordings, the effects of xylazine on the intrinsic excitability of *ex vivo* pyramidal cells from 300 μm coronal slices of rat medial prefrontal cortex. Layer V pyramidal cells in male and female Sprague-Dawley (100-150g) rat prefrontal cortex were visually identified by their shape and presence of apical dendrites and confirmed by biocytin staining. These pyramidal cells were intentionally targeted because they possess projection fibers to subcortical structures involved in the generation of behavioral responses. Pyramidal cells were injected in current-clamp mode with 1s current pulses from -100 to 350 pA with 50 pA steps, with an intertrial interval of 2 s. Cells were grouped in two major types based on the firing pattern evoked by current stimuli: regular spiking and inactivating burst types. The effect of xylazine was evaluated at 10 and 100 μM. The results showed that 5 min superfusion with xylazine produced an increase in the DC gain of regular spiking neurons as indicated by a increase in action potential frequency (higher f-I slope). This result was not observed for the inactivating burst type cells. Future studies will include assessment of fast, medium and slow afterhyperpolarizations, which are affected by changes in intrinsic excitability. These results constitute the first efforts to understand the effect of this adulterant at the level of the neuronal circuits involved in addiction.

Disclosures: **P. Sanabria-Ramirez:** None. **K. Colon:** None. **N. Moreira:** None. **S. Alegre:** None. **A. Fret:** None. **J. Rojas:** None. **N. Betancourt:** None. **C.A. Jimenez-Rivera:** None.

Poster

822. Psychostimulants and Other Drugs of Abuse

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 822.20/YY9

Topic: G.08. Drugs of Abuse and Addiction

Title: The rewarding and reinforcing effects of the novel ketamine analog methoxetamine in rats: evidence of its abuse potential.

Authors: ***C. D. BOTANAS**[1], J. DE LA PEÑA[1], I. DELA PENA[1], H. KIM[1], Y. LEE[2], J. CHEONG[1];
[1]Pharm., Uimyung Res. Inst. For Neurosci., Seoul, Korea, Republic of; [2]Lab. of Medicinal Chemistry, Sch. of Pharmacy, Kyunghee Univ., Seoul, Korea, Republic of

Abstract: Recently, a growing number of emergency cases due to a novel ketamine analog drug, methoxetamine (MXE), were reported in several countries. However, relatively little is known about the rewarding and reinforcing profiles of this compound. In the present study, we aimed to investigate the rewarding and reinforcing effects of MXE through the conditioned place preference (CPP) and self-administration (SA) paradigms in rats. Locomotor activity during the

conditioning phase of the CPP was also analyzed. In addition, we investigated the role of the dopaminergic and serotonergic system on the rewarding effects of MXE by performing experiments in rats treated with haloperidol (0.2 mg/kg), a dopamine receptor antagonist, and ketanserin (2 mg/kg), a serotonin receptor antagonist, prior to MXE (2.5 mg/kg) conditioning. In all of these experiments, ketamine was used as reference drug. MXE (2.5 and 5 mg/kg) produced CPP in rats, an effect comparable to that of ketamine (5 mg/kg). Intriguingly, MXE did not induce any locomotor alterations while ketamine decreased the locomotor activity of the rats. In the SA test, rats showed modest SA of MXE (0.25, 0.5, 1.0 mg/kg/infusion), while ketamine (0.5 mg/kg/infusion) was robustly self-administered. Haloperidol blocked the acquisition of MXE and ketamine CPP while ketanserin inhibited that of MXE only. These data indicate that MXE, similar to ketamine, has rewarding and reinforcing properties in rats, suggesting that the drug has a potential for abuse. It also shows that the dopaminergic and serotonergic system may play a role in the rewarding effects of MXE. Importantly, this study advocates monitoring and prompt regulation of MXE and its related substances.

Disclosures: C.D. Botanas: None. **J. de la Peña:** None. **I. dela Pena:** None. **H. Kim:** None. **Y. Lee:** None. **J. Cheong:** None.

Poster

823. Drugs of Abuse: Extracellular Matrix and Inflammation

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 823.01/YY10

Topic: G.08. Drugs of Abuse and Addiction

Support: P01-DA008227

Leon Levy Foundation

Title: Role for granulocyte colony stimulating factor in the rewarding effects of cocaine

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Abstract: There is growing evidence showing that dysregulation of the immune system plays a role in the pathophysiology of psychiatric disorders. Recently, evidence has begun to accumulate that cocaine alters immune signaling in ways that may drive pathological use behaviors. In this study we used broad serum profiling to determine which inflammatory proteins are altered by cocaine exposure in rodents, and used those results to interrogate how those proteins modify

behavior. In this initial analysis, serum from animals receiving high dose self- or experimenter-administered cocaine was analyzed for 24 cytokines, chemokines, and growth factors using quantitative multiplex analysis. These analyses demonstrated multiple immune factors that were modulated by cocaine. However, granulocyte colony stimulating factor (G-CSF) was the only factor for which serum levels showed linear correlation with the extent of cocaine locomotor sensitization and levels of cocaine self-administration. To determine if serum levels of G-CSF play a role in behavioral adaptations to cocaine, animals were pre-treated with systemic injections of G-CSF during locomotor sensitization and conditioned place preference (CPP) procedures. G-CSF treated animals showed no differences in baseline locomotor activity or response to acute cocaine injection, but did show significantly enhanced locomotor sensitization to a 7.5mg/kg dose of cocaine. Similarly, treatment with systemic G-CSF during CPP training enhanced the formation of cocaine CPP at lower doses (3.75 & 7.5mg/kg). To determine if systemic administration of G-CSF has direct effects on cocaine-induced neuronal activation, we performed an experiment looking at induction of the immediate early gene *c-Fos* in multiple brain regions of animals treated with acute doses of G-CSF and/or cocaine. We found that animals treated with G-CSF alone had similar levels of *c-Fos* expression to saline only controls in all brain regions examined. Treatment with cocaine produced the expected induction of *c-Fos* in many brain regions. However, treatment with G-CSF and cocaine in combination produced a more robust increase in *c-Fos* in both the nucleus accumbens and prefrontal cortex, but not in other brain regions examined. These experiments provide evidence that alterations in this peripherally derived cytokine play an important role in regulating cocaine-related behaviors and changes in neuronal activation.

Disclosures: D.D. Kiraly: None. **E.S. Calipari:** None. **B. Labonte:** None. **S.J. Russo:** None. **E.J. Nestler:** None.

Poster

823. Drugs of Abuse: Extracellular Matrix and Inflammation

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 823.02/YY11

Topic: G.08. Drugs of Abuse and Addiction

Support: University of Adelaide early career researcher award

Title: Is depressive like behaviour during abstinence from chronic alcohol associated with intestinal permeability and brain immune signalling?

Authors: *J. L. HOLMES[1], M. R. HUTCHINSON[2], F. E. CORRIGAN[1];
[1]Sch. of Med., [2]Univ. of Adelaide, Adelaide, Australia

Abstract: With an ever increasing number of studies implicating inflammatory signalling in psychiatric disorders there is a growing need for animal models that can disentangle inflammatory events that may shape animal behavior. Recent human studies have identified a sub-population of alcoholic patients with altered microbiome and intestinal permeability which is associated with depression during abstinence. Importantly, studies in rodents have shown alcohol induced permeability to be associated with gut bacterial endotoxin being trans-located into the blood, contributing to a peripheral inflammatory response. Therefore, this study has been designed to investigate an animal model that may replicate alcohol induced intestinal permeability and its relationship with depressive-like behavior, with a focus on inflammatory signalling. Individually housed male C57 mice were given access to 10% alcohol in a two bottle choice paradigm for 6 weeks. Following 6 weeks of free access alcohol was removed. Mice were randomly allocated into groups and tested for intestinal permeability and saccharin preference on 0, 1, 4, 7 and 14 days of abstinence. Mice were euthanized 2 hours following the saccharin preference test, brains and serum were collected to characterize central and peripheral immune signalling at various stages of withdrawal. Further, serum will be analysed for presence of gut bacterial derived endotoxin which may enter the circulation due to increased intestinal permeability contributing to both a peripheral inflammatory response and brain cytokine signalling events. This study will identify if intestinal permeability reported in alcoholic subjects can be replicated in a simple rodent model of alcohol drinking. Furthermore, the molecular analysis of serum and brain protein will help characterize inflammatory mechanisms that may contribute to anhedonic behavioural outcome in the saccharin preference test.

Disclosures: J.L. Holmes: None. **M.R. Hutchinson:** None. **F.E. Corrigan:** None.

Poster

823. Drugs of Abuse: Extracellular Matrix and Inflammation

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 823.03/YY12

Topic: G.08. Drugs of Abuse and Addiction

Support: Developmental Exposure Alcohol Research Center Grant P50AA017823

NIA Grant AG043467

Title: Late aging-associated increases in neuroinflammation do not significantly alter induction of neuroimmune genes by acute alcohol intoxication.

Authors: *A. GANO, T. L. DOREMUS-FITZWATER, T. DEAK;
Psychology, Binghamton Univ., Binghamton, NY

Abstract: Natural aging is associated with a transition of the CNS toward an inflamed state, as evidenced by increased signs of microglial activation and cytokine expression. Our recent work has shown that acute ethanol intoxication produces a highly replicable pattern of rapid alterations in neuroimmune gene expression (RANGE) that are characterized by increased IL-6 and IκBα, but decreased IL-1β and TNFα. The following studies tested whether RANGE evoked by acute ethanol would differ as a function of natural aging using a cross sectional design in male and female Fischer (F) 344 rats. To do this, brains (N=48; n=8/group) were harvested 3 or 18 h following acute challenge with saline or ethanol (3.0 g/kg i.p.) to assess cytokine changes during intoxication and withdrawal. Trunk blood was collected for measurement of corticosterone (CORT) and blood ethanol concentrations (BECs). During intoxication, analysis of ethanol-induced RANGE in the hippocampus via real time RT-PCR replicated our prior findings (i.e., increased IL-6 and IκBα; suppressed IL-1β and TNFα). These effects were largely resolved by 18 h and were similar across sex. A subsequent study then assessed RANGE in the hippocampus of male and female F344 rats over a broader age range (3, 9, 18, and 24 mos old) 3 h following an ethanol (3.5 g/kg i.p.) or saline challenge. Once again, no significant sex differences emerged, so further analyses were collapsed across sex. Interestingly, basal increases were observed in several neuroimmune genes, including IL-6, MCP-1, and CD14 in the oldest age groups relative to 3 mo olds. Despite these baseline increases in inflammatory markers during late aging, ethanol-induced RANGE were observed in every age group and were of comparable magnitude across the lifespan. Modest increases in basal CORT were observed in late aging, yet ethanol-induced increases in CORT were comparable across age. BECs ranged from 335-393 mg/dL and generally did not differ by age. Loss of righting reflex (LORR) was assessed and neither latency to achieve LORR, nor LORR duration, differed across age or sex. To the extent that gene expression changes observed as a function of natural aging and alcohol exposure can be used to infer state of inflammation, these findings suggest that neuoroimmune responses evoked by acute alcohol intoxication and withdrawal remain highly consistent across the lifespan, despite increased signs of neuroinflammation that accompany late aging. Ongoing studies are addressing aging-related changes using alternative approaches for the assessment of neuroinflammation (e.g., protein expression, microglial activation), as well as more protracted regimens of ethanol exposure.

Disclosures: **A. Gano:** None. **T.L. Doremus-Fitzwater:** None. **T. Deak:** None.

Poster

823. Drugs of Abuse: Extracellular Matrix and Inflammation

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 823.04/YY13

Topic: G.08. Drugs of Abuse and Addiction

Support: NIH Grant DA007606

Title: Ethanol enhances methamphetamine neurotoxicity: role of inflammation

Authors: *A. L. BLAKER[1,3], S. LIANGPUNSAKUL[2], B. K. YAMAMOTO[1];
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[3]Dept. of Neurosciences, Univ. of Toledo Col. of Med., Toledo, OH

Abstract: Ethanol (EtOH) and methamphetamine (Meth) abuse are highly comorbid; however, the neuropharmacological consequences of this comorbid drug taking behavior are unknown. Individually, each drug causes long-lasting decreases of 5HT and dopamine content in the brain. Since EtOH is known to produce peripheral inflammation, we tested the hypothesis that serial exposure to EtOH and Meth results in an initial proinflammatory response to EtOH in the peripheral circulation that subsequently enhances the depletions of 5HT and dopamine produced by Meth within the brain. Male Sprague Dawley rats were exposed to either one week of EtOH (6g/kg/day) via oral gavage or permitted intermittent voluntary access to EtOH over 28 days. Rats were then administered injections of Meth (10mg/kg x 4 injections) or saline on the following day. At 2 and 24 hours after the last oral gavage dose of EtOH, the gut endotoxin lipopolysaccharide (LPS) was elevated in serum compared to control rats. The subsequent exposure to Meth increased concentrations of LPS within serum over those in the EtOH alone treated rats. Meth alone did not increase LPS. The proinflammatory mediator, IL-1β was increased in serum at 2 hours after the last Meth injection in water-gavaged rats and increased to a greater extent in EtOH+Meth rats, suggesting a possible synergistic inflammatory response to the serial administration of the drugs. One week after Meth, 5HT and dopamine content within the striatum were depleted to a greater extent in EtOH+Meth rats compared to those treated with EtOH alone or Meth alone. In separate experiments, rats were allowed the choice of drinking EtOH and water every other day in their home cages for 4 weeks. Rats escalated their voluntary intake of EtOH over time to at least 6g/kg EtOH per day. Preliminary results indicate a supra-additive effect of EtOH+Meth on the depletions of striatal dopamine and 5HT that paralleled the depletions produced by the administration of Meth after the oral gavage of EtOH. Future studies are underway to determine whether the blockade of inflammation during EtOH drinking or gavage only will mitigate the enhanced monoamine depletions produced by the serial exposure to EtOH and Meth.

Disclosures: **A.L. Blaker:** None. **S. Liangpunsakul:** None. **B.K. Yamamoto:** None.

Poster

823. Drugs of Abuse: Extracellular Matrix and Inflammation

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 823.05/YY14

Topic: G.08. Drugs of Abuse and Addiction

Title: Binge methamphetamine self-administration behavior is attenuated by treatment with the anti-inflammatory drug, ibudilast

Authors: *K. D. FISCHER, B. K. YAMAMOTO;
Pharmacol. and Toxicology, Indiana Univ. Sch. of Med., Indianapolis, IN

Abstract: Methamphetamine (Meth) is a widely abused, highly addictive psychostimulant and its abuse results in a wide range of neurotoxic consequences. One consequence of Meth is the degradation of monoamine synaptic terminals. Furthermore, it has been established that neuroinflammation is a mediator of this neurotoxicity. Meth is known to increase neuroinflammation through the release of proinflammatory mediators produced from activated glia cells. Interestingly, compounds that attenuate glial cell activation have also been shown to reduce Meth-induced behavioral effects. Ibudilast, a non-selective phosphodiesterase inhibitor, glial cell modulator and anti-inflammatory agent, suppresses the release of proinflammatory cytokines from activated microglia and astrocytes and has been shown to attenuate Meth sensitization, Meth self-administration (SA) and reinstatement to Meth SA. A majority of the SA reports have utilized either limited (2-3 hr/day) or extended (6-8 hr/day) SA access periods. However, it has recently been shown that allowing rats unrestricted access to Meth SA for longer periods of time, referred to here as a chronic binge Meth SA paradigm, more accurately mimics Meth-taking behavior in humans. Here, we wanted to determine if treatment with ibudilast would attenuate chronic binge Meth SA behavior in rats. Adult, male Sprague-Dawley rats were trained to self-administer Meth for 96 hr. rounds. Rats were exposed to three SA rounds in total that were each interrupted by 96 hr. withdrawal periods whereby rats were left in their home cages. During each day of withdrawal, rats were treated with ibudilast (7.5 mg/kg, ip; 2X/day) or vehicle. Our preliminary results demonstrate that rats treated with ibudilast during withdrawal take significantly less Meth than vehicle treated rats during both rounds two and three. Additionally, when compared to the first round of Meth SA, vehicle treated rats exhibited an escalated SA trend during rounds 2 and 3, taking 116% and 106% of Meth administered during round 1, respectively. In contrast, ibudilast treated rats exhibited a deescalated trend during rounds 2 and 3, taking 52.4% and 41.3% of Meth administered during round 1, respectively. Our efforts will next be focused on exploring the mechanism underlying the ibudilast-induced attenuation of Meth SA behavior. Based on several reports demonstrating robust neuroinflammatory responses induced by Meth administration that can be blocked by treatment with anti- inflammatory agents, we will begin our efforts by looking at differential activation

patterns in cytokines TNF-α and IL-1β as well as other astrocytic proinflammatory markers including GFAP and COX-2.

Disclosures: **K.D. Fischer:** None. **B.K. Yamamoto:** None.

Poster

823. Drugs of Abuse: Extracellular Matrix and Inflammation

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 823.06/ZZ1

Topic: G.08. Drugs of Abuse and Addiction

Title: Cocaine induced proinflammatory signaling in the nucleus accumbens and medial prefrontal cortex exacerbates drug seeking.

Authors: *K. T. BROWN, S. LEVIS, T. FABISIAK, C. O'NEIL, A. NORTHCUTT, L. WATKINS, R. BACHTELL;
Neurosci., Univ. of Colorado Boulder, Boulder, CO

Abstract: The etiology of cocaine addiction has traditionally been characterized by allostatic neuroadaptations of the mesolimbocortical circuitry consisting of the ventral tegmental area (VTA), nucleus accumbens (NAc), and medial prefrontal cortex (mPFC). However, recent evidence also implicates proinflammatory signaling regulated by microglia, the brain's resident macrophage, in addiction-related processes. Chronic cocaine induces proinflammatory cytokine expression in the VTA, NAc, and mPFC, in part, through activity at toll-like receptor 4 (TLR4), a pattern recognition receptor that binds xenobiotic associated molecular patterns and danger associated molecular patterns and induces transcription of proinflammatory cytokines. TLR4 has been implicated in addiction-related processes by modulating drug-induced extracellular dopamine release in the NAc shell and altering the acute rewarding effects of cocaine. Furthermore, previous work indicates that pharmacological antagonism of TLR4 in the VTA attenuates cocaine-induced reinstatement of drug seeking. Here, we expanded these previous findings to the NAc shell and mPFC, two brain regions necessary for the reinstatement of drug seeking. To this end, we first demonstrated that acute cocaine and chronic cocaine self-administration enhance the expression of proinflammatory cytokine mRNA in the NAc shell and mPFC. Next, we used a rodent model of relapse behavior to test the influence of inflammation on drug seeking. Male Sprague-Dawley rats self-administered cocaine daily in 2-hour sessions for 15 days. Following self-administration, animals underwent extinction training and were tested in a cocaine-induced reinstatement paradigm while receiving bilateral microinjection of the TLR4 antagonist LPS-RS and interleukin-1 receptor antagonist (IL1-ra). Antagonism of TLR4 significantly reduced cocaine seeking during cocaine reinstatement, and preliminary evidence

suggests a reduction in cocaine seeking with IL1-ra. Data will also be presented indicating a role of proinflammatory signaling in the mPFC in cocaine seeking during reinstatement testing. Together, these studies build on the emerging hypothesis that cocaine increases neuroinflammatory processes that exacerbate the development of drug addiction.

Disclosures: **K.T. Brown:** None. **S. Levis:** None. **T. Fabisiak:** None. **C. O'Neil:** None. **A. Northcutt:** None. **L. Watkins:** None. **R. Bachtell:** None.

Poster

823. Drugs of Abuse: Extracellular Matrix and Inflammation

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 823.07/ZZ2

Topic: G.08. Drugs of Abuse and Addiction

Support: CIHR Grant

Title: The effects of inflammation on motivation and reinstatement in cocaine self-administration

Authors: *M. ATHANASSIOU[1], E.-A. MINOGIANIS[2], A.-N. SAMAHA[2], D. STELLWAGEN[1];
[1]McGill Univ., Montreal, QC, Canada; [2]Pharmacol., Univ. de Montréal, Montreal, QC, Canada

Abstract: Drugs of abuse, such as cocaine, trigger immune signaling in the brain, although the impact of this signaling remains unclear. Our recent work using a behavioural sensitization model (Lewitus et al., 2016) identified microglial tumor necrosis factor (TNF) as an adaptive response to cocaine, limiting both the synaptic and behavioural changes induced by the drug. The current study investigates in rats whether pharmacological activation of microglial TNF also influences the motivation to self-administer cocaine and the vulnerability to relapse to drug use following a period of forced abstinence. First, we will test the ability of MPLA, a microglial TNF activator, to attenuate the motivation to take cocaine by assessing breakpoints under a progressive ratio (PR) schedule of drug reinforcement. Male Sprague Dawley rats will be fitted with an IV catheter and trained in standard operant chambers on an fixed ratio 3 (FR3) schedule, by associating a cue (light) with a lever-press for a reward (cocaine infusion). Once stable performance is established, animals will be given an acute injection of either MPLA or saline 24 hours prior to a PR session. Lower breakpoints would indicate a blunted motivation to seek cocaine. Second, we will examine whether microglial activation could reduce the reinstatement of cocaine self-administration after a period of forced abstinence from the drug. Rats will be trained to self-administer cocaine; this behaviour will then be extinguished with daily 90-minute

extinction sessions for two consecutive weeks. Following microglial activation, rats will either be re-exposed to the discrete cue (light) or given a priming dose of cocaine (15mg/kg, IP). They will be placed back into the operant chambers for a final 2-hour reinstatement test. Significantly lower infusions would indicate a blunted reinstatement of cocaine. These findings would suggest that MPLA, or similar microglia activation, may help blunt craving in established addicts and reduce the odds of relapse.

Disclosures: M. Athanassiou: None. **E. Minogianis:** None. **A. Samaha:** None. **D. Stellwagen:** None.

Poster

823. Drugs of Abuse: Extracellular Matrix and Inflammation

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 823.08/ZZ3

Topic: G.08. Drugs of Abuse and Addiction

Support: Supported by NIH grant P50 AA017823

Title: Intermittent alcohol during adolescence produces altered cytokine reactivity when rats are re-challenged as adults: sex differences and stimulus specificity

Authors: *A. S. VORE, T. L. DOREMUS-FITZWATER, A. GANO, T. DEAK; Binghamton Univ., Binghamton, NY

Abstract: Adolescent alcohol use comprises a significant public health concern and is often characterized by binge-like consumption patterns. Though maladaptive drinking patterns commonly begin during adolescence, how these early exposures shape later neuroimmune response to ethanol and other HPA-axis activating stimuli is not well understood. The current study aims to better characterize the long-term consequences of early ethanol use. In this study, male and female adolescent Sprague-Dawley rats received four cycles of ethanol (4 g/kg) or vehicle exposure starting on postnatal day (P) 32 (± 3). Each cycle consisted of 3-days of intragastric (i.g.) ethanol or vehicle intubations followed by a 2-day period of rest/withdrawal. Following the completion of the fourth cycle, rats were allowed to age undisturbed until adulthood. At P71 (± 2), ethanol- and vehicle-exposed rats received either an acute challenge of 2.5 g/kg ethanol (intraperitoneally; i.p.) or an equivolumetric control dose of saline. Brains and bloods were collected 90 minutes following injection for assessment of blood ethanol concentrations (BECs) and gene expression (via RT-PCR). As expected, BECS ranged from 283-316 mg/dL with females exhibiting marginally higher BECs. Rats that received adolescent ethanol exposure also showed modestly but not significantly higher BECs during the adult

ethanol challenge relative to their vehicle counterparts. Gene expression analyses of IL-6, IL-1, TNF-A, and IκBα were measured in hippocampus. While all targets showed significant changes in expression following the adult challenge, animals with a history of adolescent ethanol exposure showed a significant sensitization in IL-6 and IκBα expression to adult ethanol challenge. These effects appeared to be much more pronounced in female rats relative to males. This is particularly interesting because in previous work we have seen that exclusively male animals showed a blunted response to LPS challenge following a procedurally identical adolescent ethanol exposure. These findings suggest that adolescent binge ethanol consumption led to substantial adaptations in neuroimmune response that persist across development; however, these changes differ as a function of both the type of challenge as well as the sex of the subject. These sex/stimulus specific changes further illuminate the complexity of characterizing the lasting consequences of adolescent ethanol exposure. Future studies more specifically characterizing these differences and beginning to identify the mechanisms that contribute to such changes are currently underway.

Disclosures: A.S. Vore: None. **T.L. Doremus-Fitzwater:** None. **A. Gano:** None. **T. Deak:** None.

Poster

823. Drugs of Abuse: Extracellular Matrix and Inflammation

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 823.09/ZZ4

Topic: G.08. Drugs of Abuse and Addiction

Support: RCMI RR003037

NIH 5R24DA012136-13

Title: Long-term voluntary oral methamphetamine administration impairs spatial learning & memory via increased hippocampal neuroinflammation and disrupted synaptic protein

Authors: *D. SHOR[1], J. A. AVILA[1,2], R. M. ZANCA[1,2], D. DRAPALA[1], N. PALEOLOGOS[1], P. A. SERRANO[1,2];
[1]Psychology, CUNY Hunter Col., New York, NY; [2]Psychology, The Grad. Ctr., New York, NY

Abstract: Methamphetamine (MA) is a highly addictive and neurotoxic stimulant that induces neurodegenerative processes in the brain. Our previous study showed that chronic bolus-MA administration (30 mg/kg i.p.) produced spatial reference and working memory deficits that occurred concomitantly with disrupted protein kinase Mζ (PKMζ) expression in the

hippocampus (Braren et al., 2014). However, it was unclear what mechanisms disrupted hippocampal synaptic plasticity, and subsequently cognitive processes, after MA administration. Furthermore, unlike binge or bolus dose-models with rodents, human MA abusers will spread out equivalent doses over hours or days. Hence, our aim in the present study was to optimize a rodent model of MA abuse that would accurately translate to human populations. Accordingly, we hypothesized that voluntary-MA abuse would produce spatial learning and memory deficits via increased neuroinflammatory mechanisms. We hypothesize that neuroinflammation disrupts the trafficking of synaptic plasticity markers in the hippocampus, which leads to cognitive deficits in-vivo. For 28 consecutive days, mice were presented with sweetened oatmeal chips containing 1 mg/kg MA, every 15 min for a 3h period. This allowed the mice to consume up to 16 mg/kg MA per day. The controls were given the same opportunity to consume 1/mg/kg water sweetened oatmeal. MA exposed mice consumed on average 5.23 mg/kg per day (an average of 146.4 mg/kg over 28 days). Following one-week of MA abstinence, spatial learning was assessed using the radial 8-arm maze (RAM). MA exposed mice showed spatial working memory deficits, confirming the results of our previous study. MA mice also had significant spatial-reference learning deficits on the RAM, exhibiting impaired performance overall as well as achieving a lower level of asymptotic performance compared to controls. Following the behavioral analyses, hippocampi were analyzed for changes in markers of neuroinflammation and synaptic markers associated with learning & memory. Our results show a significant increase in GFAP and COX2 expression compared to controls. Conversely, PKMζ and the GluA2 subunit expression were significantly decreased after MA treatment. These results suggest that chronic MA exposure increases markers for neuroinflammation over time and may decrease the necessary synaptic trafficking of PKMζ and GluA2 during spatial learning resulting in poor memory performance.

Disclosures: **D. Shor:** None. **J.A. Avila:** None. **R.M. Zanca:** None. **D. Drapala:** None. **N. Paleologos:** None. **P.A. Serrano:** None.

Poster

823. Drugs of Abuse: Extracellular Matrix and Inflammation

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 823.10/ZZ5

Topic: G.08. Drugs of Abuse and Addiction

Support: NIH Grant DA038009

Title: Repeated administration of the designer cathinone and bath salt drug MDPV produces a proinflammatory state

Authors: *M. POMPILUS[1], T. REDLER[2], T. YANG[2], L. M. COLON-PEREZ[1], C. MARTYNIUK[2], J. ZUBCEVIC[2], M. FEBO[1];
[1]Psychiatry, [2]Physiological Sci., Univ. of Florida, Gainesville, FL

Abstract: Use of drugs known as 'legal highs' or 'bath salts' continues to be a national concern as new molecular variants of these psychoactive cathinones continue to emerge. The bath salt constituent 3,4-methylenedioxypyrovalerone (MDPV) is often detected in blood of patient's presenting at emergency rooms with a psychosis-like syndrome involving agitation, panic, confusion/cognitive impairment, violent behavior, depression, and other adverse behavioral symptoms. Animal studies indicate that inhibition of mesolimbic dopamine reuptake mediates the rewarding actions of MDPV's. However, the aforementioned adverse effects of repeated MDPV emerge days-to-weeks after last use. Here we determined the effects of acute and chronic MDPV on peripheral and brain inflammatory markers. It was hypothesized that an increased neuroinflammatory state occurs with repeated administration, and this might underlie the adverse effects of MDPV. Adult male Long Evans rats (250-400g) were treated with a single daily injection of physiological saline (n = 8) or MDPV (1 mg kg^{-1}, i.p; n =8) on 5 days. Acutely exposed rats (n=8) received 4 days of saline and a final injection on day 5 with MDPV. Locomotor activity and ultrasonic vocalizations (USVs: 25-50kHz) were measured on days 1, 2 and 5. Twenty-four hours after the last injection, rats were euthanized, brains flash frozen, stored at -80°C and processed for quantitative RT-PCR, and blood collected and processed for Fluorescence Activated Cell Sorting (FACS). MDPV produced behavioral sensitization by day 2, which was still observed by day 5. USVs were significantly reduced at 24 h after the first injection and effects were still apparent on 25-35kHz USVs on day 5. Repeated MDPV (1 mg kg^{-1}), but not a single exposure, increased blood levels of cell surface markers, CD3 (T cells) and CD68 (monocytes/macrophages), and reduced CD4 (perhaps indicating tissue infiltration). We also observed an interesting pattern of cytokine expression in CNS. Frontal cortical IL-6, IL-10 and TNFα were elevated only in repeatedly exposed rats. In the ventral striatum we observed a reduction in these cytokines compared with control saline rats. Finally, there was no effect of repeated MDPV in the hypothalamus; however, a trend towards increased expression was observed with acute exposure. Collectively, these results show strong support for an activated immune response with chronic MDPV exposure.

Disclosures: M. Pompilus: None. **T. Redler:** None. **T. Yang:** None. **L.M. Colon-Perez:** None. **C. Martyniuk:** None. **J. Zubcevic:** None. **M. Febo:** None.

Poster

823. Drugs of Abuse: Extracellular Matrix and Inflammation

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 823.11/ZZ6

Topic: G.08. Drugs of Abuse and Addiction

Support: NIDA Grant DA034721

NIDA Grant T32 DA07244

Title: Astrocyte modulation of heroin-conditioned immune effects

Authors: *J. E. PANICCIA, M. E. JONES, C. L. LEBONVILLE, D. T. LYSLE;
Dept. of Psychology and Neurosci., Univ. of North Carolina-Chapel Hill, Chapel Hill, NC

Abstract: Opioid abuse is associated with an increased risk of infectious diseases, due in part to the direct effect of heroin on peripheral immune responses, such as nitric oxide (NO). Interestingly, the effect of heroin can be conditioned to distinct environmental contexts, such that in the absence of heroin, exposure to the context alone suppresses measures of NO. Previous research in our laboratory has established that the functional integrity of the circuit between the ventral tegmental area, basolateral amygdala (BLA), and nucleus accumbens shell is crucial for the expression of heroin-conditioned immunomodulation. Furthermore, recent research has suggested that astrocytes play a critical role in the disruption of drug seeking behavior for different drugs of abuse. The present studies examine the role of astrocytes in the BLA as a potential mediator of the expression of heroin-conditioned immunomodulation. To this end, we bilaterally infused AAV5-GFAP-HA-HM3Dq-IRES-mCitrine, a Gq-coupled designer receptor exclusively activated by designer drugs (DREADDs) under a glial fibrillary acidic protein promoter (GFAP), into the BLA of adult male Lewis rats. Following virus incubation, rats underwent five conditioning sessions in which rats received injections of heroin (1 mg/kg s.c.) and were then placed into a distinct context. Six days following the final heroin conditioning session, rats were tested for the expression of heroin-conditioned immunomodulation. Specifically, on test day, animals were injected with vehicle or clozapine-N-oxide (CNO; 3 mg/kg, s.c.) to activate the DREADDs prior to re-exposure to the context. Upon removal from the context, rats were challenged with lipopolysaccharide (LPS) to induce an immune response. Measurements of immunomodulation of NO was achieved through nitrate/nitrite assay, as well as ongoing analysis of splenic mRNA and protein levels of inducible nitric oxide synthase (iNOS). Animals administered vehicle prior to re-exposure to the heroin-paired context exhibited suppressed levels of plasma nitrate/nitrite, indicative of compromised NO production. In contrast, animals given CNO to activate the GFAP-Gq-DREADDs, had plasma nitrate/nitrate levels comparable to control groups not re-exposed to the context. Thus, activation of Gq-DREADDs in astrocytes within the BLA abolished the expression of immunosuppression to a previously heroin-paired context. To fully understand the role of astrocyte function in the expression of heroin-conditioned immunomodulation, our ongoing analysis is investigating the mechanisms of action by which astrocytes are involved in the conditioned suppression of NO.

Disclosures: **J.E. Paniccia:** None. **M.E. Jones:** None. **C.L. Lebonville:** None. **D.T. Lysle:** None.

Poster

823. Drugs of Abuse: Extracellular Matrix and Inflammation

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 823.12/ZZ7

Topic: G.08. Drugs of Abuse and Addiction

Support: CNPq

CAPES

UFRGS

UFCSPA

Title: Does the environmental enrichment change oxidative stress parameters in the hippocampus and frontal cortex of cocaine-conditioned rats?

Authors: *R. GOMEZ[1], L. FREESE[2], G. CALETTI[2], S. BANDIERA[4], M. S. NIN[2], L. STEFFENS[3], A. STEINMETZ[3], D. J. MOURA[3], H. M. T. BARROS[3];
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Abstract: Drug abuse is a multifactorial problem with complex interactions between environmental and genetic factors. Cocaine acts as a potent genotoxic drug in rodent brains and produces neuronal injury, acting through diverse mechanisms, including mitochondrial impairment and activation of cell signaling pathways associated with the stress response. It have been suggested that environmental enrichment (EE) mimicking positive life experiences, prevents the drug addiction. EE enhances motivational mechanisms and decreases injury from neurodegenerative and neuroinflammatory disorders including the cocaine use. We aimed here to evaluate the neuroprotective effect of EE in the hippocampus and in the frontal cortex of cocaine-conditioned rats, measuring DNA damage and oxidative stress parameters. Fifty male Wistar rats (21 PND) were raised in a standard (ST) or in an enriched environment (EE) until adulthood (90 PND). The EE rats (7 -10/cage) raised in a large cage (70×60×80cm) divided in 3 floors connected by two ladders and containing cardboard tunnels and 5-6 toys, replaced weekly. The ST rats (2-3/cage) raised in a standard polycarbonate cage (40×33×18 cm). In the adult age, they were exposed to the Conditioning Place Preference (CPP) protocol, and administered with 15 mg/kg cocaine, via i.p. After 11 days, last day of the CPP protocol, animals were killed and the frontal cortex and the hippocampus were removed. Subgroups were considered in according

to: the animals that were conditioned and the animal that were not conditioned to cocaine. Oxidative profile was determined by DCFH-DA assay and SOD and CAT activity. Our results showed that EE significantly decreased the CAT activity in both, frontal cortex and hippocampus of cocaine-conditioned rats ($P < 0.05$). We may infer that hydrogen peroxide was lower in EE rats than ST rats, evidencing an antioxidant property of EE in an specific brain area. DCF parameter showed a non significant decreasing ($P = 0.076$) in the frontal cortex. Thus, EE presents a neuroprotective effect in the frontal cortex, an area known to be implicated in impulsivity and decision-making.

Disclosures: **R. Gomez:** None. **L. Freese:** None. **G. Caletti:** None. **S. Bandiera:** None. **M.S. Nin:** None. **L. Steffens:** None. **A. Steinmetz:** None. **D.J. Moura:** None. **H.M.T. Barros:** None.

Poster

823. Drugs of Abuse: Extracellular Matrix and Inflammation

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 823.13/ZZ8

Topic: G.08. Drugs of Abuse and Addiction

Support: U01 AA020913

P60 AA006420

R21 AA024198

R01 AA021491

Title: Time course and regional selectivity of matrix metalloproteinases activation in a mouse model of ethanol dependence

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Abstract: Alcohol use disorders represent a spectrum of pathological patterns of alcoholic beverage consumption, which are characterized by compulsive drinking and negative affect during abstinence. *In vivo* chronic ethanol exposure produces changes in neuronal morphology and function, which are hypothesized to be the cellular basis for behavioral alterations associated with ethanol dependence. Previous studies have provided evidence for a potential role of matrix metalloproteinases (MMPs) in the etiology of ethanol dependence. These enzymes are responsible for degrading components of the extracellular matrix that makes up the interstitial material of the brain parenchyma, as well as the basement membrane of the brain-blood barrier

and the perineuronal nets that surround some neurons. Our preliminary data shows an upregulation of MMP-9, but not MMP-2, gelatinase activity in the medial prefrontal cortex (mPFC) of mice exposed to chronic intermittent ethanol (CIE). Here, we seek to characterize the time-course and regional selectivity of MMP activation in the brain of mice escalating their ethanol intake as a result of dependence. Adult male mice were exposed to alternated weeks of limited-access two-bottle choice (2BC) ethanol drinking and CIE (dependent mice) or air (non-dependent mice) inhalation. A first group of mice was euthanized after one CIE-2BC cycle (PV1), while a second group was subjected to four CIE-2BC cycles (PV4). Brains were collected in both groups, and tail blood was sampled at the end of each 2BC week (PV1-PV3) in the second group. *In situ* zymography will be used to track the upregulation of gelatinase activity over time and map affected brain regions. In addition, double immuno-labeling will allow to determine the isoform(s) and cell type(s) responsible for increased MMP activity. We hypothesize that MMP-9 activation is a prerequisite for the structural and functional changes driving ethanol drinking escalation; we therefore anticipate that MMP-9 activation will be stronger at PV1 than at PV4. Furthermore, we expect that MMP-9 hyperactivity will be detected in brain regions implicated in behavioral disturbances associated with alcohol dependence, such as the mPFC, amygdala or hippocampus. Our preliminary findings indicate that basal MMP-9 activity in the cortex mostly stems from neurons but it is possible that chronic ethanol exposure triggers MMP-9 activity from glial cells. Finally, blood samples will be analyzed by gel zymography to determine whether the CIE-2BC mouse model of ethanol dependence is associated with elevated serum levels of MMP-9 activity, which could potentially validate MMP-9 as a blood biomarker of alcohol dependence.

Disclosures: H.K. Sidhu: None. **M. Kreifeldt:** None. **C. Contet:** None.

Poster

823. Drugs of Abuse: Extracellular Matrix and Inflammation

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 823.14/ZZ9

Topic: G.08. Drugs of Abuse and Addiction

Support: R01AA020394

Title: Synaptic plasticity in extended amygdala and anterior cingulate cortex and negative reinforcement learning related to escalation of alcohol self-administration in alcohol-dependent rats: role of matrix metalloproteinases

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Abstract: Matrix metalloproteinases (MMPs) are extracellular proteases which degrade the extracellular matrix, contributing to synaptic remodeling. MMPs are secreted as an inactive pro-form and are activated following the removal of the pro-domain. MMP inhibition by intracerebroventricular (ICV) infusions of the broad spectrum MMP inhibitor attenuates escalation of alcohol self-administration (SA) during acute withdrawal in alcohol-dependent rats. However, MMP inhibition does not alter escalated alcohol SA after alcohol-mediated negative reinforcement learning has occurred. MMP-2, -3 and -9 are MMP subtypes implicated in neural plasticity and learning. In the present study, we examined whether MMP-2, -3 or -9 expression and/or activity levels are upregulated in specific brain regions associated with reinforcement and aversion including anterior cingulate cortex (ACC), hippocampus (Hipp), amygdala (Amyg), and nucleus accumbens (NAc) during acute withdrawal in alcohol-dependent rats. Rats were trained to self-administer alcohol and then subjected to an alcohol-dependence induction procedure using intermittent alcohol vapor exposure (14 h alcohol exposure / 10 h alcohol withdrawal daily). Following the one-month of alcohol vapor exposure, rats were divided into four experimental groups: initial escalation (IE) with a pharmacological control (IPC) and stable escalation (SE) with a pharmacological control (SPC) group. IE and SE groups of rats were tested for alcohol SA during 6hr withdrawal from alcohol but IPC and SPC group did not have access to SA but received an intraperitoneal injection of alcohol equal to the amount of alcohol self-administered by IE and SE group, respectively. Three hours after the SA session of initial escalation (1st SA session) or stable escalation (the last SA session after responding for alcohol was stabilized), rats were sacrificed and their brains were taken for Western blot analysis to evaluate the levels of pro- and active-forms of MMP-2, -3 and -9. Both pro- and active forms of MMP-9 but not MMP-2 and -3 in the Amyg and NAc were elevated in the IE group compared to the IPC and SE groups, and interestingly, active MMP-9 (~ 92kD only) in the ACC was decreased in the IE group compared to the IPC and SE groups. No changes were found in Hipp MMP expression under the conditions studied. These data suggest that specialized amygdaloaccumbal plasticity is recruited under conditions of negative reinforcement learning with concomitant decreases in ACC plasticity that underlie escalated alcohol self-administration in alcohol dependence.

Disclosures: B. Go: None. **B.M. Walker:** None.

Poster

823. Drugs of Abuse: Extracellular Matrix and Inflammation

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 823.15/ZZ10

Topic: G.08. Drugs of Abuse and Addiction

Support: NIH grant DA003906

NIH grant DA012513

NIH grant DA015369

Title: Integrins and focal adhesion kinase as a signaling pathway for mmp-9 induction of transient synaptic plasticity in cocaine relapse

Authors: *C. GARCIA-KELLER, A.-C. BOBADILLA, M. SCOFIELD, S. M. SPENSER, C. MONFORTON, P. W. KALIVAS;
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Abstract: Chronic cocaine exposure produces neuroplasticity within the nucleus accumbens core (NAcore) that leads to increased vulnerability to relapse, even after protracted abstinence. Matrix metalloproteinases (MMPs) are inducible endopeptidases that degrade extracellular matrix (ECM) proteins (such as fibronectin, laminin and thrombospondin) as well as non-ECM signaling molecules, and reveal an RGD domain that binds and signals through integrins. Integrins are heterodimeric receptors composed of subunits αβ, and their primary signaling kinases are the focal adhesion kinase (FAK) and integrin linked kinase (ILK). Previous results show that β3 integrin is upregulated after cocaine self-administration and MMP-9 activity is increased during cued-reinstatement of cocaine and heroin, and promotes transient synaptic plasticity (t-SP: increases in spine head diameter and AMPA/NMDA). Here we endeavor to understand if β3 integrin signaling through FAK is necessary to promote synaptic growth and regulate actin polymerization during t-SP produced during drug-seeking.
To study the increases of spine head diameter induced by MMP activation we use an antisense morpholino to reduce the expression of β3 Integrin during cued-reinstatement. β3 Integrin down-regulation reduced cued-reinstatement and spine head diameter compared with standard control morpholino. Additionally, microinjection of a FAK inhibitor into the NAcore blocked cue-reinstated behavior, while this inhibitor had no impact on cued sucrose seeking. In contrast, and ILK inhibitor was without effect on reinstatement. Immunohistochemistry on NAcore labeled spines with AAVC2-hSYN-ChR2-YFP virus, revealed increased p-FAK (active) localization in dendritic spines of extinguished and reinstated cocaine animals compared with yoked-saline. In summary, our data demonstrate that β3 Integrin and FAK signaling are involved in the synaptic plasticity produced in NAcore during cue-induced reinstatement of cocaine seeking. **Support:** NIH grant DA003906, NIH grant DA012513, NIH grant DA015369 (PWK)

Disclosures: C. Garcia-Keller: None. **A. Bobadilla:** None. **M. Scofield:** None. **S.M. Spenser:** None. **C. Monforton:** None. **P.W. Kalivas:** None.

Poster

823. Drugs of Abuse: Extracellular Matrix and Inflammation

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 823.16/ZZ11

Topic: G.08. Drugs of Abuse and Addiction

Support: NIH DA 033404

Washington State Initiative Measure No. 171

Title: Knockdown of cartilage link protein-1 within the medial prefrontal cortex disrupts perineuronal nets and acquisition of cocaine preference

Authors: *J. H. HARKNESS[1], M. SLAKER[2], B. SORG[2];
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Abstract: Acquisition of cocaine-induce conditioned place preference (CPP) in rodents can be impaired by disruption of extracellular matrix aggregations called perineuronal nets (PNNs). Disruption of PNNs may benefit future treatment of human cocaine addiction. PNNs surrounding synapses of fast-spiking, parvalbumin-containing GABAergic interneurons are important for stabilization of synapses following learning, and for limiting plasticity after the critical period. We have demonstrated the bacterial enzyme chondroitinase-ABC administered in the prelimbic medial prefrontal cortex (PL mPFC) of rats results in degradation of extracellular matrices. However, this enzyme non-specifically targets chondroitin-sulfate proteoglycan containing structures. A vivo-morpholino [1:5] knockdown of cartilage link protein-1 (Crtl-1) localized to the PL mPFC of adult rats resulted in degradation specific to PNNs. Functional and behavioral results of Crtl-1 knockdown trend toward those of chondroitinase-ABC. In the present work, we tested a higher concentration [1:2.5] of vivo-morpholino to knockdown Crtl-1, administered prior to acquisition of cocaine-induced CPP. PNN formations were measured by immunohistochemistry and staining with *Wisteria floribunda* agglutinin. We developed code to interface with NIH-distributed ImageJ software for the automation of both single- and double-labeled sample analysis. In combination with previous results, these results indicate that knockdown of Crtl-1 using a morpholino can specifically degrade PNNs, and may disrupt acquisition of cocaine CPP. Automation of PNN intensity resulted in high concordance (>97%) with PNN intensity data collected by trained researchers. Furthermore, our software standardized analysis and reduced the possibility of bias, while completing analysis roughly 99% faster than by hand. Grants: NIH DA 033404 and Washington State Initiative Measure No. 171

Disclosures: **J.H. Harkness:** None. **M. Slaker:** None. **B. Sorg:** None.

Poster

823. Drugs of Abuse: Extracellular Matrix and Inflammation

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 823.17/ZZ12

Topic: G.08. Drugs of Abuse and Addiction

Support: FPU12/04059

PSI2011- 29181

Title: Expression of cFOS & Perineuronal nets in the cerebellum of mice trained to acquire cocaine-induced preference conditioning. Effects of re-exposure to the cue.

Authors: *M. CARBO-GAS[1], J. MORENO-RIUS[1], I. GIL-MIRAVET[1], D. CARULLI[2], C. SANCHIS-SEGURA[1], M. MIQUEL[1];
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Abstract: Several memory processes underlie motivational trigger of drug-seeking & drug-taking behaviour. One of them is the acquisition of preference memories towards drug-related cues. Recently, we have found two cerebellar hallmark signatures of conditioned preference for cocaine: an increase in cFOS expression in cells at the apex of the granule cell layer in addition, stronger expression of the perineuronal nets (PNNs) surrounding Golgi interneurons at the same region of the cerebellar vermis. No one of these cerebellar features was seen if mice did not develop a preference for the cocaine-related cue. To ascertain whether the cerebellar signatures of conditioned preference for cocaine are related to the expression of the Pavlovian memory or they may be linked to the motivational selection driven by the cue, we confined mice with the CS+ after the preference test, a procedure to reactivate the Pavlovian memory related to cocaine. Mice were trained to acquire a preference for an olfactory stimulus paired with cocaine. Then, 24 hours after the preference test, mice were confined for 30 minutes with the CS+ and perfused 70 minutes after the reactivation. Remarkably, we found that animals that acquired preference towards CS+ did not show the higher cerebellar expression of cFOS after the reactivation test previously demonstrated. However, they still expressed stronger PNNs compared with the animals that did not develop the preference for the cocaine-related cue. Therefore, our findings suggest that cFOS expression in the apex of the cerebellar cortex may be related to the behavioural selection towards cocaine-related cue. Also, the results indicate that PNN expression in Golgi neurons could be a more stable and persistent mechanism for Pavlovian memory.

Disclosures: **M. Carbo-Gas:** None. **J. Moreno-Rius:** None. **I. Gil-Miravet:** None. **D. Carulli:** None. **C. Sanchis-Segura:** None. **M. Miquel:** None.

Poster

823. Drugs of Abuse: Extracellular Matrix and Inflammation

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 823.18/ZZ13

Topic: G.08. Drugs of Abuse and Addiction

Support: Ministerio de Economía y Competitividad Grant PSI2015-68600-P

UJI Grant 14I307.01/1

Title: Extended access to cocaine self-administration persistently upregulates perineuronal nets in Golgi cerebellar neurons

Authors: *J. MORENO-RIUS[1], C. NICOLAS[2], I. GIL-MIRAVET[1], M. CARBO-GAS[1], M. SOLINAS[2], M. MIQUEL[1];
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Abstract: Escalation of drug intake is a necessary step towards the development of drug addiction. In experimental animals, escalation can be induced by giving them extended access (6h) to drug self-administration. Notably, escalation is associated with some behavioural features consistent with the addiction phenotype, including high motivation for the drug, higher probability of relapse, and drug-related compulsive-like behaviours. It has been suggested that escalation is the result of persistent modifications in plasticity processes induced by a prolonged experience with the drug in the striatumcortico-limbic circuitry. Some recent findings have suggested a role for the cerebellum in drug-related plasticity processes. Animals that developed preference towards a cocaine-paired cue show two cerebellar hallmarks signatures associated with such memory, an increase in c-FOS expression in granule cells and a stronger perineuronal net (PNN) expression in Golgi cells in the dorsal part of the granule cell layer. Recent studies have demonstrated that PNNs in different regions of the striatum-cortico limbic networks are directly involved in the formation or maintenance of drug-induced memories. In the present study, we investigated the effects of Short (1h) vs Long (6h) access to cocaine self-administration after either short (7 days) or long (28 days) withdrawal periods on the expression of PNNs in Golgi neurons. The evaluation of PNNs was addressed in the vermis and hemispheres of the cerebellum using biotinylated Wisteria floribunda agglutinin (WFA) and immunolabelling for neuronal activity markers as GABA and glutamate vesicular transporters. Results showed that long access to cocaine persistently upregulates Golgi PNNs in the cerebellum. This effect was not found after short access to cocaine. Noticeably, the regulation of Golgi PNNs was not affected by the length of the withdrawal period. Therefore, the history of drug self-administration appeared to be the crucial factor in the regulation of Golgi PNNs. These results pointed to PNNs as a plasticity mechanism involved in the development or maintenance

of an escalated drug intake, and further strengthens the previously appointed role for the cerebellum in the neurobiology of addiction.

Disclosures: **J. Moreno-Rius:** None. **C. Nicolas:** None. **I. Gil-Miravet:** None. **M. Carbo-Gas:** None. **M. Solinas:** None. **M. Miquel:** None.

Poster

824. Alcohol: Behavioral Studies II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 824.01/ZZ14

Topic: G.08. Drugs of Abuse and Addiction

Support: NIH Grant AA013517

NIH Grant AA07471

NIH Grant AA11852

NIH Grant DA032457

NIH Grant MH077708

AG043425

AFOSR FA9550-12-1-0355

Title: Acoustic characteristics of ultrasonic vocalizations are predictive of alcohol consumption in long-evans rats

Authors: ***N. MITTAL**[1], J. RENO[2], A. MARTINEZ[2], S. PRASLA[2], W. T. MADDOX[3], T. SCHALLERT[2], C. DUVAUCHELLE[2];
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Abstract: Emotional status plays an important role in alcohol abuse; however, studying emotional states in preclinical models remains difficult. Ultrasonic vocalizations (USVs) have been verified as a reliable, real-time measure of emotional status in rodents. Positive affect USVs (approximately 50-55 kHz range) are typically elicited in response to rewarding or pleasurable stimuli, such as food, drugs and sex. Negative emotions are associated with USVs in the 22-28 kHz range, which often occur in response to aversive stimuli, such as pain, fear and predator presence. In addition, our laboratory has revealed that negative affect USVs are associated with the propensity for excessive alcohol intake because rats selectively bred for high alcohol-

drinking behavior spontaneously emit a large amount of 22-28 kHz USVs even before alcohol experience. Long-Evans rats are a very popular choice for alcohol research studies because they often drink larger amounts of alcohol than other commonly used rat lines. However, one of the disadvantages of using Long-Evans rats is the great variability in drinking levels across animals. Therefore, the goal of the present study was to determine whether USV acoustic characteristics could be used to predict and/or confirm alcohol consumption in Long-Evans rats. To do this, we first recorded Baseline USVs in a home cage environment during 4-hr sessions, 3 days/week for 2 weeks. Following Baseline sessions, animals were given 24-hr alcohol access (three bottle choice: water, 15% EtOH, 30% EtOH) 3 days/week for 4 weeks. The 24-hr alcohol access sessions began at the beginning of the dark cycle and USVs were recorded for the first four hours during each session. At the end of the experiment, animals classified as High Drinkers (Week 4 minimum intake 4 g/kg/day, positive trendline slope across all drinking days) and Low Drinkers (Week 4 below 4 g/kg/day, negative trendline slope across all drinking days) were compared using linear mixed modeling (LMM) and linear discriminant analyses (LDA). Our findings showed significant differences in certain baseline acoustic parameters of positive- and negative-affect associated USVs were predictive of future drinking behavior (e.g., High versus Low Drinkers). Moreover, USV characteristics were altered as the result of alcohol experience, with High and Low Drinkers showing significant group differences. Together these data provide evidence that USV acoustic characteristics may be predictive of future alcohol drinking levels in the Long-Evans rat line.

Disclosures: **N. Mittal:** None. **J. Reno:** None. **A. Martinez:** None. **S. Prasla:** None. **W.T. Maddox:** None. **T. Schallert:** None. **C. Duvauchelle:** None.

Poster

824. Alcohol: Behavioral Studies II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 824.02/AAA1

Topic: G.08. Drugs of Abuse and Addiction

Support: RO1 AA019793

T32 AA07468

Title: Ethanol withdrawal-induced hyperalgesia transferred to neighboring prairie voles

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Abstract: Recent studies in our laboratory have shown increased sensitivity to mechanical pain stimuli in C57BL/6J mice and that this hyperalgesia gets transferred to control "bystander" mice housed in the same room via olfactory cues. It is important to know whether this social transfer is specific to mice, or can be observed in other species. Previous research demonstrated that socially monogamous prairie voles can voluntarily consume large doses of alcohol. Therefore, the present study investigated whether alcohol withdrawal-induced hyperalgesia and its social transfer can be observed in prairie voles. Adult female prairie voles were housed within a cage divided by a barrier with a sibling housed on the other side. One animal received ethanol in a 24-hour 2-bottle choice procedure with increasing concentrations of ethanol (3-10%), while the sibling animal had access to just water. Following one week, the ethanol bottle was removed for 24 hours and replaced with water. After this 24-hour period, pain sensitivity was measured using von Frey filaments in a separate room. This paradigm was repeated the following week. We found that alcohol withdrawal lead to hypersensitivity in female prairie voles. Interestingly, those animals that had access to only water had similar mechanical hypersensitivity thresholds to their ethanol-drinking siblings, similarly to what we see in C57BL/6J mice. These studies show that pain can be consistently induced by social stimuli across different rodent species.

Disclosures: **A.T. Walcott:** None. **A.E. Ryabinin:** None.

Poster

824. Alcohol: Behavioral Studies II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 824.03/AAA2

Topic: G.08. Drugs of Abuse and Addiction

Title: Effects of various alcoholic beverages on learning and memory in mice

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Abstract: Alcohol is the one of the major causes of disability of learning and memory. It is well demonstrated that ethanol (EtOH) affects several neurotransmitter in the brain, such as GABA, glutamate, serotonin and dopamine. While the type of alcohol exists a lot, research has not demonstrated what kind of alcoholic beverages affect learning and memory. To our knowledge, there have been no prior experimental studies about the effects of long-term consumption of alcoholic beverages, red wine, Japanese rice wine (sake) or whisky on the behavioral assessment. In the present study, we evaluated the spatial memory or the passive avoidance learning among control mice and chronic treated with 10% EtOH, red-wine, sake or whisky. Six-week-old male

C57BL6J mice were fed with 10% EtOH, red-wine, sake or whisky (ethanol content adjusted to 10%) for 7 weeks. All animals were behaviorally tested on the Morris water maze and passive avoidance test in order to assess their spatial learning and fear learning memory at the end of administration period, respectively. In red-wine treated mice learned the water maze task at a higher rate than control group. In contrast, no significant differences were found between controls and sake or whisky treated mice in behavioral tasks. We also examined the level of mRNA in mice hippocampal neurotrophic factors (BDNF, NGF) or NMDA receptor, which plays an important role of memory function. However, no significant differences were obtained between control and alcoholic beverages. Thus, our findings demonstrate that chronic consumption of red-wine dose not lead to a decline in hippocampal dependent spatial memory. This may be due to the ability of polyphenols, which is more included in red-wine than sake or whisky.

Disclosures: N. Hashikawa-Hobara: None. **K. Katsuki:** None. **A. Matsumoto:** None. **N. Hashikawa:** None.

Poster

824. Alcohol: Behavioral Studies II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 824.04/AAA3

Topic: G.08. Drugs of Abuse and Addiction

Support: R01 1131046-1-74356

Title: Nicotine facilitates cue-triggered approach in alcohol exposed. rats

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Abstract: Drug seeking behavior and the motivation to consume a drug can be regulated by the presence of drug-associated stimuli (“cues”). These drug cues can further become attractive and acquire incentive salience, thereby eliciting approach (or “sign-tracking”) to the cue itself. In the case of alcohol, Srey et al. (2015) previously demonstrated that a Pavlovian alcohol cue elicited sign-tracking following extended conditioning in animals with a history of alcohol exposure. Because nicotine is frequently used in conjunction with alcohol and can promote sign-tracking toward reward cues and other environmental stimuli (Loney et al. 2016, in prep), we tested whether nicotine would alter the approach responses elicited by alcohol cues. Long-Evans rats (n = 19) were first given intermittent access to 15% ethanol over 12, 24-h sessions, whereas

unexposed rats (n = 18) only had access to water. Rats were then tested in a Pavlovian conditioned approach paradigm during which a cue (an illuminated lever) predicted the delivery of 15% ethanol over 27 test sessions (12 presentations per session). Rats were injected with either nicotine (0.4 mg/kg S.C.) or saline before each of these sessions. Preliminary results from this ongoing study indicate that alcohol exposure enhanced approach to the alcohol delivery cup ("goal-tracking"), and that nicotine may have facilitated this approach in both alcohol exposed and unexposed groups. Further, nicotine selectively enhanced approach to the cue ("sign-tracking") in alcohol exposed rats. Thus, we suggest that nicotine promotes relapse to drinking by increasing the incentive salience of alcohol cues. Therefore, preventing relapse in individuals with a history of alcohol abuse may benefit from concurrent treatment of nicotine dependence.

Disclosures: H.A. Pearson: None. **G. Loney:** None. **P. Meyer:** None.

Poster

824. Alcohol: Behavioral Studies II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 824.05/AAA4

Topic: G.08. Drugs of Abuse and Addiction

Support: Randolph-Macon College Chenery Research grant

Randolph-Macon College Craigie Research grant

Title: Acute ethanol exposure during late mouse neurodevelopment results in long term deficits in memory retrieval, but not in social responsiveness

Authors: *E. B. CLABOUGH[1], K. HOULE[3], M. ABDI[2];
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Abstract: Prenatal alcohol exposure can result in neurological changes in affected individuals and may result in the emergence of a broad spectrum of neurobehavioral abnormalities termed Fetal Alcohol Spectrum Disorders (FASD). The effects of ethanol exposure during development are both time and dose dependent. Although many animal models of FASD use more chronic ethanol exposure, acute developmental alcohol exposure may also cause long lasting neuronal changes. Our research employed behavioral measures to assess the effects of a single early postnatal ethanol intoxication event in mice. Mice were dosed at postnatal day 6 (P6; a 2.5g/kg dose of ethanol or a saline control administered twice, two hours apart) as a model of third

trimester drinking in humans. This exposure was followed by behavioral assessment in male mice at 1 month (1M) and at 4 months of age (4M) using the Barnes maze (for learning/memory retrieval), open field behavior, and a social responsiveness task. Ethanol-exposed mice appeared to be less motivated to complete the Barnes maze at 1M, but were able to successfully learn the maze. However, deficits in long-term spatial memory retrieval were observed in ethanol-exposed mice when measured at 4M. No significant differences were found in open field behavior or social responsiveness at P30 or 4M of age. Ultimately, we conclude that acute ethanol exposure at P6 in mice leads to mild but long lasting deficits in long-term spatial memory. Results suggest that even brief acute exposure to high ethanol levels during the third trimester equivalent of human pregnancy may have a permanent negative impact on the neurological functioning of the offspring.

Disclosures: E.B. Clabough: None. **K. Houle:** None. **M. Abdi:** None.

Poster

824. Alcohol: Behavioral Studies II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 824.06/AAA5

Topic: G.08. Drugs of Abuse and Addiction

Title: Alcohol consumption and exposure does not impair go/no-go discrimination learning but causes over-responding on go trials in rats

Authors: *H. FISHER[1], M. BREEN[1], T. HITE[1], T. RABY[1], M. RAY[1], A. ANJI[2], M. KUMARI[2], C. PICKENS[1];
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Abstract: Alcohol use is associated with impaired impulsivity in humans. However, it is unclear whether alcohol use leads to neurological changes that cause impulsivity, or whether impulsivity leads to more alcohol use. To investigate this question, we assigned male Long-Evans rats to one of four groups: Alcohol Access (Alcohol), Alcohol Access + Saline Injection (Alcohol+Saline), Alcohol Access + Alcohol Injection (Alcohol+Alcohol), or Water only (Water). The rats received chronic intermittent access (CIA) to alcohol (24-h access to 20% alcohol 3X per week) or water alone for 6 weeks to examine the effects of alcohol consumption. The Alcohol+Injection subsets received 9.5 ml/mg i.p. injections of either 20% alcohol or saline prior to the 24-h alcohol access period. On the final day of alcohol access, the rats' blood ethanol content was measured 30 min following injections/the start of the access period. Three days after the final alcohol access day, rats were trained and tested in a go/no-go discrimination task for 9 days. In this task, the right and left lever were extended one at a time in alternating order, with a

cue light illuminated above the extended lever. Responses on one lever-light compound (active lever/S+) were reinforced on an intermittent reinforcement schedule. Responses to the other lever-light compound (inactive lever/S-) were not reinforced. The Alcohol+Alcohol group voluntarily drank an average of ~4 g/kg/24-h across the 6 weeks, while the other 2 alcohol groups drank an average of 7-8 g/kg/24-h, suggesting that the Alcohol+Alcohol group was exposed to less alcohol, even including the injection dose. However, rats in the Alcohol+Alcohol group had higher measured peak BECs (average = 195 mg/dl) than the other two groups (average = ~80 mg/dl). We found no difference between the groups during discrimination learning (as measured by the percent of trials in which rats responded). However, every alcohol group showed greater over-responding (responses/trial) on the S+ lever during discrimination learning compared to the Water group. Our results suggest alcohol consumption does not impair go/no-go discrimination learning, either in rats with higher peak blood alcohol levels (Alcohol+Alcohol) or higher cumulative levels of alcohol exposure (Alcohol; Alcohol+Saline). Alcohol consumption did affect over-responding on the S+ lever, suggesting alcohol consumption is sufficient to cause over-responding. Future studies will examine possible alterations in prefrontal cortex function following alcohol consumption that could account for the over-responding effect.

Disclosures: **H. Fisher:** None. **M. Breen:** None. **T. Hite:** None. **T. Raby:** None. **M. Ray:** None. **A. Anji:** None. **M. Kumari:** None. **C. Pickens:** None.

Poster

824. Alcohol: Behavioral Studies II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 824.07/AAA6

Topic: G.08. Drugs of Abuse and Addiction

Support: NIH/NIAAA R21 AA022367

NIH/NCATS UL1 TR001449

NIH/NCATS KL2 TR001448

Title: Influence of alcohol on cortical arousal in distressed violent partners.

Authors: *B. C. FINK[1], E. D. CLAUS[3], J. F. CAVANAGH[2], D. A. HAMILTON[2], B. C. HOWELL[2], S. SALWAY[1];
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Abstract: Intimate partner violence (IPV) is a significant public health problem for which there are currently no effective treatments. Alcohol use is present in most instances of IPV and is associated with an increase in the frequency and severity of IPV. Because over-arousal is the state most likely to facilitate emotionally driven aggression, the current study investigated the influence of alcohol on cortical arousal when participants were exposed to evocative partner stimuli. We hypothesized that normal increases in cortical arousal after acute alcohol exposure are potentiated by evocative partner stimuli. To test this hypothesis, ten (six female, four male) distressed violent (DV) partners participated in a placebo-controlled alcohol administration study during which electroencephalography (EEG) measures of cortical arousal were collected while participants engaged in an emotion-regulation task. A 2 (alcohol vs. placebo beverage) x 2 (evocative vs. neutral partner stimuli) analysis of variance of EEG power spectra responses was conducted. Results show statistically significant differences in activation in Beta (13-30 Hz, alertness & vigilance) and Alpha (8-12 Hz, wakefulness), and reduced activation in Theta (4-8 Hz, low alertness) and Delta (0-4 Hz, drowsiness) frequencies in response to evocative partner clips versus neutral partner clips under acute alcohol exposure. The results from this study suggest that under conditions of acute alcohol exposure, participants evidence cortical responses consistent with over-arousal. These findings provide preliminary evidence that the increase in the frequency and severity of IPV may be the result of a process of over-arousal. These findings also suggest that over-arousal may be an important target for novel intervention with IPV.

Disclosures: **B.C. Fink:** None. **E.D. Claus:** None. **J.F. Cavanagh:** None. **D.A. Hamilton:** None. **B.C. Howell:** None. **S. Salway:** None.

Poster

824. Alcohol: Behavioral Studies II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 824.08/AAA7

Topic: G.08. Drugs of Abuse and Addiction

Support: Faculty for Undergraduate Neuroscience Equipment Loan Grant

Title: Moderate chronic fetal alcohol exposure causes motor learning deficits in adult outbred swiss-webster mice

Authors: *T. H. REEKES[1], T. VINYARD, III[1], W. ECHOLS[1], A. EUBANK, III[1], M. BOULDIN[1], W. MURRAY[1], S. BREWER[1], B. BROWN[1], H. WILLIS, Jr[1], Z. TABRANI[1], C. FAVERO[2], E. B. D. CLABOUGH[1];
[1]Biol., Hampden-Sydney Col., Hampden Sydney, VA; [2]Ursinus Col., Collegeville, PA

Abstract: Prenatal ethanol exposure can negatively affect development, causing physical and/or cognitive deficits in the offspring. Behavioral changes are typically characterized in the early postnatal period, but they can also persist into adulthood. The extent of Fetal Alcohol Spectrum Disorder (FASD) abnormalities depends upon the amount and manner of ethanol intake, leading to the development of a large variety of animal models. In order to mimic the genetically diverse human condition, we examined an outbred strain of mice exposed to chronic gestational ethanol and characterized subsequent behavioral alterations during adulthood. To detect deficits in cognitive ability and/or motor function, we ran the mice through tests designed to detect either memory/learning ability or motor strength/skill. We tested cognitive responses using the Barnes Maze and the Open Field Aversion Test, and motor skills using Kondziela's Inverted Screen Test and the rotorod. As adults, the FASD mice showed no significant differences on grip strength, open field, or the Barnes maze; however, we found that outbred mice who had experienced moderate prenatal ethanol exposure were slower to learn the rotorod as adults, though they did not differ in overall performance. Our data suggests a specific FASD vulnerability in motor learning ability, and also opens the door to further investigation on the effect of ethanol on brain areas involved in motor learning, including the striatum.

Disclosures: **T.H. Reekes:** None. **T. Vinyard:** None. **W. Echols:** None. **A. Eubank:** None. **M. Bouldin:** None. **W. Murray:** None. **S. Brewer:** None. **B. Brown:** None. **H. WIllis:** None. **Z. Tabrani:** None. **C. Favero:** None. **E.B.D. Clabough:** None.

Poster

824. Alcohol: Behavioral Studies II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 824.09/AAA8

Topic: G.08. Drugs of Abuse and Addiction

Support: NIH AA021445

Title: Compulsive alcohol drinking involves focusing on optimal responding

Authors: *F. W. HOPF[1], D. DAREVSKY[2];
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Abstract: Purpose: Alcohol addiction remains a major social, economic and emotional cost. Compulsive drives, where drinking continues even in the face of negative consequences (loss of job, family or freedom), represent a particular and potent obstacle to successful treatment. Our lab's recent findings suggest that compulsive drinking involves conflict between desired intake and feared consequences, which recruits cortical circuits and specific NMDAR subtypes,

providing a specific intervention for compulsive drives for alcohol. Also, binge drinking is particularly harmful for developing addiction and damaging organs, and is characterized by concentrated drinking in less time in order to reach greater intoxication (due to larger blood alcohol peaks). Thus, we used a lickometer system to examine whether rats exhibited concentrated patterns of intake, and perhaps increased motivation for intoxicating effects, during what has been considered binge-like or compulsion-like alcohol consumption. Methods: Adult male rats drank alcohol under an intermittent schedule (Monday, Wednesday and Friday overnights) which is known to strongly escalate drinking, a sign of addictive behavior. After ~3 months, rats drank 20 min/day, 5 days/week for ~1 month, and then intake patterns were assessed using lickometers. For each rat (n=14) we analyzed 4 alcohol-only sessions (binge intake) and 4 sessions of alcohol adulterated with bitter quinine (compulsion-like drinking). Different parameters of licking were analyzed using multiple linear regression and other methods. Results: We used different time values as a cutoff to consider a series of licks to have occurred within the same bout. With the widely used 1 sec cutoff, our results support we find both binge and compulsive drinking to be focused around an optimal responding pattern, with compulsive drinking slightly but significantly more focused than binge-like licking. We also studied how using different bout cutoff measures allowed us to define more precisely parts of responding that were more likes “microbouts” that were gathered into a longer “macrobout” that allowed very sustained intake and thus larger predicted intoxication effects. Conclusions: Concentrated patterns of intake during binge-like or compulsion-like alcohol consumption could imply increased motivation for stronger acute pharmacological effects of alcohol.

Disclosures: F.W. Hopf: None. **D. Darevsky:** None.

Poster

824. Alcohol: Behavioral Studies II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 824.10/AAA9

Topic: G.08. Drugs of Abuse and Addiction

Support: AA006420 (OG)

AA020608 (OG)

AA022977 (OG)

Title: Voluntary induction of alcohol dependence in rats self-administering alcohol vapor

Authors: *O. GEORGE, M. D. COLE, G. DE GUGLIELMO;
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Abstract: A major issue in the alcohol field is the lack of animal models of the voluntary induction and maintenance of alcohol dependence in outbred rodents. While outbred rats will readily self-administer alcohol, the amount of alcohol consumed usually does not produce blood alcohol levels (BALs) that are clinically relevant to alcoholism and does not produce somatic, affective, or motivational withdrawal symptoms. Currently, the most widely used animal models use forced exposure to a liquid diet or passive exposure to chronic intermittent ethanol (CIE) vapor to produce clinically relevant BALs and motivational withdrawal. These animal models were instrumental in determining the consequences of chronic exposure to alcohol on the body and brain function, but they cannot be used to unveil the neuronal networks that mediate the voluntary (*vs*. passive) induction and maintenance of alcohol dependence. Here, we describe the development and validation of a novel animal model of the voluntary induction of alcohol dependence using self-administration of alcohol vapor in outbred rats, termed Voluntary Chronic Intermittent Ethanol (V-CIE). We first developed a novel apparatus that allows rats to self-administer alcohol vapor for 8 h/day and achieve BALs of ~150 mg%. The apparatus is composed of a standard rat home cage equipped with a nosepoke hole and a cue light on each side of the chamber, connected to a custom-made alcohol vaporization system that is controlled by a Med Associates smart card. Animals were trained to self-administer alcohol vapor under continuous and intermittent access. The data showed that naive outbred rats that were given intermittent access to alcohol vapor self-administration progressively increased their responding for alcohol to reach BALs in 150-200 mg% range and exhibited somatic signs of withdrawal during acute abstinence. The rats also exhibited increased motivation to self-administer alcohol vapor during abstinence when tested under a progressive-ratio schedule of reinforcement. Finally, the rats exhibited increased anxiety-like behavior, and hyperalgesia during abstinence. These results validate V-CIE as a novel animal model of voluntary induction and maintenance of alcohol dependence in outbred rats. The V-CIE model may be particularly useful for unveiling the neuronal networks that are responsible for the voluntary induction and maintenance of alcohol dependence and may improve translational studies by providing preclinical researchers with an animal model with better face validity than previous animal models.

Disclosures: O. George: None. **M.D. Cole:** None. **G. de Guglielmo:** None.

Poster

824. Alcohol: Behavioral Studies II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 824.11/AAA10

Topic: G.08. Drugs of Abuse and Addiction

Support: R00AA021782 (JRB)

R01AA12882 (SFL)

Title: Long-term binge-like ethanol drinking is predicted by rearing behavior in Long-Evans rats

Authors: S. PANDEY[1], P. BADVE[1], S. F. LEIBOWITZ[2], *J. R. BARSON[1,2];
[1]Neurobio. and Anat., Drexel Univ. Col. of Med., Philadelphia, PA; [2]Behavioral Neurobio., The Rockefeller Univ., New York, NY

Abstract: While behaviors such as risk-taking, sensation-seeking, and anxiety have been shown to predict long-term alcohol abuse in humans, there are few studies linking these behaviors to binge-like ethanol drinking in rodents. In the present study, we investigated if such behaviors might reliably identify rats prone to long-term excessive ethanol drinking. Ethanol-naïve adult male Long-Evans rats (N=23) were first examined for their activity in novel activity chamber, activity in a familiar activity chamber, exploration in a hole board apparatus, and anxiety in an elevated plus maze; they were then tested over nine weeks for ethanol drinking using the intermittent-access 20% ethanol 2-bottle-choice drinking paradigm. Average daily drinking ranged from 1.2 to 8.7 g/kg, with 30-minute intake resulting in blood ethanol concentrations ranging from 0 to 123 mg/dl. As a predictor of average weekly intake, only vertical time (duration of rearing) in a novel activity chamber emerged through multiple regression analysis as a significant variable ($\beta=0.65$, $p<0.01$). Consistent with this, a significant positive correlation was observed between vertical time in the novel chamber and weekly ethanol drinking across all eight weeks after the first week of access ($r=+0.53$ to $+0.71$, $p<0.01$) and, using tertile split, drinking was found to be significantly higher among rats with more compared to less vertical time in the chamber (6.5 vs. 3.7 g/kg, $p<0.05$). Vertical time in a familiar chamber, however, showed significant positive correlations with drinking only during some of the access weeks (weeks 1, 2, 5, 6, and 9; $r=+0.42$ to $+0.46$, $p<0.05$), and time spent in the open arm of an elevated plus maze showed a significant positive correlation with drinking only during week 1 ($r=+0.44$, $p<0.05$). In order to determine if time spent rearing in a novel chamber might reflect a stable trait, a separate group (N=16) of ethanol compared to water drinkers (n=8/group) was tested 30 minutes after the start of daily access and was found to show no difference in vertical time in the novel chamber ($p=0.41$) despite showing an increase in horizontal time ($p<0.05$). This suggests that vertical time in a novel activity chamber is unaffected by a history of ethanol drinking. All together, these results demonstrate that individuals prone to higher levels of long-term binge-like ethanol drinking can be identified by increased time spent rearing in a novel activity chamber. This strong predictor should allow for an exploration of the neurobiological underpinnings of alcohol abuse.

Disclosures: **S. Pandey:** None. **P. Badve:** None. **S.F. Leibowitz:** None. **J.R. Barson:** None.

Poster

824. Alcohol: Behavioral Studies II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 824.12/AAA11

Topic: G.08. Drugs of Abuse and Addiction

Title: Decreased sensitivity to the initial rewarding effects of EtOH in high alcohol preferring vs. low alcohol preferring mice.

Authors: *Z. J. KOZICK[1], N. J. GRAHAME[3], J. E. GRISEL[2];
[1]Bucknell Univ., Danville, PA; [2]Bucknell Univ., Lewisburg, PA; [3]Psychology, IUPUI, Indianapolis, IN

Abstract: Research indicates that alcohol consumption is a complex trait, impacted by many environmental and genetic factors. In order to investigate genetic substrates of alcoholism, high alcohol preferring (HAP) and low alcohol preferring (LAP) mice were selectively bred from common progenitors. After about 12 generations, the difference in voluntary consumption is profound: HAPs readily voluntarily consume 12 g/kg/day, while LAPs barely exceed 2 g/kg/day. Our research is aimed at exploring the relationship between consumption and the pleasure associated with drug effects. We assessed initial subjective reward to different doses of alcohol using a conditioned place preference (CPP) paradigm. This paradigm allows us to measure the preference that mice have for a context associated with a first exposure to alcohol compared to one associated with saline. We tested HAP and LAP mice following a range of doses and HAP mice find EtOH rewarding at higher doses than LAP mice. These data support the contention that high drinking may reflect an attempt to compensate for reduced reward sensitivity. A better understanding of the factors that contribute to excessive alcohol consumption may lead to more effective treatments and intervention for alcoholism.

Disclosures: Z.J. Kozick: None. **N.J. Grahame:** None. **J.E. Grisel:** None.

Poster

824. Alcohol: Behavioral Studies II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 824.13/AAA12

Topic: G.08. Drugs of Abuse and Addiction

Support: NIH NIAAA 020537

Title: The effects of chronic intermittent ethanol exposure on the extinction and recall of fear memories-the impact of sex.

Authors: *J. T. GASS, R. NEWSOM, J. MCGONIGAL;
Neurosciences, Med. Univ. South Carolina, Charleston, SC

Abstract: Alcohol Use Disorder (AUD) and fear-related disorders share many overlapping neural circuits. AUD and PTSD are highly comorbid, with rates as high as 41-79%. Even with increasing rates of PTSD in recent years, there has been little investigation into the neural mechanisms associated with this disorder that may interact with alcohol abuse. Current extinction-based exposure therapies are ineffective but a renewed interest in the neurocircuitry involved in extinction learning may provide critical insights necessary to develop novel pharmacological interventions. While prevalence rates for AUD/PTSD comorbidity differ between the sexes, very few studies have examined this in rodent models. Thus the current studies examined the impact of chronic intermittent ethanol (CIE) exposure on fear conditioning, extinction of fear behaviors, extinction memory recall, and cue induced ethanol consumption in both male and female rats. Rats were first exposed to a rodent model of PTSD using fear conditioning with an "ABA" experimental design. After fear conditioning, rats were exposed either CIE or air exposure for two weeks. Prior to the ethanol/air exposures, each rat was briefly placed in the fear environment to activate the fear memory. Rats were then exposed to an extinction training regimen of daily sessions of 10 extinction trials consisting of tone (CS) presentations only. A "contextual" recall test followed 2 days after extinction. CIE female rats acquired fear conditioning at a faster rate compared to all other groups. However, both male and female rats exposed to CIE showed an increased resistance to fear extinction and this effect was enhanced in male CIE rats. CIE also resulted in a deficit in extinction memory recall in male rats only. Treatment with CDPPB, an mGlu5 modulator, attenuated extinction deficits observed in male CIE rats. Additionally, exposure to fear related cues significantly increased alcohol consumption in male CIE rats compared to controls. We are currently examining the ability of CDPPB to attenuate CIE-induced extinction deficits in females and the ability of fear cues to increase alcohol intake in CIE females. These results suggest that exposure to chronic alcohol after fear memory reactivation has differential effects in males and females. CIE leads to deficits in the ability to extinguish fear behaviors in both sexes and deficits in extinction memory recall in CIE males. CDPPB attenuates these deficits suggesting that enhancement of glutamatergic activity facilitates learning during extinction training. Together, these results suggest novel pharmacological targets for the treatment of individuals who suffer from AUD/PTSD comorbidity.

Disclosures: **J.T. Gass:** None. **R. Newsom:** None. **J. McGonigal:** None.

Poster

824. Alcohol: Behavioral Studies II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 824.14/AAA13

Topic: G.08. Drugs of Abuse and Addiction

Support: NHMRC Grant 1061979

NHMRC Grant 1049427

NIH Grant NS59910

ARC Grant FT1110884

Title: Investigating the neuronal effects of prolonged alcohol and sugar use and identifying novel pharmacotherapeutics that reduce consumption following long-term intake.

Authors: *P. M. KLENOWSKI[1], O. L. PATKAR[1], M. SHARIFF[1], A. BELMER[1], M. J. FOGARTY[2], M. C. BELLINGHAM[2], S. E. BARTLETT[1];
[1]Queensland Univ. of Technol., Brisbane, Australia; [2]Univ. of Queensland, Brisbane, Australia

Abstract: Prolonged alcohol and sugar abuse can cause significant changes to brain structure and function. Moreover, repeated cycles of binge-like intake and abstinence are thought to produce adaptive changes that facilitate the transition to dependence. We have used an intermittent two-bottle choice drinking paradigm to 1) determine the long-term effects of binge-like ethanol and sugar consumption on neuronal morphology and activity in brain areas implicated in the development of addiction and 2) identify novel pharmacotherapeutics that reduce consumption following long-term intake. We show that long-term ethanol consumption significantly alters the morphology and neuronal activity of pyramidal neurons in the medial prefrontal cortex and the basolateral amygdala. Additionally, long-term consumption of sucrose in a binge-like manner altered the morphology of medium spiny neurons in the nucleus accumbens shell. We have also identified pindolol and varenicline as novel treatment options to reduce alcohol and sugar consumption respectively, following long-term intake.

Disclosures: **P.M. Klenowski:** None. **O.L. Patkar:** None. **M. Shariff:** None. **A. Belmer:** None. **M.J. Fogarty:** None. **M.C. Bellingham:** None. **S.E. Bartlett:** None.

Poster

824. Alcohol: Behavioral Studies II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 824.15/AAA14

Topic: G.08. Drugs of Abuse and Addiction

Support: NIH Grant AA021233

Title: Alcohol sensitivity and alcohol induced toxicity increase with aging in *Drosophila*

Authors: *A. K. DENOBREGA, A. P. MELLERS, E. NOAKES, K. PIQUE, L. C. LYONS; Biol. Science, Program of Neurosci., Florida State Univ., Tallahassee, FL

Abstract: Alcohol abuse and its physiological consequences during middle age and in older adults is a serious problem given the rising populations in these age groups and the increased sensitivity to alcohol in aged individuals (CDC, 2015). Alcohol consumption and the incidence of alcohol abuse are increasing in middle-aged and older adults. The patterns of alcohol consumption differ considerably between age groups as older individuals drink more frequently but consume fewer drinks at a time (Institute of Alcohol Studies, 2013). Although increased sensitivity to alcohol-induced motor and cognitive impairments can be observed in aged rodents as well as humans, little research has been done to identify the effects of acute alcohol on aged individuals (Novier et al., 2015). To understand changes in alcohol toxicity with aging, it is necessary to identify the endogenous factors affecting alcohol sensitivity as these changes start to occur during middle age. Compared to the neuronal complexity of mammalian systems, the simple circuitry of *Drosophila melanogaster* makes *Drosophila* a valuable model for identifying important factors and mechanisms in alcohol neurobiology (Guarnieri & Heberlein, 2003) as well as an excellent model for aging studies (Giebultowicz, 2015). Previously, we found that the circadian clock regulates acute behavioral sensitivity to alcohol in young flies (Van der Linde & Lyons, 2011, De Nobrega & Lyons, 2016). In the current studies, we investigated the role of the circadian clock on alcohol sensitivity during aging in flies. We found that as flies age, alcohol sensitivity to a single exposure to alcohol increases and the circadian regulation of alcohol sensitivity weakens. The greatest changes in alcohol sensitivity occurred during the subjective day with flies becoming increasingly more sensitive to alcohol. Furthermore, the circadian clock modulates alcohol-induced mortality with significantly greater toxic effects of alcohol observed greater during the subjective night. Alcohol-induced mortality increases primarily during the subjective day in older flies. We found similar results using a 3-day repeat binge model of alcohol exposure. Importantly, these studies determined that aging-induced alcohol toxicity changes first occur during early middle age. Overall our results indicate that as flies age, the sensitivity to alcohol increases and the circadian regulation of alcohol behaviors dampens with

the greatest changes observed during the subjective day, suggesting that the circadian clock acts as a protective buffer against the toxic effects of alcohol.

Disclosures: **A.K. Denobrega:** None. **A.P. Mellers:** None. **E. Noakes:** None. **K. Pique:** None. **L.C. Lyons:** None.

Poster

824. Alcohol: Behavioral Studies II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 824.16/AAA15

Topic: G.08. Drugs of Abuse and Addiction

Support: NIAAA Grant AA020929

NIAAA Grant AA014095

NIAAA Grant AA010761

VA Medical Research

Title: Fear conditioned cues increase voluntary ethanol intake in mice with a history of chronic intermittent ethanol exposure.

Authors: *H. HAUN[1], I. ROBBINS[1], J. GASS[1], M. LOPEZ[1], H. BECKER[2,1];
[1]Med. Univ. of South Carolina, Charleston, SC; [2]Med. Univ. of South Carolina & VAMC, Charleston, SC

Abstract: Previous studies have shown that chronic intermittent ethanol (CIE) exposure can produce deficits in the extinction of fear-conditioned memories in mice. CIE exposure also induces escalation of voluntary ethanol intake. This study aimed to evaluate the effect of fear conditioning (FC) and extinction (EXT) of fear responses on voluntary ethanol intake within the CIE-Drinking model. Adult male C57BL/6J mice were allowed to drink ethanol in their home cage 24 hr/day (15 % ethanol vs. water). After a baseline drinking period, mice were exposed to weekly cycles of either chronic intermittent ethanol vapor (CIE group) or air (CTL group) exposure (16 hr/day for 4 days). At 72 hrs after each CIE (or air) exposure cycle, mice resumed drinking for five days. Once the expected increase in voluntary ethanol intake was observed in CIE mice, FC and EXT took place 3 hrs before mice were allowed to drink ethanol. During FC, half of the CTL and CIE mice were placed in a conditioning box and received foot-shock presentations signaled by a tone. A history of CIE exposure did not affect FC acquisition (freezing during tone presentations). Also, FC did not affect ethanol intake in CTL or CIE mice

compared to mice that did not experience FC. After another cycle of CIE (or air) exposure, mice were tested for EXT of the fear response over five consecutive days. As expected, EXT was impaired in CIE mice compared to CTL mice (percent time freezing was 69.3±6.9 sec for CTL and 78.2±6.4 sec for CIE on the first day ($p<0.05$)). Further, repeated sessions of EXT resulted in enhanced voluntary ethanol intake in CIE mice but not CTL mice when compared to CTL and CIE treatment alone (CTL=10 g/kg; CIE=12 g/kg; CTL+EXT=10g/kg; CIE+EXT=14g/kg). In a separate study, we probed extinction circuitry to determine if inhibition of infralimbic cortex (IL) projections to the basolateral amygdala (BLA) impairs extinction similar to the effect of CIE exposure. Briefly, AAV virus containing the hM4Di DREADD was infused into the IL and guide cannulae were inserted above the BLA. Four weeks after surgery, FC and EXT took place, and clozapine-*N*-oxide (CNO) was infused into the BLA 5 min prior to EXT sessions. Inactivation of IL projections to the BLA resulted in significantly impaired extinction across 3 days, mimicking the effect of CIE on extinction. Together, these results show that exposure to cues associated to stress favors higher levels of ethanol intake, particularly in ethanol dependent mice. Results also suggest that IL-BLA projections are necessary for extinction of stress-associated memories. Future studies will determine if excitation of the IL-BLA circuit can enhance extinction in mice with a history of CIE exposure.

Disclosures: H. Haun: None. **I. Robbins:** None. **J. Gass:** None. **M. Lopez:** None. **H. Becker:** None.

Poster

824. Alcohol: Behavioral Studies II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 824.17/AAA16

Topic: G.08. Drugs of Abuse and Addiction

Title: Single-exposure conditioned place preference to alcohol in Sprague-Dawley rats: Evidence for a generalizable model of initial sensitivity to alcohol

Authors: *T. B. NENTWIG, K. P. MYERS, J. E. GRISEL;
Psychology, Bucknell Univ., Lewisburg, PA

Abstract: Despite urgent need and ample effort, the neural and behavioral predisposition for alcohol use disorders remains poorly understood. Numerous studies suggest the initial sensitivity to alcohol's reinforcing properties is an important endophenotype in understanding the trajectory toward excessive drinking (Ray et al., 2016). Previous findings in our lab demonstrate robust, reliable conditioned place preference to a single moderate dose of alcohol in mice (Grisel et al., 2014). Here, we provide similar evidence for single exposure conditioned place preference (SE-

CPP) to alcohol in adult male Sprague-Dawley rats. The SE-CPP is a 3-day procedure conducted over the span of 5 days, including conditioning on days 1 and 3, and testing on day 5. We used an unbiased, three-compartment Plexiglas apparatus comprised of two distinct floor tile patterns in the conditioning compartments and a stimulus-neutral, white floor in the center compartment. On each conditioning day, rats were relegated to either conditioning compartment for 30 minutes, immediately following an intraperitoneal (i.p.) injection of 1.0g/kg of ethanol (EtOH) or equivolume saline (counterbalanced across floor type). On the test day, rats received an i.p. injection of saline and then were placed in the center of the apparatus, allowing free movement throughout the apparatus. Rats preferred the EtOH-paired floor to the saline-paired floor, and time on the EtOH-paired floor was significantly above chance. These results extend our previous findings in mice and generalize our model of single-exposure conditioned place preference as an assay for initial sensitivity to the rewarding properties of alcohol.

Disclosures: T.B. Nentwig: None. **K.P. Myers:** None. **J.E. Grisel:** None.

Poster

825. Alcohol: Brain Circuitry I

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 825.01/AAA17

Topic: G.08. Drugs of Abuse and Addiction

Support: NIAAA Grant T32-07456

NIH Grant AA022977

NIH Grant AA020608

Title: Whole brain Fos mapping in alcohol dependent and non-dependent rats: the impact of withdrawal, anticipation of drinking, and alcohol drinking

Authors: *A. J. KIMBROUGH[1], O. GEORGE[2];
[1]CNAD, The Scripps Res. Inst., LA Jolla, CA; [2]CNAD, The Scripps Res. Inst., La Jolla, CA

Abstract: Withdrawal from drugs of abuse produces severe negative affective states often leading to further drug use to dampen these effects. Some of the symptoms of withdrawal from alcohol include increased anxiety-like behavior, depression-like behavior, hyperalgesia and a profound craving for alcohol. Several brain regions have been identified as being active during withdrawal from alcohol drinking. However, it is not known whether the brain regions are active in response to anticipation of drinking, the effects of withdrawal, or a combination of the two. Thus, we sought to delineate the differences between anticipation for drinking and withdrawal on

brain activity using a novel approach to reconstruct whole brain activation of Fos. Rats (n=24) were trained to self administer alcohol for 30 minutes daily on a FR1 schedule until a stable baseline of responding was reached. Rats were then made dependent (n=12) to alcohol using chronic intermittent ethanol vapor (CIE). Briefly, animals were exposed to 14 hours of ethanol daily, allowed 10 hours off and maintained at blood alcohol levels of 150-250% during testing. Subsequent behavioral testing occurred 6-8-h into withdrawal in dependent rats. Another group of rats was exposed to air (non-dependent; n=12). After stabilization of escalation of alcohol drinking rats were perfused and the brains collected for Fos immunohistochemistry. Brains were collected from dependent and non-dependent rats before (dependent-anticipation; n=6; non-dependent-anticipation; n=6) and after (dependent-drinking; n=6; non-dependent-drinking; n=6) self administration. Additionally, brains were collected from a vapor dependent group with no prior drinking experience (withdrawal only; n=6) and naïve animals (n=5). Sections were then captured using a slide scanner and analyzed for Fos neuronal counts in various brain regions. As expected, dependent rats showed escalated intake for alcohol after vapor exposure compared to non-dependent rats. Analysis of groups that underwent drinking experience (both non-dependent and dependent) is currently underway. Identification of the neuronal network underlying alcohol withdrawal *vs* anticipation of alcohol drinking *vs.* alcohol drinking will be described.
Supported by: Grant: AA022977, AA020608, NIAAA Grant T32-07456

Disclosures: A.J. Kimbrough: None. **O. George:** None.

Poster

825. Alcohol: Brain Circuitry I

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 825.02/AAA18

Topic: G.08. Drugs of Abuse and Addiction

Support: Russian Science Foundation Grant #14-28-00229

Title: Acute alcohol administration before Task 2 learning diminishes Task 1 memory assemblies reactivation mapped by Fos expression

Authors: *O. E. SVARNIK[1], I. I. RUSAK[2], A. I. BULAVA[2], Y. I. ALEXANDROV[2]; [1]Inst. of Psychology RAS, Moskva, Russian Federation; [2]Inst. of Psychology RAS, Moscow, Russian Federation

Abstract: Although ethanol has been shown to impair acquisition of memory, its effect on consolidated memories is not clear. Recent reports revealed that memory retrieval converted consolidated memory into a labile state and initiated the reconsolidation process. To examine

effects of acute ethanol administration on the reactivation of recent memory of Skill 1 during the acquisition of Skill 2 we trained rats two operant tasks sequentially: a water-acquisition task first and a food-acquisition task second. The operant water-acquisition task was to touch a lever by the left or right vibrissal pad in order to receive a drop of water. Animals overtrained Skill 1 over a period of several days. After that animals had one session of the operant food-acquisition task of pedal pressing in another cage, which they have been pre-exposed to during daily 5-minute sessions. The acquisition of Task 2 was either under alcohol (0.5 g/kg) administration or without it. Animals were sacrificed 75 minutes after the end of that session. Expression of c-Fos was studied by immunocytochemistry in the retrosplenial and the barrel cortices. Task 2 acquisition induced more Fos-positive neurons in the barrel cortex of the hemisphere contralateral to the vibrissal pad used during Task 1 than in the one of the ipsilateral hemisphere. No differences between the hemispheres were found in the retrosplenial cortex. The number of Fos-positive neurons in the correspondent barrel cortex after the second task was significantly higher in good learners of the first task. The number of Fos-positive neurons after the second task was unrelated to the success in learning of the second task. Our results suggest that c-Fos expression in the barrel cortex after the food-acquisition learning occurred in those neurons that were already specialized in relation to the operant water-acquisition task and underwent reactivation. Animals under alcohol administration were less active than normal but did not differ in a learning rate. We also found that ethanol attenuated induction of c-Fos expression in the barrel cortex preventing further differentiation of that experience.

Disclosures: O.E. Svarnik: None. **I.I. Rusak:** None. **A.I. Bulava:** None. **Y.I. Alexandrov:** None.

Poster

825. Alcohol: Brain Circuitry I

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 825.03/AAA19

Topic: G.08. Drugs of Abuse and Addiction

Title: The effects of chronic binge alcohol exposure on amphetamine reward behavior, correlation with nucleus accumbens c-Fos expression

Authors: *L. O'LOUGHLIN, C. IRVING, J. NORENA, S. GALER, P. IVAIN, C. CHADWICK, K. ELISMAN, J. A. SCHROEDER;
Connecticut Col., New London, CT

Abstract: The use of psychostimulants and alcohol is widely prevalent on college campuses and schools are taking notice by adding prevention and treatment programs for students. Since

alcohol is the most available and typically the first drug of choice for college students, it is often deemed a gateway drug to other drugs of abuse. This study looked at the effects of chronic binge alcohol exposure on amphetamine reward behavior in rats measured via conditioned place preference. Rats were exposed to either a 1% sucrose or a 1% sucrose/1% alcohol solution for 4 hours/days for 21 days and then underwent a 6 day biased amphetamine conditioned place preference paradigm. Both groups displayed a significant place preference to amphetamine, however there was no significant difference between the degree of amphetamine place preference between the alcohol and sucrose groups $t(14) = -1.478$, $p = .162$. However, there was a significant positive correlation between alcohol consumption and place preference change $r(7) = .857$, $p = .007$. Overall, rats consumed significantly more sucrose solution than alcohol/sucrose solution. This study also looked at the effects of c-fos expression in the nucleus accumbens, the major reward center in the brain. Alcohol rats showed a greater activation in the nucleus accumbens core compared to the sucrose group $t(6) = 8.300$, $p = .0002$. Future studies will examine alternative alcohol administration procedures as well as the effects of sucrose exposure on psychostimulant reward behavior.

Disclosures: L. O'Loughlin: None. **C. Irving:** None. **J. Norena:** None. **S. Galer:** None. **P. Ivain:** None. **C. Chadwick:** None. **K. Elisman:** None. **J.A. Schroeder:** None.

Poster

825. Alcohol: Brain Circuitry I

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 825.04/AAA20

Topic: G.08. Drugs of Abuse and Addiction

Title: Stress increases alcohol self-administration via excitatory GABA signaling within the ventral tegmental area

Authors: *A. OSTROUMOV, A. THOMAS, B. KIMMEY, J. KARSCH, W. DOYON, J. DANI;
Univ. of Pennsylvania, Philadelphia, PA

Abstract: A number of epidemiological studies demonstrate that stress increases alcohol intake in humans, but the mechanisms of this interaction remain largely unknown. Alterations in alcohol consumption suggest stress-induced changes in the function of the brain reward circuitry, including mesolimbic dopamine system. Here we demonstrate in rats that exposure to a single restraint stress increases alcohol self-administration over many days, which was associated with a decrease in dopamine (DA) signaling in the ventral tegmental area (VTA) and nucleus accumbens (NAc). Electrophysiological recordings showed that this decreased DA signaling was

mediated by increased GABAergic inhibition onto DA neurons in the VTA. Following stress, local VTA GABA neurons showed a higher firing rate in response to alcohol compared to non-stressed controls. The increase in alcohol-mediated GABA neuron firing after stress was blocked by bath application of picrotoxin, suggesting $GABA_A$-receptor mediated excitation. Furthermore, stress caused functional down-regulation of K^+, Cl^- cotransporter KCC2, impairing chloride homeostasis in VTA GABA neurons, an effect that could contribute to cell excitability in the presence of alcohol. Blocking stress hormone receptors or excitatory GABA signaling in the VTA prevented the attenuated alcohol-induced dopamine response and prevented the increased alcohol self-administration. These results demonstrate that stress alters the neural and behavioral responses to alcohol through a neuroendocrine signal that promotes excitatory GABA transmission.

Disclosures: **A. Ostroumov:** None. **A. Thomas:** None. **B. Kimmey:** None. **J. Karsch:** None. **W. Doyon:** None. **J. Dani:** None.

Poster

825. Alcohol: Brain Circuitry I

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 825.05/AAA21

Topic: G.08. Drugs of Abuse and Addiction

Support: Division of Intramural Clinical and Biological Research of the National Institute on Alcohol Abuse and Alcoholism

Title: Dissociation between ethanol effects on the striatal projections to the substantia nigra and the globus pallidus

Authors: ***K. P. ABRAHAO**, D. M. LOVINGER;
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Abstract: The striatum and its projections mediate action selection and different learning processes. Evidence is emerging that ethanol can alter the function of striatal synapses and neurons. These cellular ethanol actions may affect the development of alcohol use disorders. However, we still need more information on the pharmacological effects of ethanol on specific neurons and synapses in the striatum and other basal ganglia regions. Previous studies showed that acute ethanol exposure depresses synaptic transmission between spiny projection neurons (SPNs, the most abundant neurons of the striatum) (Patton et al., 2016). The SPNs also send GABAergic projections to two main targets: the subtantia nigra pars reticulata (the striatonigral or direct pathway); and the globus pallidus external segment (the striatopallidal or indirect

pathway). The effects of ethanol on projections to these specific targets remain unknown. We used a combination of whole-cell patch clamp recording and optogenetics tools to evaluate the acute ethanol effects on striatonigral and striatopallidal GABAergic synapses. We found that while 50mM ethanol depressed inhibitory postsynaptic currents (IPSCs) at striatonigral synapses, the same ethanol dose slightly potentiated IPSCs at striatopallidal synapses. Ongoing studies are examining the mechanisms underlying these effects and further characterizing the pre-synaptic action of ethanol in the substantia nigra and the globus pallidus. These findings elucidate specific pharmacological effects of ethanol at the synaptic outputs from the striatum. It will be interesting to determine how these effects contribute to the actions of this drug in the basal ganglia that produce intoxication and contribute to alcohol use disorders.

Disclosures: K.P. Abrahao: None. **D.M. Lovinger:** None.

Poster

825. Alcohol: Brain Circuitry I

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 825.06/AAA22

Topic: G.08. Drugs of Abuse and Addiction

Support: NIH Grant AA020919

NIH Grant DA035958

Title: Peripheral dopamine D2 receptors mediate acute ethanol effects on dopamine transmission in the mesolimbic reward system

Authors: *J. D. OBRAY[1], A. J. PAYNE[1], D. M. HEDGES[1], B. GARCIA[1], B. BITTER[1], S. MCCARTHY[1], M. WOODBURY[1], S. HOPE[1], J. G. LEE[2], E. Y. JANG[2], C. H. YANG[2], S. C. STEFFENSEN[1];
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Abstract: Dopamine (DA) D2 autoreceptor (D2R) expression in the midbrain and striatum is a well-known biomarker for brain DA levels. Markers of D2R expression are not only detectable in the brain, but are also expressed in peripheral tissues, including blood, where DA appears to play a pivotal role in mediating communication between the nervous and immune systems. The aim of this study was to evaluate the role of peripheral D2Rs in DA and ethanol effects on DA release in the mesolimbic DA system and ethanol reward in rats. Using fluorescence assisted cell sorting and immunohistochemistry, D2Rs were found to be expressed on all blood WBCs

(granulocytes: 22%; lymphocytes: 35% and monocytes: 45%) as well as in microglia and neurons in the ventral tegmental area (VTA) and in the nucleus accumbens (NAc). *In vitro*, lymphocyte D2R expression was affected by exposure to DA (EC_{50} = 1 uM), while D2R expression in WBCs was unaffected by exposure to ethanol (to 100 mM). *In vivo*, D2R expression in monocytes decreased by 50% 2 hrs after administration of the centrally-acting D2R antagonist eticlopride (1.0 mg/kg IV) and increased by 75% 2 hrs after administration of the centrally-acting D2R agonist quinpirole (0.1 mg/kg IV). Surprisingly, intravenous administration of DA (0.1-3.0 mg/kg) markedly enhanced DA release 2400% in the NAc with a lag of 20 min, which was blocked by the peripheral D2R antagonist domperidone (5 mg/kg), as measured by microdialysis paired with HPLC-ED. Intravenous DA resulted in complex behavioral effects depending upon dose, which included freezing at higher doses and hyperactivity at lower doses. Immunohistochemical studies revealed expression of D2Rs in brain microglia after IV DA or IP ethanol (2.0 g/kg) injection. Most importantly, ethanol enhancement of DA release in the NAc was blocked by IV administration of domperidone. These findings suggest that ethanol, DA and DAergic drugs evince relatively rapid changes in brain and blood D2 receptor expression, that appear to be inversely correlated. In addition, ethanol enhancement of DA release appears to be mediated by a peripheral mechanism involving D2Rs on monocytes. These results challenge the dogma regarding direct ethanol actions on mesolimbic DA transmission. Experiments are ongoing to evaluate the role of peripheral D2Rs in mediating ethanol reward.

Disclosures: **J.D. Obray:** None. **A.J. Payne:** None. **D.M. Hedges:** None. **B. Garcia:** None. **B. Bitter:** None. **S. McCarthy:** None. **M. Woodbury:** None. **S. Hope:** None. **J.G. Lee:** None. **E.Y. Jang:** None. **C.H. Yang:** None. **S.C. Steffensen:** None.

Poster

825. Alcohol: Brain Circuitry I

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 825.07/AAA23

Topic: G.08. Drugs of Abuse and Addiction

Support: NIH Grant AA020919

NIH Grant DA035958

Title: Functional switch in GABA(A) receptors on VTA GABA neurons by acute and chronic ethanol involves brain-derived neurotrophic factor

Authors: *S. S. PISTORIUS, A. C. NELSON, T. J. WOODWARD, H. J. PARK, S. D. BAIR, D. M. MATTHEWS, S. C. STEFFENSEN;
Neurosci., Brigham Young Univ., Provo, UT

Abstract: The motivational effects of opiates and ethanol switch from a dopamine (DA)-independent to a DA-dependent pathway during drug dependence. A corresponding change occurs in ventral tegmental area (VTA) GABA(A) receptors on VTA GABA neurons in opiate-dependent animals, which switch from a GABA-induced hyperpolarization of VTA GABA neurons to a GABA-induced depolarization. The aim of this study was to evaluate GABA(A) receptor-mediated synaptic transmission to VTA neurons under ethanol-naïve, acute and dependent conditions. To accomplish these studies, we used standard cell-attached mode electrophysiology to evaluate acute and chronic ethanol effects on VTA GABA neuron firing rate in CD-1 GAD GFP mice. In saline-injected controls, superfusion of the GABA(A) receptor agonist muscimol decreased VTA GABA and DA neuron firing rate in a dose-dependent manner (IC_{50} = 100 nM). In animals given a single, in vivo intoxicating dose of ethanol (4.0 g/kg) 24 hours before recording, VTA GABA neuron firing rate became relatively resistant to the effects of muscimol. Administration of the NMDA receptor antagonist MK-801 15 min before ethanol injection restored the sensitivity of VTA GABA neurons to muscimol inhibition. Seven days after a single ethanol injection, VTA GABA neuron firing rate was again susceptible to muscimol's inhibitory effects, similar to saline-injected controls. Mice rendered dependent on ethanol by twice daily injections of 3.0 g/kg ethanol for two weeks, or chronic intermittent ethanol (CIE) vapor exposure (200 mg% BAL) for 3 weeks, were relatively resistant to the effects of muscimol, compared to air-exposed controls. Seven days after the last exposure to ethanol vapor, VTA GABA neuron firing rate was still resistant to the inhibitory effects of muscimol. BDNF expression was increased in both the VTA and the nucleus accumbens (NAc) during withdrawal from CIE, even 7 days after, but not after a single *in vivo* injection of ethanol. Dopamine neuron firing rate was sensitive to muscimol, but GABA(A) receptor sensitivity to muscimol did not adapt to acute or chronic ethanol exposure. Work is in progress to evaluate the effects of inactivating the trkB receptor on ethanol effects on VTA neurons and drinking behavior. These findings suggest that VTA GABA neurons exclusively undergo a switch in GABA(A) receptor function in ethanol-dependent animals, similar to opiate-dependent animals. However, there appears to be transient GABA(A) plasticity after a single exposure to ethanol that is mediated by NMDA receptors and not by BDNF. These findings may explain why VTA GABA neurons become hyperexcitable during withdrawal from chronic ethanol exposure.

Disclosures: S.S. Pistorius: None. **A.C. Nelson:** None. **T.J. Woodward:** None. **H.J. Park:** None. **S.D. Bair:** None. **D.M. Matthews:** None. **S.C. Steffensen:** None.

Poster

825. Alcohol: Brain Circuitry I

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 825.08/AAA24

Topic: G.08. Drugs of Abuse and Addiction

Support: NIH Grant AA020919

NIH Grant DA035958

Title: Glutamate NMDA receptor-mediated plasticity in the ventral tegmental area by acute and chronic ethanol

Authors: *A. C. NELSON, T. J. WOODWARD, H. J. PARK, S. S. PISTORIUS, S. D. BAIR, D. M. MATTHEWS, S. C. STEFFENSEN, 84602;
Brigham Young Univ., Provo, UT

Abstract: Recent studies have shown evidence that ventral tegmental area (VTA) dopamine (DA) neurons undergo glutamate (GLU) NMDA receptor-mediated plasticity with drugs of abuse including alcohol. Local circuit GABA neurons, which likely mediate inhibition of DA neurons in the VTA, are important, but understudied, substrates for alcohol effects in the mesolimbic DA system. We have previously reported that VTA GABA neurons are sensitive to physiologically-relevant concentrations of ethanol, exhibit tolerance to acute ethanol, and evince marked hyperactivity during withdrawal from chronic ethanol, which may explain the deficits in DA transmission associated with alcohol dependence. We evaluated GLU NMDA receptor mediated synaptic transmission to VTA GABA neurons during withdrawal from acute and chronic ethanol. Mice in the dependent condition were housed in ethanol vapor chambers with ethanol at 16 hr/day for 3 weeks. To accomplish these studies, we used standard whole-cell, patch-clamp electrophysiological techniques to evaluate excitatory GLU-mediated evoked and spontaneous synaptic transmission to VTA GABA neurons in naïve GAD GFP mice, which facilitated identification of VTA GABA neurons in the slice preparation. Withdrawal from a single *in vivo* exposure to ethanol (4 g/kg), administered 24 hr prior to recording, enhanced the AMPA/NMDA EPSC ratio in VTA GABA neurons. In addition, the frequency, but not the amplitude, of sEPSCs were markedly increased 24 hr after ethanol injection, suggesting that GLU NMDA receptor-mediated plasticity accompanies withdrawal from a single exposure to ethanol. However, the amplitude, but not frequency of mEPSCs was significantly decreased. During withdrawal from a chronic exposure to ethanol there is no significant difference in amplitude or frequency of mEPSCs or AMPA/NMDA ratio. These findings have important implications for understanding the adaptations in the mesolimbic DA reward pathway along the continuum to alcohol dependence.

Disclosures: **A.C. Nelson:** None. **T.J. Woodward:** None. **H.J. Park:** None. **S.S. Pistorius:** None. **S.D. Bair:** None. **D.M. Matthews:** None. **S.C. Steffensen:** None.

Poster

825. Alcohol: Brain Circuitry I

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 825.09/AAA25

Topic: G.08. Drugs of Abuse and Addiction

Support: Wellcome Trust Fellowship grant for VV (093705/Z/10/Z).

Title: Overlapping microstructural and functional connectivity disturbances in binge drinkers: a shift in cortico-limbic neural balance

Authors: ***L. MORRIS**[1], N. G. DOWELL[2], M. CERCIGNANI[2], N. HARRISON[2], V. VOON[1]; [1]Univ. of Cambridge, Cambridge, United Kingdom; [2]Brighton and Sussex Med. Sch., Brighton, United Kingdom

Abstract: Young adult binge-drinkers represent a model for the examination of endophenotypic risk factors for alcohol misuse and early exposure to repeated binge cycles. Chronic or harmful alcohol use leads to neurochemical, structural and morphological neuroplastic changes, particularly in regions associated with reward processing and motivation. We investigate microstructural abnormalities in 29 binge-drinkers compared to 39 matched healthy controls. We use a novel diffusion magnetic resonance imaging (MRI) acquisition and analysis with three-compartment modeling (of intracellular, extracellular and cerebrospinal fluid) to determine brain tissue microstructure features including neurite density and orientation dispersion index (the latter capturing dendritic complexity in gray matter). Binge-drinkers had reduced dorsolateral prefrontal cortex (dlpfc) but increased ventral striatal grey matter orientation dispersion index. Both dlpfc and ventral striatal orientation dispersion were linked to alcohol use severity and a measure of binge-like patterns of alcohol use. Ventral striatal complexity was additionally associated with impulsivity. Multi-echo resting-state functional MRI data were also examined in the same individuals. Binge drinks had decreased connectivity between fronto-parietal regions and increased connectivity between ventral striatum and dlpfc associated with alcohol use severity. We demonstrate decreased complexity and connectivity of higher-order fronto-parietal systems, alongside enhanced complexity of reward-related motivational systems and prefrontal-limbic connectivity. Together the findings illustrate novel microstructural and dissociable functional abnormalities in binge drinkers, highlighting a shift from higher-order cortical towards cortico-limbic processing that may reflect an influence of alcohol bingeing on critical neurodevelopmental processes in an at-risk young adult group.

Disclosures: **L. Morris:** None. **N.G. Dowell:** None. **M. Cercignani:** None. **N. Harrison:** None. **V. Voon:** None.

Poster

825. Alcohol: Brain Circuitry I

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 825.10/AAA26

Topic: G.08. Drugs of Abuse and Addiction

Support: Swedish Research Council (2009-2782 and 2011-4646 and 2015-03219)

LUA/ALF (grant no. 148251) from the Sahlgrenska University Hospital

NovoNordisk

Swedish Society for Medical Research

Title: Neuromedin u regulates alcohol intake and alcohol-induced reward in rodents via the mesolimbic dopamine system

Authors: *D. P. VALLÖF, A. LYDIA KALAFATELI, J. ENGEL, E. JERLHAG;
Dept. of Pharmacol., Univ. of Gothenburg, Goeteborg, Sweden

Abstract: Alcohol use disorder (AUD) is characterized by compulsive drug seeking, loss of control and craving. The social-economic burden for this relapsing psychiatric disorder is substantial and the clinical efficacy of available medications is limited. By investigating the neurochemical mechanisms through which alcohol activates the cholinergic dopaminergic reward link (cholinergic projection from the laterodorsal tegmental area (LDTg) to the ventral tegmental area (VTA) together with dopaminergic neurons of the VTA projecting to the nucleus accumbens (NAc)) novel targets for treatment of AUD may be identified. In contrast to the common view of the function of gut-brain peptides, such as neuromedin U (NMU), to regulate food intake and appetite a novel role in reinforcement mediation has been implied.
Given that the anorexigenic effects of NMU are mediated via NMU2 receptors, which are expressed in several reward related areas in the brain, we hypothesize that these receptors in the reward related area might regulate alcohol reinforcement.
The present series of experiments were designed to evaluate the effect of local administration of NMU, into the NAc, VTA or LDTg on alcohol-induced locomotor stimulation, expression of conditioned place preference (CPP) as well on food intake in mice. In addition, the effect of NMU into NAc on alcohol consumption was evaluated in rats. Local administration of NMU into the NAc significantly attenuated alcohol-induced locomotor stimulation, expression of CPP

and reduced intake of palatable food in mice as well as reduced alcohol intake in rats. Intra-VTA or intra-LDTg NMU administration had no effect on alcohol-induced locomotor stimulation, expression of CPP or intake of palatable food. However, Intra-VTA or intra-LDTg NMU administration reduced the intake of normal chow in mice. Collectively, these data suggest that intra-NAc NMU administration, rather than intra-VTA and intra-LDTg, had an effect on alcohol reinforcements and palatable food. It could be suggested that accumbal NMU2 receptors are involved in the development of AUD.

Disclosures: **D.P. Vallöf:** Other; Elisabet Jerlhag. **A. Lydia Kalafateli:** Other; Elisabet Jerlhag. **J. Engel:** Other; Elisabet Jerlhag. **E. Jerlhag:** Other; Elisabet Jerlhag.

Poster

825. Alcohol: Brain Circuitry I

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 825.11/BBB1

Topic: G.08. Drugs of Abuse and Addiction

Support: 2 R01 DA009411-16

Title: Restraint stress increases acquisition of operant ethanol self-administration in part through stress hormone receptors in the VTA

Authors: ***W. M. DOYON, JR**, N. NEALE, J. A. DANI;
Neurosci., Univ. of Pennsylvania, Philadelphia, PA

Abstract: While many variables contribute to excessive drinking, exposure to stressful life events represents a significant risk factor for increased ethanol use and relapse. To examine the relationship between stress and ethanol intake, we exposed Long-Evans rats to 1 hr of immobilization stress (acute restraint) 15-20 hrs prior to their first EtOH exposure. This single stressful experience was sufficient to increase operant self-administration of 4% EtOH (+0.12% saccharin) for as long as we measured (~12 days). Restraint stress did not alter saccharin intake, suggesting that the stress did not increase general locomotor or hedonic behavior but was specific to ethanol. Blockade of stress hormone receptors with RU486, either by systemic or local administration within the posterior VTA, prevented the stress from increasing ethanol intake. However, in stressed rats that had already transitioned to higher ethanol drinking, RU486 pretreatment did not reliably decrease daily ethanol consumption. To examine other potential mechanisms that contribute to the maintenance of higher ethanol self-administration, we pretreated the animals with minocycline, a microglia inhibitor with anti-inflammatory properties. Minocycline (i.p.) decreased ethanol intake significantly on three different test days compared to

baseline; In addition, local administration of minocycline into the VTA decreased drinking. These results suggest that distinct mechanisms contribute to the acquisition and maintenance of ethanol self-administration induced by stress.

Disclosures: **W.M. Doyon:** None. **N. Neale:** None. **J.A. Dani:** None.

Poster

825. Alcohol: Brain Circuitry I

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 825.12/BBB2

Topic: G.08. Drugs of Abuse and Addiction

Support: NIH Grant AA013983

NIH Grant NS073574

NIH Grant P30 NS047243

Title: GABAA receptor delta-subunit knockdown in the VTA results in sex-specific decreases in binge-like alcohol consumption.

Authors: *L. M. DARNIEDER[1], L. C. MELÓN[2], J. F. DEBOLD[3], K. A. MICZEK[3], J. MAGUIRE[2];
[1]Tufts Univ. Sackler Sch. of Grad. Biomed, Boston, MA; [2]Dept. of Neurosci., Tufts Univ. Sch. of Med., Boston, MA; [3]Dept. of Psychology, Tufts Univ., Medford, MA

Abstract: Binge drinking is an increasingly prevalent form of alcohol consumption and has recently become more common in female drinkers. It involves the ingestion of relatively large (4-5 standard drinks) quantities of alcohol over a short time period, resulting in blood alcohol levels of 0.08 g/dl (NIAAA). Binge drinking also results in a wide array of sex-specific differences in brain and cognitive development that can be seen in both clinical populations and rodent models. Importantly, sex-specific differences are evident in underlying mesocorticolimbic (reward) circuitry, including in the modulation of GABAergic inhibitory neurotransmission. Broadly speaking, extrasynaptic $GABA_A$ receptors ($GABA_A$Rs) incorporating the δ subunit mediate the tonic form of GABAergic inhibition and have been suggested to be particularly sensitive to alcohol. However, it remains controversial whether or not extrasynaptic $GABA_A$Rs are real targets for physiologically and behaviorally relevant concentrations. As such, disentangling the respective contributions of synaptic versus extrasynaptic $GABA_A$Rs in mediating the effects of low dose alcohol has remained difficult. Thus, we sought to better understand the contribution of δ-subunit containing extrasynaptic $GABA_A$ receptors to male and

female binge-like consumption in a region critical to mesocorticolimbic circuitry—the ventral tegmental area (VTA). Male and female floxed *Gabrd* mice were given bilateral, stereotaxic injections into the VTA of either AAV-Cre-GFP or AAV-GFP, thereby allowing for Cre-specific elimination of δ-containing $GABA_A$ receptors. Mice were allowed three weeks for viral expression to occur before being subjected to one cycle of the binge-like drinking protocol, Drinking in the Dark, using 20% ethanol (v/v). Our results indicated that female subjects with VTA-specific δ-excision had a significant decrease in alcohol consumption during the first three days of 2 h access as well as on the final, 4 h binge session. Male subjects had no significant differences in intake. Based on these results, we hypothesize that δ-subunit mediated inhibition in the VTA is (1) integral to the maintenance of binge drinking and (2) that it has a sex-specific role. Future work will both examine whether or not this difference is regulated through changes in ovarian hormones and if this effect is specific to extrasynaptically located $GABA_A$Rs.

Disclosures: L.M. Darnieder: None. **L.C. Melón:** None. **J.F. DeBold:** None. **K.A. Miczek:** None. **J. Maguire:** None.

Poster

825. Alcohol: Brain Circuitry I

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 825.13/BBB3

Topic: G.08. Drugs of Abuse and Addiction

Support: AA022048

AA013573

AA015148

Title: The OX1R is the primary orexin receptor subtype within the ventral tegmental area and central nucleus of the amygdala that selectively modulates binge-like ethanol drinking

Authors: *J. OLNEY[1,2], M. NAVARRO[1,2], T. THIELE[1,2];
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Abstract: Although centrally synthesized exclusively within the hypothalamus, orexin (OX) neurons project to various structures throughout the brain and act on two receptors, OX1R and OX2R, to modulate a host of physiological functions including reward and stress- both of which are important factors that contribute to the motivation to consume alcohol. We and others have recently reported that peripherally administered OXR antagonists curtail binge-like ethanol

drinking; however, these studies were unable to address the specific OX pathways that modulate this behavior. Thus, in an effort to better characterize this circuitry, the present study was designed to elucidate the participation of each OXR within specific brain regions involved in reward- and stress-processing. The "drinking-in-the-dark" paradigm was used to assess binge-like drinking of ethanol or sucrose following bilateral infusion of either the selective OX1R antagonist, SB-334867, or the selective OX2R antagonist, TCS-OX2-29, directly into the ventral tegmental area (VTA) or central nucleus of the amygdala (CeA) of C57BL/6J mice. We observed a marked reduction in initial levels of binge-like ethanol drinking following inhibition of OX1Rs in the VTA and CeA. Additionally, our results suggest that OX2R signaling within the CeA may participate in binge-like ethanol drinking as well. Moreover, subsequent investigations revealed that blocking OX1Rs in these regions did not alter anxiety-like behavior as measured via an open-field locomotor test or the elevated-zero maze. Interestingly, contrary to previous studies that delivered similar compounds systemically, we found no evidence that signaling onto the OX1R in these regions modulates binge-like sucrose consumption. Together, these data demonstrate that hypothalamic OX acts primarily on the OX1R in the VTA and CeA to modulate binge-like ethanol drinking behavior and that separate OX circuitry may govern responding to distinct reinforcers. What is more, the fact that these manipulations did not impact anxiety-like behavior suggests that the OX system likely modulates binge-like ethanol drinking via reward-related circuitry rather than stress-related circuitry. (Supported by NIH grants AA022048, AA013573, & AA015148).

Disclosures: **J. Olney:** None. **M. Navarro:** None. **T. Thiele:** None.

Poster

825. Alcohol: Brain Circuitry I

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 825.14/BBB4

Topic: G.08. Drugs of Abuse and Addiction

Support: NIAAA T32 AA07462

NIAAA AA022821

NIAAA AA007611

NIAAA AA02268

ABMRF

Title: Altered mesocorticolimbic synchrony in selectively bred alcohol preferring versus outbred rats engaged in a cued alcohol drinking task

Authors: *A. M. MCCANE[1], S. AHN[3], L. RUBCHINSKY[2], S. S. JANETSIAN[1], D. N. LINSENBARDT[1], C. L. CZACHOWSKI[1], C. C. LAPISH[1];
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Abstract: Alterations in the mesocorticolimbic (MCL) system have been implicated in numerous substance use disorders, including alcohol use disorder (AUD). Adaptations in this system are associated with enhanced drug seeking behaviors following exposure to cues predicting drug availability. While the biological and neurochemical basis of these adaptations have been characterized it is not known how repeated exposure to drugs, and, importantly, drug-paired cues, alters systems-level neural processing of the MCL system. In the present experiments, we first measured changes in neural activity across the MCL system and second assessed how pharmacological manipulation of cortical dopamine (DA) influenced these measures. Subjects were alcohol preferring (P) and Wistar rats engaged in a Pavlovian conditioning paradigm where the illumination of a stimulus light signaled the availability of an ethanol solution. Upon reaching stable responding in this task, animals were implanted with microelectrodes in the ventral tegmental area (VTA), prefrontal cortex (PFC), and nucleus accumbens (NA) to acquire local field potentials (LFPs). The enzyme catechol-O-methyltransferase (COMT) is the primary mechanism of DA metabolism in the PFC. To assess how cortical DA modulation impacted neural synchrony and corresponding behavioral measures, the COMT inhibitor Tolcapone was administered prior to conditioning sessions on drug test days. Stimulus-evoked voltage changes were observed following the presentation of a light stimulus signaling the availability of ethanol in both lines, and were most pronounced in the PFC of P rats. Phase analyses of the LFPs in the theta band (5-11 Hz) revealed that synchrony was stronger between the NA and PFC than the PFC-VTA or VTA-NA. However, P rats showed reduced NA-PFC synchrony relative to Wistars, except during drinking where robust increases in synchrony were observed. Administration of Tolcapone reduced both alcohol consumption and PFC-NA synchrony in P rats but not Wistars. Alterations in PFC-striatal connectivity has been reported in individuals with AUD. These data highlight the importance of cortico-striatal synchrony in drug seeking behaviors and suggest that extended drinking and/or genetic risk for excessive drinking results in changes in functional connectivity in this neural circuit. Furthermore, these data suggest the potential clinical utility of COMT inhibitors as a therapies for AUD.

Disclosures: **A.M. McCane:** None. **S. Ahn:** None. **L. Rubchinsky:** None. **S.S. Janetsian:** None. **D.N. Linsenbardt:** None. **C.L. Czachowski:** None. **C.C. Lapish:** None.

Poster

825. Alcohol: Brain Circuitry I

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 825.15/BBB5

Topic: G.08. Drugs of Abuse and Addiction

Support: NIAAA R01AA021505 (JW)

NINDS NS074895 (FS)

Development Funds from TAMHSC-VPR (FS and JW)

Title: stroke triggers nigrostriatal plasticity and increases alcohol consumption in rats

Authors: *J. WANG, C. C. HUANG, E. A. R. HELLARD, T. MA, X. WANG, A. SELVAMANI, F. SOHRABJI;
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Abstract: Excessive alcohol consumption is known to be a risk factor for stroke, but the effect of stroke on alcohol intake is unknown. Here, we report that stroke-induced infarction of the dorsolateral striatum (DLS) produced significant increases in alcohol preference, operant self-administration, and relapse. These increases were accompanied with enhanced neuronal activity in the dorsomedial striatum (DMS) and midbrain, two nigrostriatal brain regions that have been tightly linked to drug and alcohol addiction. Specifically, the excitability of DMS and midbrain neurons was increased post-stroke. Furthermore, glutamatergic strength onto DMS D1-neurons was potentiated, whereas GABAergic strength onto DMS-projecting midbrain dopamine neurons was suppressed. Lastly, systemic inhibition of dopamine D1 receptors reverses the stroke-induced increase in operant alcohol self-administration. Given that DMS D1-neurons positively control drug intake, these results suggest that the stroke-induced DLS infarction evoked abnormal plasticity in nigrostriatal dopamine neurons and DMS D1-neurons, contributing to increased post-stroke alcohol seeking and relapse.

Disclosures: J. Wang: None. **C.C. Huang:** None. **E.A.R. Hellard:** None. **T. Ma:** None. **X. Wang:** None. **A. Selvamani:** None. **F. Sohrabji:** None.

Poster

825. Alcohol: Brain Circuitry I

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 825.16/BBB6

Topic: G.08. Drugs of Abuse and Addiction

Support: NIH Grant NS075136

NIH Grant NS091144

The Klingenstein Foundation

NIH Grant MH086403

NIH Grant MH091193

Title: The effect of ethanol metabolite on GABA co-release from nigrostriatal pathway

Authors: *J.-I. KIM, S. GANESAN, L. CHEN, J. DING;
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Abstract: It is understood that repeated binge-like drinking is a gateway to alcoholism, but it is less well established precisely how repeated ethanol exposure leads to an increased likelihood of alcohol preference. Alterations in the dopaminergic system are particularly relevant to alcohol preference because dopamine (DA) is involved in multiple forms of addiction. It is known that, in addition to DA, DA neurons can co-release fast-acting neurotransmitters including glutamate and γ-aminobutyric acid (GABA), suggesting that these additional neurotransmitters co-released by DA neurons may be involved in developing alcohol preference. We previously showed that GABA co-released from midbrain DA neurons was mainly synthesized by the non-canonical GABA synthesizing enzyme, aldehyde dehydrogenase 1a1 (ALDH1a1), whose mutation is linked to human alcoholism. Interestingly, we also found that ethanol could attenuate GABA co-transmission in the striatum, resulting in a reduction of dopaminergic IPSCs in spiny projection neurons (SPNs). However, the mechanism behind this observation remains unknown. In this study, we demonstrate that ethanol does not directly inhibit the oxidation of gamma-amminobutyraldehyde (ABAL) by ALDH1a1, a precursor molecule for GABA synthesis in DA neurons. Instead, we find that an ethanol metabolite can inhibit ALDH1a1 and its synthesis of GABA. In addition, direct treatment of the ethanol metabolite can mimic ethanol action, resulting in a similar decrease in dopaminergic IPSCs in striatal SPNs. Biochemical assays further confirm that the ethanol metabolite works as a potent competitor and inhibits ABAL oxidation, a key step for GABA synthesis mediated by ALDH1a1. These findings suggest that ethanol may exert its influence on dopaminergic GABA co-release via its metabolites. Therefore, ethanol metabolites may also play a critical role in developing alcohol use disorders.

Disclosures: **J. Kim:** None. **S. Ganesan:** None. **L. Chen:** None. **J. Ding:** None.

Poster

825. Alcohol: Brain Circuitry I

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 825.17/BBB7

Topic: G.08. Drugs of Abuse and Addiction

Support: Swedish Research Council (2009-2782 and 2011-4646 and 2015-03219), Swedish Society for Medical Research, The Swedish brain foundation, LUA/ALF (grant no. 148251) from the Sahlgrenska University Hospital, Torsten Söderberg

Alcohol research council of the Swedish alcohol retailing monopoly and the foundations of Adlerbertska, Fredrik and Ingrid Thuring, Tore Nilsson, Längmanska, Wilhelm and Martina Lundgren, Knut and Alice Wallenberg, Magnus Bergvall, Anérs, Jeansons

Åke Wiberg, NovoNordisk, Gothenburg Psychiatry Research Foundation, the Swedish Society of Medicine

Title: Accumbal and laterodorsal glucagon-like peptide 1 receptors regulate alcohol-mediated behaviors in rodents

Authors: *E. JERLHAG, J. A. ENGEL, D. VALLÖF;
Univ. of Gothenburg, Goteborg, Sweden

Abstract: Alcohol use disorder (AUD), relapsing psychiatric disorder, is characterized by compulsive drug seeking, craving and loss of control and is a substantial social-economic cost. The reinforcing properties of alcohol are mediated via activation of the cholinergic-dopaminergic reward link, circuits consisting of the cholinergic projection from the laterodorsal (LDTg) to the ventral tegmental area (VTA) together with dopamine producing neurons in VTA projecting to the nucleus accumbens (NAc). The common view of gut-brain peptides, such as glucagon-like peptide-1 (GLP-1), has recently expanded beyond food intake regulation to include modulation of reinforcement. In the present series of experiments the effect of local administration of a GLP-1 receptor agonist, Ex4, into the NAc, VTA or LDTg on the well-documented effects of alcohol on the mesolimbic dopamine system, namely locomotor stimulation and conditioned place preference (CPP), was investigated in mice. We show that intra-NAc administration of Ex4 prevents alcohol-induced locomotor stimulation and CPP in mice as well as decreases the intake of alcohol intake in rats. Moreover, local administration of Ex4 into the VTA did not affect the ability of alcohol to increase the locomotor activity or to conditioned a place preference, in mice.

Finally we showed that intra-LDTg administration of Ex4 prevents alcohol induced locomotor stimulation and CPP in mice. Collectively the present study show that the neurochemical underpinnings of GLP-1 regulated alcohol reinforcement in rodents involve accumbal as well as laterodorsal GLP-1 receptors. It may thus be concluded that GLP-1 signaling may constitute targets for novel treatment strategies for patients with AUD.

Disclosures: **E. Jerlhag:** Other; EJ has received financial support from the NovoNordisk Foundation. **J.A. Engel:** None. **D. Vallöf:** None.

Poster

825. Alcohol: Brain Circuitry I

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 825.18/BBB8

Topic: G.08. Drugs of Abuse and Addiction

Support: NIAAA/NIH AA023183 (N.S.)

NIDA/NIH DA033533 (N.S)

NIDA/NIH DA037294 (N.S.)

NIAAA/NIH AA020960 (P.P.S.)

NIAAA/AA021667 (P.P.S.)

NIAAA/NIH AA021549 (F.W.)

NIAAA/NIH AA018010 (F.W.)

Title: Neuronal ensembles for behavioral maladaptation: alcohol cue-activated neurons in the nucleus accumbens core mediate the "incubation" of alcohol seeking

Authors: N. SUTO[1], A. LAQUE[1], V. REPUNTE-CANONIGO[1], G. DE NESS[1], G. E. WAGNER[1], T. KERR[1], D. WATRY[1], B. T. HOPE[2], P. SANNA[1], *F. WEISS[1];
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Abstract: As is the case for cue-induced alcohol craving in recovering alcoholics, cue-induced alcohol seeking in alcohol-experienced animals progressively intensifies during protracted abstinence. The brain mechanisms responsible for this behavioral maladaptation or “incubation” of alcohol seeking are not yet known. Given that the nucleus accumbens (NAc) plays a major

role in the environmental control of appetitive behavior, we hypothesized that cue-induced neural activity in this site contributes to the incubation of alcohol seeking. Male Wistar rats were trained to lever-press for alcohol. Insertion of a lever signaled an alcohol session during which each press on the lever resulted in alcohol delivery paired with a light cue. Alcohol sessions were then discontinued and rats remained in homecages until testing for alcohol seeking on the first and fourteenth days of abstinence (D1 & D14). All experimental conditions were identical to those during alcohol sessions, except water substituted alcohol. Lever pressing (extinction response) significantly increased over the fourteen day abstinence (D1 vs. D14). This incubation of cue-induced alcohol seeking accompanied a similarly time-dependent increase in cue-induced neural activity, as indicated by a greater number of neurons expressing the activity marker Fos, in NAc core and shell. However, basal lever pressing on D1 accompanied a significant number of Fos+ neurons in NAc core but not shell - suggesting that cue-induced neural activity in NAc core, rather than shell, drives alcohol seeking. Therefore, we next examined the effects of selective disruption of alcohol 'cue-activated' neurons in NAc core on the (1) execution and (2) incubation of alcohol seeking. For this, male Fos-lacZ transgenic rats were trained as the Wistar rats but tested for alcohol seeking on the first, third and fourteenth days of abstinence (D1, D3 & D14). Daun02 or vehicle was injected into NAc core following the D1 test. In Fos-lacZ rats, Daun02 (prodrug) is converted into daunorubicin (cytotoxin) only in Fos+ neurons, thereby inducing selective apoptosis. Selective disruption of alcohol cue-activated neurons on D1 spared the basal expression (evident on D3) but prevented the intensification (evident on D14) of lever pressing. Thus, cue-induced neural activity in NA core appears to mediate the incubation rather than the execution of cue-induced alcohol seeking. Neuroadaptations unique to distinct sets of alcohol cue-activated neurons or "neuronal ensembles" in NAc core likely trigger the behavioral maladaptation that manifests as the intensified response to alcohol cues during protracted abstinence.

Disclosures: **N. Suto:** None. **A. Laque:** None. **V. Repunte-Canonigo:** None. **G. De Ness:** None. **G.E. Wagner:** None. **T. Kerr:** None. **D. Watry:** None. **B.T. Hope:** None. **P. Sanna:** None. **F. Weiss:** None.

Poster

825. Alcohol: Brain Circuitry I

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 825.19/BBB9

Topic: G.08. Drugs of Abuse and Addiction

Title: Complementary roles for accumbens shell output pathways in preventing and promoting relapse to alcohol seeking

Authors: *G. GIBSON, A. A. PRASAD, J. FRADKIN, J. M. POWER, G. P. MCNALLY; UNSW Australia, Sydney, Australia

Abstract: The nucleus accumbens shell (AcbSh), located in the ventral striatum, plays a critical role in both promoting and preventing relapse to drug seeking and motivated behaviours. The circuit level mechanisms for these dual roles has remained unclear. Here we show that these dual roles can be linked to distinct output pathways from the AcbSh. First we used dual retrograde tracing to map the anatomical relationships between AcbSh medium spiny neurons at the origins of the AcbSh - ventral tegmental area (VTA) and AcbSh - lateral hypothalamus pathways, showing that distinct AcbSh neurons are at the origin of these two pathways. Next we combined retrograde tracing with RNA scope to determine the identities of AcbSh neurons at the origins of these two output pathways. Then, we studied the causal roles of these two pathways in two forms of relapse to alcohol seeking: renewal (i.e. Context-induced reinstatement) and reacquisition. We show that the AcbSh - ventral tegmental area (VTA) pathway mediates renewal and reacquisition of alcohol seeking. Chemogenetic activation of the VTA or optogenetic silencing of the AcbSh-VTA pathway significantly attenuated relapse to alcohol seeking. Optogenetic stimulation of this pathway had no effect on relapse to alcohol seeking, however rats would perform an operant response to receive optogenetic stimulation of this pathway. In contrast, we show that the AcbSh - lateral hypothalamus pathway protects against relapse to alcohol seeking. Chemogenetic silencing of LH or optogenetic stimulation of the AcbSh - LH pathway prevents renewal and reacquisition of alcohol seeking. This protective effect of stimulation of the the AcbSh - LH pathway was behaviourally specific because optogenetic stimulation had no effect on initial or well established alcohol seeking and had no effect on motivation to respond for alcohol.

Disclosures: G. Gibson: None. **A.A. Prasad:** None. **J. Fradkin:** None. **J.M. Power:** None. **G.P. McNally:** None.

Poster

825. Alcohol: Brain Circuitry I

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 825.20/BBB10

Topic: G.08. Drugs of Abuse and Addiction

Support: CNPq

CAPES

UFRGS

UFCSPA

Title: Taurine effects on behaviors and in α_2 $GABA_A$ receptor subunit or BDNF mRNA expression in the frontal cortex of chronically treated or alcohol-abstinent rats

Authors: *F. B. ALMEIDA[1], A. W. HANSEN[2], G. CALETTI[1], S. BANDIERA[2], L. FREESE[1], H. M. T. BARROS[1], R. GOMEZ[2];
[1]Programa de Pós-Graduação em Ciências da Saúde: Farmacologia e Toxicologia, UFCSPA, Porto Alegre, Brazil; [2]Programa de Pós Graduação em Farmacologia e Terapêutica, UFRGS, Porto Alegre, Brazil

Abstract: Alcohol abuse is a public health problem and causes more than 3 million deaths a year. Alcohol withdrawal syndrome increases the risk of relapse and drug-based control of the symptoms may prevent it. Our objective was to investigate the effect of taurine on behaviors and on the expression of α_2-containing $GABA_A$ receptor ($GABA_AR$) and BDNF mRNA in the frontal cortex after chronic alcohol treatment or abstinence in rats. Sixty adult male Wistar rats were allocated into 3 groups: control (CTR), alcoholics (ALC) and 5 days abstinent (ABS) (n = 20/group). CTR received tap water and ALC and ABS groups received 2 g/kg alcohol, twice daily, by oral gavage for 30 days. At day 31, rats were reallocated (n = 10/group) to receive saline or taurine (100 mg/kg, i.p.) for 5 days. During this period, CTR and ABS rats received tap water and ALC rats received 2 g/kg alcohol, twice a day, by oral gavage. On day 33, 1 h after the last taurine/saline and tap water/alcohol administration, rats were exposed to the open field test (OFT) and behaviors were video recorded for further analysis. Rats were killed 24 h later and frontal cortex dissected for α_2 $GABA_AR$ subunit and BDNF mRNA expression by real-time quantitative PCR (qPCR). Our results showed that taurine treatment decreased the rearing in CTR100 rats ($P = 0.024$). Five days alcohol-abstinence also decreased the rearing in ABS rats ($P = 0.011$) and taurine reversed it ($P = 0.021$), showing an interaction between the taurine treatment and the abstinent condition ($P = 0.005$). ALC rats showed a higher ambulatory frequency than CTR or ABS rats in the OFT ($P < 0.001$). Additionally, we showed that taurine decreased the α_2 $GABA_AR$ subunit expression in CTR rats ($P = 0.002$), with no effect on ALC or ABS groups. On the other hand, the BDNF mRNA expression increased only in the ALC group and was reversed by taurine administration ($P = 0.038$). Taurine, a $GABA_AR$ agonist, increased the exploratory behavior, not related to changes on α_2 $GABA_AR$ or BDNF expression in the frontal cortex of rats. Taurine treatment did not follow the same pattern of response between non-alcoholic and alcoholic/abstinent individuals, evidencing changes on neuronal plasticity induced by chronic consume of alcohol or by direct interaction of taurine and alcohol in the same neurotransmitter system.

Disclosures: **F.B. Almeida:** None. **A.W. Hansen:** None. **G. Caletti:** None. **S. Bandiera:** None. **L. Freese:** None. **H.M.T. Barros:** None. **R. Gomez:** None.

Poster

825. Alcohol: Brain Circuitry I

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 825.21/BBB11

Topic: G.08. Drugs of Abuse and Addiction

Support: NIH Grant AA018779

amuel C. Johnson for Genomics of Addiction Program at Mayo Clinic

Ulm Foundation

Godby Foundation

Marriott Foundation

Title: Adolescence chronic caffeine exposure increases immature mPFC dendritic spine density and promotes depressive-like behavior and alcohol drinking in mice

Authors: *D. J. HINTON, K. E. NETT, Y. CHOI, A. OLIVEROS, D. HAINES, S. CHOI, D.-S. CHOI;
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Abstract: Caffeine is the most commonly used drug in the world. Chronic caffeine is associated with a reduction of DNA methylation in cardiac and somatic muscle. However, little is known about the role of caffeine in DNA methylation in the brain. In the present study, we examined the role of chronic caffeine during adolescence on DNA methylation in the medial prefrontal cortex (mPFC) and behaviors associated with psychiatric disorders in mice. Adolescent mice self-administered caffeine (1 mg/ml) beginning at 4 weeks of age for 4 weeks. We utilized reduced representation bisulfite sequencing (RRBS) to determine global DNA methylation in the mPFC. When we analyzed DNA methylation in the promoter region of genes, the top hit was reduced DNA methylation of Wiskott-Aldrich Syndrome Protein Family Member 1 (wave1) in response to chronic caffeine. Importantly, this reduction in DNA methylation was associated with a reduction in WAVE1 protein expression as measured by Western blot. Since WAVE1 plays an important role in actin dynamics and actin reorganization, we examined dendritic spine density in the mPFC in response to chronic caffeine. We found that filopodia and long/thin spine density was increased in response to chronic caffeine, suggesting a reduction in the elimination of immature spines. Next, we examined the effect of chronic caffeine exposure on behaviors. Mice exposed to chronic caffeine exhibited hyperactivity during the dark cycle with no change in activity during the light cycle in their home cage. Conversely, when mice chronically exposed to caffeine were placed in a novel open-field environment, no difference in exploratory behavior during the dark cycle and decreased exploratory activity during the light cycle was observed.

When anxiety-like behavior was evaluated, mice chronically exposed to caffeine behaved similar to mice drinking water during the dark cycle but were more anxious during the light cycle. Similarly, mice exposed to chronic caffeine exhibited increased depressive-like behavior only during the light cycle. Finally, mice exposed to chronic caffeine consumed more ethanol than mice exposed to water during a 24 hour 2-bottle choice drinking experiment. Overall, these data suggest that chronic caffeine intake during adolescence alters DNA methylation and increases immature mPFC dendritic spine density, which may result in increased depressive-like behavior and alcohol drinking.

Disclosures: **D.J. Hinton:** None. **K.E. Nett:** None. **Y. Choi:** None. **A. Oliveros:** None. **D. Haines:** None. **S. Choi:** None. **D. Choi:** None.

Poster

825. Alcohol: Brain Circuitry I

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 825.22/BBB12

Topic: G.08. Drugs of Abuse and Addiction

Support: NSF Graduate Research Fellowship Program: DGE-1144081

IMSD Graduate Fellowship: 5R25GM055336

NIAAA: R01AA019682

Title: The role of the insular cortex in modulating alcohol self-administration related behaviors

Authors: *A. A. JARAMILLO, S. B. STEWART, B. FORTINO, Z. A. MCELLIGOTT, J. BESHEER;
Univ. of North Carolina at Chapel Hill, Chapel Hill, NC

Abstract: In humans, the insular cortex (IC) is known to be involved in interoceptive states and decision making processes. Additionally, preclinical models have verified the role of the IC in drug-seeking and self-administration of various drugs of abuse. However, a role of the IC in modulating alcohol-related behaviors has not been fully established. Thus, our overall goal was to examine the role of the IC in modulating operant alcohol self-administration in male Long Evans rats. First, to validate the use of a chemogenetic approach by which to inactivate the IC, rats were microinjected with inhibitory Designer Receptors Exclusively Activated by Designer Drugs (DREADDs; hM4D(G_i)) in the IC. DREADD expression and functional validation were confirmed with immunohistochemistry and electrophysiological recordings. Next, to determine the functional role of the IC in modulating self-administration, rats (n=12) were microinjected

with the G_i DREADDs in the IC and trained to self-administer alcohol (15% v/v+2% sucrose w/v). On the test day, rats received pretreatment with 1 mg/kg clozapine-N-oxide (CNO; IP), to activate the DREADDs 30, 45, or 60 min prior to a self-administration session. A significant escalation in self-administration was observed when CNO was administered 45 min prior to the self-administration session. Finally, to determine the role of the IC in modulating the effects of an alcohol-preload on self-administration, rats received CNO (1 mg/kg, IP) before an alcohol-preload injection (0.5 or 1.0 g/kg, IG) and then underwent a self-administration session. A significant decrease in self-administration was observed following IC inactivation and 0.5 g/kg preload. These results demonstrate a potential role for the IC in modulating alcohol self-administration.

Disclosures: A.A. Jaramillo: None. **S.B. Stewart:** None. **B. Fortino:** None. **Z.A. McElligott:** None. **J. Besheer:** None.

Poster

825. Alcohol: Brain Circuitry I

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 825.23/BBB13

Topic: G.08. Drugs of Abuse and Addiction

Support: NIH R01AA021505

TRSA John P. McGovern Award

Title: Distinct synaptic strengthening of the striatal direct and indirect pathways drives alcohol consumption

Authors: *Y. CHENG[1], C. HUANG[2], T. MA[3], X. WEI[3], X. WANG[3], J. LU[3], J. WANG[3]; [1]Neurosci. Exptl. and Theraputics, Texas A&M Hlth. Sci. Ctr., College Station, TX; [3]Dept. of Neurosci. and Exptl. Therapeut., [2]Texas A&M Hlth. Sci. Ctr., Bryan, TX

Abstract: Repeated exposure to addictive drugs and alcohol triggers glutamatergic and GABAergic plasticity in many neuronal populations. The dorsomedial striatum (DMS), a brain region critically involved in addiction, contains medium spiny neurons (MSNs) expressing dopamine D1 or D2 receptors, which form direct and indirect pathways, respectively. It is unclear how alcohol-evoked plasticity in the DMS contributes to alcohol consumption in a cell type-specific manner. Mice were trained to consume alcohol using an intermittent- access alcohol two-bottle-choice drinking procedure. Slice electrophysiology was used to measure glutamatergic and GABAergic strength in DMS D1- and D2-MSNs of alcohol- drinking mice

and their controls. *In vivo* chemogenetic and pharmacological approaches were employed to manipulate MSN activity and their consequences on alcohol consumption were measured. We found that repeated cycles of alcohol consumption and withdrawal in mice strengthened glutamatergic transmission in D1-MSNs and GABAergic transmission in D2-MSNs. The latter change is accompanied with enhanced phosphorylation of glycogen synthase kinase-3β (GSK3β) and enhanced expression of GABAA receptor β3 subunits. *In vivo* chemogenetic excitation of D1-MSNs, mimicking glutamatergic strengthening, promoted alcohol consumption; the same effect was induced by D2-MSN inhibition, mimicking GABAergic strengthening. Importantly, suppression of GABAergic transmission *via* D2 receptor- GSK3β signaling dramatically reduced excessive alcohol consumption, as did selective inhibition of D1-MSNs or excitation of D2-MSNs. These results provide insight into the synaptic and cell type- specific mechanisms underlying alcohol addiction and identify targets for the development of new therapeutic approaches to alcohol abuse. This research was supported by NIAAA (R01AA021505, JW) and TRSA (YC).

Disclosures: Y. Cheng: None. **C. Huang:** None. **T. Ma:** None. **X. Wei:** None. **X. Wang:** None. **J. Lu:** None. **J. Wang:** None.

Poster

825. Alcohol: Brain Circuitry I

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 825.24/BBB14

Topic: G.08. Drugs of Abuse and Addiction

Support: Finnish Foundation for Alcohol Studies

Title: Pallidal overexpression of mu-opioid receptors sensitizes alcohol-preferring AA rats to naltrexone's effects on ethanol intake

Authors: *J. K. UHARI-VÄÄNÄNEN[1,3], M. YLITALO[1], M. KOSKELA[2], B. K. HARVEY[4], V. OINIO[1,3], A. RAASMAJA[1], M. T. AIRAVAARA[2], P. PIEPPONEN[1], K. KIIANMAA[3]; [1]Fac. of Pharm., [2]Inst. of Biotech., Univ. of Helsinki, Helsinki, Finland; [3]Dept. of Hlth., Natl. Inst. for Hlth. and Welfare, Helsinki, Finland; [4]Natl. Inst. of Health, Natl. Inst. on Drug Abuse, Intramural Res. Program, Baltimore, MD

Abstract: The alcohol-preferring AA (Alko Alcohol) and alcohol-avoiding ANA (Alko Non-Alcohol) lines of rats have proven useful in exploring the neural basis of ethanol addiction. Strain-specific differences found in the effects of opioids, in mu-opioid receptor density in different brain areas and in the release of opioid peptides following ethanol intake suggest that

the central opioidergic system plays a role in controlling ethanol intake. As the opioidergic system in the ventral pallidum probably participates in the mediation of drug reward, the aim of the present study was to clarify the role of pallidal mu-opioid receptors in the regulation of ethanol intake in AA rats. Male AA rats that voluntarily drank 10% (v/v) ethanol-solution in a 90 min time-restricted, intermittent ethanol intake paradigm received microinfusions of human mu-opioid receptor gene overexpressing viral vectors (AAV-hMOR), control vectors (AAV-GFP) or vehicle into the ventral pallidum. The effects of the treatments on ethanol intake were examined for five weeks. After this, all of the rats received injections of an opioid receptor antagonist naltrexone (0.1 and 0.3 mg/kg, s.c) and, thereafter, an opioid receptor agonist morphine (3 mg/kg, repeatedly, s.c) before the ethanol drinking sessions to study the effects of antagonists and agonists on ethanol intake. After the behavioral experiments the rats were sacrificed and pallidal human and rat mu-opioid receptor mRNA expression was analyzed by qPCR. In addition, mu-opioid receptor overexpression was visualized from brain slices by immunohistochemical means. Ethanol intake did not differ between the three different treatment groups during the five week follow up period. The 0.3 mg/kg dose of naltrexone decreased ethanol intake in all groups. However, the 0.1 mg/kg dose of naltrexone decreased ethanol intake only in the AAV-hMOR group. Morphine did not modify intake of ethanol significantly in any of the different treatment groups. qPCR results show that human mu-opioid receptor mRNA was expressed only in the AAV-hMOR group, whereas rat mu-opioid receptor mRNA expression did not differ between the groups. Immunohistochemical stainings verified overexpression of human mu-opioid receptors. The results provide further support for the idea that pallidal mu-opioid receptors participate in regulating ethanol intake and that they may have a role in mediating the suppressive effects of naltrexone on ethanol intake.

Disclosures: **J.K. Uhari-Väänänen:** None. **M. Ylitalo:** None. **M. Koskela:** None. **B.K. Harvey:** None. **V. Oinio:** None. **A. Raasmaja:** None. **M.T. Airavaara:** None. **P. Piepponen:** None. **K. Kiianmaa:** None.

Poster

825. Alcohol: Brain Circuitry I

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 825.25/BBB15

Topic: G.08. Drugs of Abuse and Addiction

Support: NIH Grant AA021657

NIH Grant AA022292

Title: Mu opioid receptors in the RMTg regulate ethanol consumption and locomotion in rats

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Abstract: The opioid system is implicated in ethanol-drinking behavior and locomotion. Prior studies have attributed these effects to the activation of mesolimbic dopamine system through the activation of μ-opioid receptors (MORs) on GABA neurons in the ventral tegmental area (VTA). Emerging evidence indicates that MORs are richly expressed in the rostromedial tegmental nucleus (RMTg), a major GABAergic afferent to dopamine neurons. To determine the role of MORs in the RMTg in ethanol drinking-related behaviors, we first examined the effects of ethanol in acute brain slices from rats. Ethanol suppressed the spontaneous firing of RMTg neurons, and the resulting GABAergic IPSCs in dopamine neurons in the VTA. Ethanol's effect was mimicked by the selective MOR agonist DAMGO, but attenuated by naltrexone, a MOR antagonist. In rats that have been trained to drink 20% ethanol in an intermittent access two-bottle choice paradigm for two months, intra-RMTg infusion of naltrexone, or naloxonazine, a selective mu1 opioid receptor antagonist, but not of the selective κ opioid receptor antagonist 5'-guanidinonaltrindole, significantly reduced ethanol intake. However, all these agents did not alter locomotor activity. Similarly, RMTg infusion of naltrexone, but not of 5'- guanidinonaltrindole, induced a robust conditioned place aversion. Conversely, RMTg infusion of DAMGO, or of DNQX and AP5 (antagonist of AMPA and NMDA receptors), or of muscimol (a selective GABAA receptor agonist), all increased ethanol consumption and locomotion. These data suggest that inhibition of endogenous mu opioid system in the RMTg induces aversion and reduction of ethanol intake, and that RMTg tonically controls ethanol consumption and locomotor activity. Thus, RMTg MORs represent a critical cellular substrate in ethanol's activation of dopamine neurons in the VTA.

Disclosures: R. Fu: None. **W. Zuo:** None. **H. Liu:** None. **L. Wu:** None. **W. Li:** None. **W. Wu:** None. **A. Hepurker:** None. **A. Kaur:** None. **J. Li:** None. **J. Ye:** None.

Poster

825. Alcohol: Brain Circuitry I

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 825.26/BBB16

Topic: G.08. Drugs of Abuse and Addiction

Support: NIH AA021657

NIH AA022292

Title: Ethanol withdrawal drives hyperalgesia via reduction of m-type potassium channels in the lateral habenula

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Abstract: Hyperalgesia that often occurs at withdrawal from chronic alcohol consumption contributes significantly to relapse drinking in both humans and rodents. Yet, the underlying mechanisms are not well understood. The lateral habenula (LHb), an epithalamic region in the brain, has been spotlighted because of its role in converging the aversive effects of abuse drugs including alcohol and its excitatory responses to noxious stimuli. We previously found increased pain sensitivity and c-fos expression in the LHb of rats withdrawn from chronic voluntary ethanol drinking. In parallel, the m-currents and the protein expression of m-channels in the LHb were reduced in rats withdrawn from repeated systemic administration (i.p.) of ethanol. Given that several m-channel enhancers have been suggested as prospective analgesics, we hypothesized that reduction of m-channels in the LHb may contribute to the hyperalgesia induced by ethanol withdrawal.
To test this hypothesis, we trained rats to drink 20% ethanol in the intermittent two-bottle free choice paradigm for 8 weeks. *Ex vivo* electrophysiological recordings revealed that at 24 h ethanol withdrawal, the spontaneous spiking of LHb neurons in brain slices was increased but their sensitivity to the m-channel blocker, XE991, was decreased. In support, the protein expression of the m-channel subunits, KCNQ2 and KCNQ3, measured by Western blot was decreased. Importantly, intra-LHb infusion of the m-channel activator, retigabine, reduced ethanol intake and hyperalgesia induced by ethanol withdrawal.
These findings suggest that withdrawal from chronic ethanol consumption reduces m-channels' function and expression in the LHb, which contributes to increased activity of LHb neurons and pain. Thus, m-channels in the LHb could be a promising target for treatment of pain induced by alcohol withdrawal.

Disclosures: **S. Kang:** None. **J. Li:** None. **J. Ye:** None.

Poster

825. Alcohol: Brain Circuitry I

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 825.27/BBB17

Topic: G.08. Drugs of Abuse and Addiction

Support: NIH Grant AA010761

NIH Grant AA007474

NIH Grant AA010983

NIH Grant AA019967

NIH Grant AA022836

Title: The role of the rostromedial tegmental nucleus in withdrawal-induced negative affect

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[3]Dept. of Psychology & Neurosci., Univ. of North Carolina, Chapel Hill, NC

Abstract: Alcohol withdrawal is associated with a hypodopaminergic state and increased negative affect, both of which are thought to play a significant role in the propensity for relapse. The rostromedial tegmental nucleus (RMTg) exerts inhibitory control over midbrain dopamine neurons and activity within this region is associated with the aversive properties of cocaine and alcohol. Together these data suggest that the RMTg plays a role in mediating drug-induced aversive states. To investigate the role of the RMTg in withdrawal and withdrawal-induced negative affect, adult male Long-Evans rats were rendered ethanol dependent using chronic intermittent exposure to ethanol vapor and cFos expression, as well as measures of anxiety-like behavior and anhedonia, were evaluated across the time course of acute withdrawal (0, 6, 12, 24 hr after final ethanol exposure). cFos expression was significantly enhanced in the RMTg during acute withdrawal with peak expression occurring at the 12 hr time point when withdrawal symptom severity is also at its peak (one way ANOVA; $p \leq 0.01$). A similar pattern of cFos expression was observed in the lateral habenula – a region that sends prominent glutamatergic projections to the RMTg ($p \leq 0.01$). Rats trained to nose-poke for intra-cranial delivery of electrical current exhibited a rightward shift in responding 12 hrs following final ethanol exposure. This corresponded to a significant increase in reward threshold compared to baseline levels measured prior to ethanol exposure. Finally, inhibition of the RMTg 12 hrs into withdrawal increased time spent and number of entries into the center of an open field. Together these data suggest that the RMTg plays an important role in withdrawal-induced negative affect and therefore may be critically involved in the neurobiological mechanisms underlying relapse.

Disclosures: **E.J. Glover:** None. **E.M. Starr:** None. **Y. Chao:** None. **N.W. Burnham:** None. **L.J. Chandler:** None. **T.C. Jhou:** None.

Poster

826. Alcohol: Brain Circuitry II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 826.01/BBB18

Topic: G.08. Drugs of Abuse and Addiction

Support: PHS NIH R01 AA023410

R21 024036

Title: Ethanol exposure *In utero*: effects on radial migration, form, and function of pyramidal neurons in the somatosensory cortex

Authors: *L. C. DELATOUR, H. H. YEH;
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Abstract: Fetal Alcohol Spectrum Disorder (FASD) is a leading cause of preventable intellectual disability. However, the mechanisms leading to the detrimental effects of *in utero* ethanol exposure on brain development are multifaceted and not fully understood. We previously reported that prenatal ethanol exposure disrupts tangential migration of GABAergic interneurons during embryonic corticogenesis. This process and the radial migration of glutamatergic pyramidal neurons are intricately interwoven, but whether ethanol exposure *in utero* affects the latter is unknown. Here, we begin to investigate the short-term effects of prenatal ethanol exposure on radial migration, and the enduring effects on pyramidal neuron form and function in the somatosensory cortex.

We employed a 3-day binge-drinking paradigm in which pregnant mice were exposed to ethanol (5% in liquid food) from embryonic day (E) 13.5 through E16.5, spanning the period of active neurogenesis and migration. In coronal cryosections containing the presumptive somatosensory cortex from E16.5 ethanol-exposed embryos, we noted aberrant distribution of Tbr1 immunofluorescence, a marker for postmitotic pyramidal neurons. BrdU pulse labeling indicated that the observed changes in migration were not due to altered neuronal proliferation. Real-time videomicroscopy will investigate further the kinetics of radial migration in embryonic slice cultures following ethanol exposure *in vivo* or *in vitro*.

Whole cell patch clamp electrophysiology was employed to monitor pharmacologically isolated spontaneous inhibitory and excitatory postsynaptic currents in pyramidal neurons in postnatal and young adult mice. Preliminary results suggest an increase in both following *in utero* ethanol exposure. A Sholl analysis conducted on neurobiotin-filled pyramidal neurons revealed a transient aberrant dendritic branching pattern in postnatal mice. Ongoing studies are (1) using optogenetics to investigate the effects of prenatal ethanol exposure on the composite strength of synapses impinging on pyramidal neurons and (2) analyzing their laminar distribution in the postnatal and young adult cortex.

Our results suggest that binge-type ethanol exposure *in utero* disrupts the radial migration of Tbr1-expressing cells, results in the precocious appearance of synaptic activity, and transiently alters pyramidal neuron morphology. We will continue to investigate the embryonic etiology of FASD by focusing on elucidating the short- and long-term effects of *in utero* ethanol exposure on pyramidal neuron migration, morphology, and function in the somatosensory cortex.

Disclosures: L.C. Delatour: None. **H.H. Yeh:** None.

Poster

826. Alcohol: Brain Circuitry II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 826.02/BBB19

Topic: G.08. Drugs of Abuse and Addiction

Support: NIH Grant R01 AA013983

Title: Prefrontal cortical NMDA receptor antagonism and alcohol-escalated aggression in mice

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Abstract: NMDA receptor (NMDAR) antagonists including memantine and ketamine may have therapeutic potential for the treatment of major depressive disorder and alcohol use disorders. However, in mice that self-administer a moderate dose of alcohol, NMDAR uncompetitive antagonists can escalate aggression. Specifically, mice that increased their frequency of attack bites after acute ethanol (1.0 g/kg) self-administration also escalated their aggression after systemic treatment with moderate doses of memantine or ketamine. However, not all mice show enhanced aggression after ethanol. Therefore, the current experiment aims to determine whether individual differences in aggressive phenotype, alcohol-heigtened aggressors (AHA) vs. alcohol non-heightened aggressors (ANA), can predict the effects of intra-mPFC memantine on alcohol-heightened aggression. First, breeding resident males were conditioned to rapidly self-administer 1.0 g/kg of ethanol (EtOH, 6% w/v) or water. Stable aggressive behavior was then evaluated during five-minute, resident-intruder confrontations. To identify mice as alcohol-heightened (AHA) or alcohol non-heightened aggressors (ANA), agonistic behavior was assessed every other day, ten minutes after EtOH or water self-administration. Subsequently, mice were implanted with indwelling cannulae aimed at the prelimbic mPFC. Ten days after recovery, animals were infused with memantine (0, 3.75, or 7.5 micrograms) after water or 1.0 g/kg of 6%

EtOH (w/v) self-administration. The highest concentration of memantine reduced aggressive behavior in AHA and ANA mice, suggesting that memantine does not have its pro-aggressive effects via NMDAR antagonism specifically in the prelimbic mPFC. Previous studies suggested that memantine may have some preference for receptors with weaker Mg2+ blocks such as the extrasynaptic NR2D-containing NMDARs. Therefore we also used Western blot analysis and revealed a trend of increased NR2D-subunit expression in AHA mice as compared to ANA mice. Future work will target the orbitofrontal mPFC for administration of memantine or NR2D-selective NMDAR antagonists. Such work may clarify the possible role of extrasynaptic NR2D-containing NMDARs in the disinhibition of aggressive behavior under the influence of moderate doses of alcohol.

Disclosures: E.L. Newman: None. **M. Terunuma:** None. **T. Wang:** None. **J.F. DeBold:** None. **K.A. Miczek:** None.

Poster

826. Alcohol: Brain Circuitry II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 826.03/BBB20

Topic: G.08. Drugs of Abuse and Addiction

Support: NIH Grant AA019682

Title: Role of mpfc to acbc projections in sensitivity to a nicotine+alcohol compound interoceptive cue

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Abstract: Nicotine and alcohol are two of the most commonly co-used substances and account for a significant portion of preventable deaths each year. As a result of being taken in combination, the interoceptive effects of each drug are frequently experienced together and over time, develop into a unique interoceptive cue associated with other reinforcing events. Considering the compounded health risks associated with co-use of nicotine and alcohol, understanding the underlying mechanisms that support this behavior is important in developing better treatment options. The medial prefrontal cortex (mPFC; prelimbic region) is known to play a role in different aspects of associative learning and drug taking behavior. In addition, the nucleus accumbens core (AcbC) has also been shown to play an important role in supporting drug-related behaviors. As such, the current experiments assess the role of mPFC and its

connections to AcbC in modulating sensitivity to a nicotine+alcohol (N+A) compound interoceptive cue. To do so, these studies utilize Designer Receptors Exclusively Activated by Designer Drugs (DREADDs) to silence mPFC in rats trained to discriminate a N+A compound cue from water. Previous studies from our lab have shown that following injection, the DREADDs traffic to the terminals of the cells they infect. As such, we have shown expression of DREADDs in AcbC following infusion into mPFC. This allows us the opportunity to assess these mPFC to AcbC projections directly by microinjecting clozapine-N-oxide (CNO) directly into AcbC. Accordingly, for these experiments, male Long-Evans rats received bilateral infusions of Cre-dependent AAV-hSyn-DIO-hM4D(Gi) into mPFC. Following recovery, rats were trained to discriminate a nicotine (0.4 mg/kg) + alcohol (1 g/kg) drug state vs. water. 6 weeks post-injection, rats were implanted with bilateral microinjection cannulae targeting AcbC. When CNO (3μM/side) was microinjected into AcbC, sensitivity to the N+A drug state was blocked. This is in contrast to previous findings in which systemic administration of CNO has shown enhanced sensitivity to this N+A cue. These findings suggest that projections from mPFC to AcbC may play an important role in modulating interoceptive sensitivity to drug cues that is different from the effects of completely silencing mPFC. Funding: AA019682

Disclosures: P.A. Randall: None. **J. Besheer:** None.

Poster

826. Alcohol: Brain Circuitry II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 826.04/BBB21

Topic: G.08. Drugs of Abuse and Addiction

Support: NIH Grant 5R37AA014983-10

NIH Grant 4P60AA011605-19

NIH Grant 1F31AA024375-01

Title: Alcohol-induced alterations in the prefrontal cortex proteome of adolescent and adult C57BL6J mice suggest calcium and glutamate signaling as functional regulators of age-dependent differences in alcohol drinking

Authors: *A. E. AGOGLIA, S. E. HOLSTEIN, C. W. HODGE;
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Abstract: Although adolescence is a critical developmental period marking the transition from childhood to adulthood, it is also characterized by increased risk for alcohol and drug use.

Adolescents have been found to consume more alcohol than adults in both animals and humans, and adolescent exposure to alcohol substantially increases the risk for lifetime alcohol use disorders. However, the neurobiological mechanisms that mediate this increased risk have not been fully characterized. Therefore, we utilized a high-throughput nonbiased proteomics screen of the adolescent and adult mouse medial prefrontal cortex in order to identify protein targets that may be involved with alcohol consumption in adolescent and adult C57BL/6J mice. Tissue was collected following two weeks of voluntary 24-hour drinking of 20% alcohol or water in the home cage. 2D-DIGE followed by MALDI TOF/TOF mass spectrometry identified 21 alcohol-sensitive proteins in the adolescent mPFC but only 12 in the adult mPFC, suggesting a protein-level enhancement of alcohol-induced insult in the adolescent brain. Of the identified proteins, several have known roles in calcium signaling and therefore in the regulation of glutamatergic function and synaptic plasticity. To determine the functional relevance of calcium signaling and glutamatergic transmission in adolescent alcohol consumption, we next assessed the sensitivity of both age groups to pharmacological manipulation of alcohol drinking in a limited-access binge model. The calcineurin inhibitor cyclosporine A (CsA) significantly reduced binge alcohol drinking in adolescents but not adults, whereas adolescents were less sensitive to reductions in alcohol drinking induced by the mGluR2/3 agonist LY379268. Taken together, these findings point to the vulnerability of the adolescent PFC to alcohol-induced protein modification and suggest that age differences in the development of the calcium and glutamatergic signaling pathways may underlie the risk for increased alcohol consumption during adolescence.

Disclosures: **A.E. Agoglia:** None. **S.E. Holstein:** None. **C.W. Hodge:** None.

Poster

826. Alcohol: Brain Circuitry II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 826.05/BBB22

Topic: G.08. Drugs of Abuse and Addiction

Support: NIH Grant R00AA021780-02

Title: Chronic ethanol exposure alters excitatory transmission from the orbitofrontal cortex to the dorsal striatum

Authors: *R. RENTERIA, C. M. GREMEL;
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Abstract: Loss of goal-directed control over our actions and subsequent reliance on habitual strategies is thought to contribute to alcohol abuse and addiction. Our preliminary data suggest

that the direct effects of ethanol via chronic intermittent ethanol (CIE) exposure, is sufficient to disrupt goal-directed strategies and bias towards habitual control over actions. In addition, we have previously shown that excitatory projections from the orbitofrontal cortex (OFC) to the dorsal striatum (DS) are necessary for goal-directed actions, in which attenuation of OFC-DS transmission results in habitual control over actions. However, little is known about how the OFC input to the DS is modulated after CIE exposure. Using whole cell patch clamp electrophysiology, we have recorded from D1 dopamine receptor expressing (D1DR) medium spiny neurons (MSNs) in the dorsomedial striatum (DMS). We used optogenetics to isolate the OFC input by injecting channelrhodopsin in OFC projection neurons. Opto-stimulation of OFC terminals in DMS shows paired pulse depression (PPD) of the OFC input to D1DR-MSNs in ethanol naïve mice. In contrast, after CIE exposure, we observe paired pulse facilitation (PPF) of the OFC input to D1DR-MSNs. In examining CIE induces changes of all excitatory inputs to D1DR-MSNs in the DMS, we did not detect any change in the amplitude or frequency of spontaneous excitatory postsynaptic currents (sEPSCs). These data suggest that CIE exposure causes a decrease in the probability of neurotransmitter release that is specific to the OFC input to D1DR-MSNs in the DMS. Further characterization of CIE-induced alterations in OFC synaptic transmission may provide insight into the mechanisms of the drug induced transition to habitual control over actions.

Disclosures: **R. Renteria:** None. **C.M. Gremel:** None.

Poster

826. Alcohol: Brain Circuitry II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 826.06/BBB23

Topic: G.08. Drugs of Abuse and Addiction

Support: AA006420 (OG)

AA020608 (OG)

AA013588 (ROM)

AA017072 (ROM)

Title: Optogenetic dissection of cea crf pathways in alcohol dependence

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Abstract: In alcohol dependent animals, withdrawal from alcohol activates a subpopulation of neurons within the central nucleus of amygdala (CeA) while inducing high levels of alcohol consumption. To understand if these neurons are important for driving excessive drinking during withdrawal, we sought to characterize their cellular phenotype and identify brain regions they regulate. Since increased alcohol consumption during withdrawal can be reduced by administration of CRF receptor antagonists into the CeA, we focused our attention on CeA CRF neurons. We used *Crh*-Cre transgenic rats combined with *in vivo* optogenetics and chemogenetics to test whether specifically inactivating CeA CRF neurons prevents excessive alcohol self-administration during withdrawal. In the first experiment rats were injected with AAV-DIO-NpHR-eYFP or AAV-DIO-eYFP (control) and implanted with an optical fiber in the CeA. They were then subjected to a chronic intermittent ethanol (CIE) procedure to induce dependence and 8 hours into withdrawal were allowed to self-administer ethanol during optogenetic inhibition. Inactivation of CeA-CRF neurons decreased alcohol drinking in dependent rats to levels observed before the animals became dependent, and completely prevented the increase in CeA Fos+ neurons normally observed during withdrawal. No effect was detected in the AAV-DIO-eYFP control group or on water or saccharin self-administration in either group. In a second experiment, rats were injected with AAV-DIO-hM4Di-mCherry in the CeA and subjected to a two-bottle choice 24h intermittent access (IA) drinking procedure. Systemic administration of the hM4Di agonist clozapine-N-oxide (4 mg/kg ip) had no effect after 4 weeks of IA drinking, but reduced IA significantly drinking after 10 weeks. In the third experiment, rats were injected with AAV-DIO-NpHR-eYFP or AAV-DIO-eYFP and optical fibers were implanted into the bed nucleus of the stria terminalis (BNST) or the parabrachial nuclei (PBN), since we recently found that CeA CRF neurons send dense projections to these regions. Inactivation of CRF terminals in the BNST recapitulated the effect on drinking observed with CeA inactivation, whereas inactivation of the PBN had no effect. Together these results demonstrate that CeA CRF neurons that project to the BNST are critical for driving excessive alcohol consumption in alcohol dependent rats.

Disclosures: G. De Guglielmo: None. **M.B. Pomrenze:** None. **M. Kallupi:** None. **E. Crawford:** None. **G.F. Koob:** None. **R.O. Messing:** None. **O. George:** None.

Poster

826. Alcohol: Brain Circuitry II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 826.07/BBB24

Topic: G.08. Drugs of Abuse and Addiction

Support: NIH Grant AA021417

Title: The role of extended amygdala corticotropin neurons in binge ethanol drinking

Authors: *J. M. IRVING[1], C. J. MAEHLER[2], K. S. GIRVEN[3], D. R. SPARTA[2];
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Abstract: Binge drinking has been linked to the progressive dysfunction of multiple organs and is considered a critical first step in the development of alcoholism. Conceptual models of alcoholism and addiction predict that repeated binge consumption of alcohol promotes negative affective states that compel the alcoholic to consume increasing amounts of ethanol. Therefore, understanding the specific neural circuit mechanisms involved in chronic binge drinking is critical. Development of better treatments is impeded by a lack of knowledge on how alcohol abuse alters underlying circuits. Corticotropin releasing factor (CRF) neurons within the extended amygdala project to reward areas of the brain, and are believed to promote negative affect and binge drinking. However, the precise CRF circuit mechanisms that drive these behaviors remain poorly understood. Here we used CRF-Cre mice to specifically manipulate CRF neuron populations within the central amygdala (CeA) and bed nucleus of the stria terminalis (BNST) to determine how chronic binge drinking cycles alters the function of these CRF populations. We hypothesized that the activity of CeA-CRF and BNST-CRF neurons increase, thereby driving binge ethanol consumption. To test this, we first recorded the activity of CRF neurons in the CeA or BNST using *in vivo* electrophysiology and optogenetics to phototag CRF neurons during multiple binge ethanol drinking sessions. Interestingly, we found a population of CRF neurons that increased their activity in response to binge ethanol consumption. However, we did observe a few sub-populations of phototagged CRF neurons with differential responses to binge ethanol drinking; BNST recordings are in progress. Additionally, ongoing experiments are using pharmacogenetic inhibition and optogenetic excitation to test if CRF neuron activity these nuclei are required or sufficient, respectively, to drive binge ethanol consumption behavior. These data suggest functional subpopulations of CRF neurons within CeA that differentially encode binge drinking behavior.

Disclosures: **J.M. Irving:** None. **C.J. Maehler:** None. **K.S. Girven:** None. **D.R. Sparta:** None.

Poster

826. Alcohol: Brain Circuitry II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 826.08/BBB25

Topic: G.08. Drugs of Abuse and Addiction

Support: NIH Grant AA013498

NIH Grant AA013517

NIH Grant AA020893

Title: Interleukin-1 modulation of GABA transmission in the mouse central amygdala after chronic ethanol exposure

Authors: *M. BAJO[1], M. A. HERMAN[1], S. KHOM[1], F. P. VARODAYAN[1], S. E. MONTGOMERY[1], A. J. ROBERTS[2], M. ROBERTO[1];
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Abstract: It has been shown that the brain IL-1 system is associated with alcohol drinking behaviors and plays a critical role in chronic alcohol-induced neurodegeneration. Our previous findings indicate that the IL-1 system regulates basal GABAergic transmission in the central nucleus of the amygdala (CeA), a crucial region involved in the transition to alcohol addiction, and also modulates the effects of acute ethanol at these synapses in ethanol naive mice. In the present study, we assessed whether ethanol dependence alters the IL-1 system and its interactions with acute ethanol at CeA GABAergic synapses. We used a 2BC-CIE (2 bottle choice-chronic interemittent ethanol vapor expsoure) paradigm to induce ethanol dependence in mice and tested the effects of IL-1β on CeA GABAergic transmission. Using whole-cell recordings, we found that superfusion of IL-1β (50 ng/ml) had similar effects on spontaneous Inhibitory Postsynaptic Currents (sIPSCs) in ethanol naive, non-dependent and dependent mice. Specifically, IL-1β increased the mean sIPSC frequency across all groups, indicating that IL-1β induces GABA release in the CeA. In all groups, IL-1β produced variable effects on sIPSC amplitudes and kinetics, suggesting that IL-1β can also alter postsynaptic $GABA_A$ receptor function. Our results suggest that chronic ethanol exposure induces limited modulation of the IL-1 system and its effects on GABAergic transmission in the CeA, which could have important implications for the role of the immune system in the development of alcohol dependence

Disclosures: **M. Bajo:** None. **M.A. Herman:** None. **S. Khom:** None. **F.P. Varodayan:** None. **S.E. Montgomery:** None. **A.J. Roberts:** None. **M. Roberto:** None.

Poster

826. Alcohol: Brain Circuitry II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 826.09/BBB26

Topic: G.08. Drugs of Abuse and Addiction

Support: NIH Grant AA017447

NIH Grant AA006420

NIH Grant AA015566

NIH Grant AA007456

Title: Oxytocin decreases central amygdala GABAergic signaling in naive but not alcohol dependent rats.

Authors: *D. KIRSON, C. S. OLEATA, M. ROBERTO;
CNAD, The Scripps Res. Inst., La Jolla, CA

Abstract: Alcohol use disorders (AUDs) are significant public health concerns, characterized by compulsive seeking and consumption of alcohol. AUDs have been linked to disruption of normal functioning of brain stress systems, as the transition to dependence recruits these systems leading to the negative affective states seen in withdrawal; the relief of which drives further drinking. The central nucleus of the amygdala (CeA) functions as a neuropeptidergic hub of stress and anxiety processing, and GABAergic signaling within the CeA is involved in the regulation of alcohol consumption. Oxytocin is a stress-related neuropeptide that has previously been shown to alter GABAergic signaling within the CeA of rodents. Oxytocin also affects alcohol addiction, dependence, and withdrawal, as administration of oxytocin decreases drinking and blocks alcohol withdrawal symptoms in humans and rodents. However, characterization of the electrophysiological effects of oxytocin and ethanol on GABAergic signaling in the CeA have not yet been reported. In this study, using intracellular sharp pipette electrophysiological recordings, we examined the effects of different doses (0.1, 0.5, 1.0 μM) of oxytocin and ethanol on CeA GABAergic signaling in both ethanol naïve and chronic intermittent ethanol vapor treated (ethanol dependent) Sprague-Dawley male rats. Acute ethanol (44 mM) application significantly increased the amplitude of locally evoked GABAergic inhibitory postsynaptic potentials (IPSPs) in CeA of both naïve and ethanol-dependent rats. Notably, oxytocin decreased evoked GABAergic IPSPs by ~20%, and blocked the acute ethanol-induced increase in CeA IPSPs in naïve rats. In dependent rats, oxytocin did not significantly alter the amplitude of GABAergic IPSPs, but still blocked the enhancing effects of acute ethanol. Additionally, in whole cell patch clamp electrophysiological recordings, oxytocin had both pre- and post-synaptic

effects on GABAergic transmission. These results provide important insight into the role of oxytocin in CeA neuronal functioning and the changes in this system that contribute to the transition to ethanol dependence. This research highlights the potential role of oxytocin in the development of novel therapeutics for the effective treatment of AUDs.

Disclosures: D. Kirson: None. **C.S. Oleata:** None. **M. Roberto:** None.

Poster

826. Alcohol: Brain Circuitry II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 826.10/CCC1

Topic: G.08. Drugs of Abuse and Addiction

Support: NIH Grant AA017447

NIH Grant AA006420

NIH Grant AA015566

NIH Grant AA007456

Title: Sex-specific differences in CB1 and ethanol effects on glutamatergic transmission in the central amygdala of msP and Wistar rats

Authors: *M. ROBERTO, C. S. OLEATA, D. KIRSON;
Scripps Res. Inst., La Jolla, CA

Abstract: The central amygdala (CeA) is involved in the processing of anxiety and stress, and has been implicated in the effects of acute and chronic ethanol consumption. Chronic ethanol disrupts stress systems in CeA, leading to aversive withdrawal symptoms. Although primarily GABAergic, CeA contains glutamatergic afferents, and we have recently reported inhibitory effects of ethanol on locally evoked glutamatergic responses in CeA of Wistar and Marchigian Sardinian Preferring (msP) rats. Notably, msP rats display enhanced anxiety, stress, and excessive alcohol drinking, simulating alcohol dependent phenotype. Endocannabinoids (eCB) are also involved in regulation of stress and ethanol, and we reported that CB1 activation decreases CeA GABAergic signaling and blocks ethanol enhancement of GABAergic signaling. Here, we sought to investigate the effects of CB1 activation via Win 55,212-2 mesylate (WIN) and antagonism via AM251 with and without acute ethanol on glutamatergic synapses in the CeA of both female and male Wistar and msP rats. Using intracellular sharp pipette electrophysiological recordings we examined the effects of these CB1 compounds on locally

evoked excitatory postsynaptic potentials (eEPSP) in CeA, and compared the effects between strains, gender, and estrus cycle. We found that acute ethanol decreased eEPSP amplitudes in male and female Wistars, and in male but not female msPs. Additionally, CB1 activation via WIN decreased eEPSP amplitudes in msPs but not Wistars, while blockade via AM251 caused a moderate decrease in eEPSP amplitudes of Wistar males only. CB1 activation or blockade co-applied with acute ethanol resulted in varied outcomes dependent on strain and gender. Collectively, these observations demonstrate sex-strain-specific differences in ethanol sensitivity and eCB signaling, suggesting possible sex-specific changes in CeA GABAergic signaling with alcohol dependence.

Disclosures: **M. Roberto:** None. **C.S. Oleata:** None. **D. Kirson:** None.

Poster

826. Alcohol: Brain Circuitry II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 826.11/CCC2

Topic: G.08. Drugs of Abuse and Addiction

Support: NIH intramural program

Title: Amygdala and prefrontal cortex modulation of punished ethanol seeking

Authors: *L. R. HALLADAY, A. KOCHARIAN, A. HOLMES;
Lab. of Behavioral and Genomic Neurosci., Natl. Inst. on Alcohol Abuse and Alcoholism, Rockville, MD

Abstract: Alcohol use disorders (AUDs) are characterized by persistent drinking despite harmful consequences, which may be due to impaired neural mechanisms regulating punished behaviors. These may include prefrontal cortex (PFC), implicated in behavioral flexibility and drug-seeking, or amygdala (AMG), known to encode stimuli's valence (negative vs positive). Neurotransmission in both PFC and AMG is affected by alcohol intake, but little is known about their role in mediating punished alcohol-seeking. To address this, we conducted in vivo electrophysiological recordings in prelimbic (PL) and infralimbic (IL) subregions of PFC or the basolateral (BLA) and central (CeA) nuclei of AMG during a punished-suppression of alcohol-seeking task. Mice that had been trained to lever press for an alcohol reward were subjected to a mild footshock when the lever was pressed. Neural recordings revealed several populations of cells in both PFC and AMG that significantly changed their firing rates either during drinking or lever pressing. Notably, a sub-population of cells in IL significantly increased their firing rate when animals approached the reward lever but did *not* press it, suggesting a role for IL in the

inhibition of responding in the face of negative outcomes. To causally address this, in another experiment we optogenetically silenced neurons expressing archaerhodopsin (ArchT). Silencing the IL significantly increased lever pressing despite having been associated with punishment. Together, these data demonstrate neuronal encoding of alcohol-seeking in both AMG and PFC, and suggest that resistance to the suppression of alcohol-seeking seen in AUDs may be related to aberrant activity in the IL cortex.

Disclosures: L.R. Halladay: None. **A. Kocharian:** None. **A. Holmes:** None.

Poster

826. Alcohol: Brain Circuitry II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 826.12/CCC3

Topic: G.08. Drugs of Abuse and Addiction

Support: MH093650 (NIMH)

MH091945 (NIMH)

DA030425 (NIDA)

Title: The PACAP system of the BNST modulates withdrawal-induced alcohol drinking and anxiety-like behavior.

Authors: *A. FERRAGUD, C. VELAZQUEZ-SANCHEZ, P. COTTONE, V. SABINO; Boston Univ. Sch. of Med., Boston, MA

Abstract: Alcohol use disorder affects 76 million people worldwide, and it is characterized by uncontrolled heavy drinking and a chronic relapsing course. While initially alcohol is consumed for its positive reinforcing effects, once a person transitions to a stage of alcohol addiction, drinking mainly occurs to alleviate the negative emotional states during withdrawal, via a negative reinforcement mechanism. The brain stress response systems are hypothesized to be recruited by excessive alcohol intake, to be sensitized by repeated withdrawal, and to contribute to the development of addiction. In this study, we investigated the PACAP system, a key mediator of the stress response, as a substrate for withdrawal-induced behavioral maladaptations. For this purpose, we used a widely-used model of chronic intermittent ethanol (CIE) vapor in rats. During acute withdrawal from alcohol vapors, CIE rats displayed a significant increase in the number of PACAP positive cells in the bed nucleus of the stria terminalis (BNST), a brain area critically involved in the negative emotional state of alcohol withdrawal. Site-specific microinfusion of the PAC1 receptor (PAC1R) antagonist PACAP(6-38) into the BNST was able

to dose-dependently block excessive alcohol intake in CIE rats, without affecting basal ethanol intake in control animals, or water intake. Importantly, intra-BNST PACAP (6-38) was also able to reverse ethanol withdrawal-induced anxiety in CIE animals. Our findings show that CIE recruits the PACAP/PAC1R system of the BNST and that these neuroadaptations mediate the heightened alcohol drinking and anxiety-like behavior observed during withdrawal. We, therefore, identified a potential neuroadaptive mechanism contributing to excessive drinking and a novel therapeutic target for alcohol use disorders.

Disclosures: **A. Ferragud:** None. **C. Velazquez-Sanchez:** None. **P. Cottone:** None. **V. Sabino:** None.

Poster

826. Alcohol: Brain Circuitry II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 826.13/CCC4

Topic: G.08. Drugs of Abuse and Addiction

Support: R01AA020394

Title: Maladaptive behavioral regulation in alcohol dependence: role of dynorphin / kappa-opioid receptor modifications in the bed nucleus of the stria terminalis

Authors: *C. ERIKSON, B. M. WALKER;
Washington State Univ., Pullman, WA

Abstract: An important emerging role of the endogenous opioid dynorphin (DYN) and its receptor, the kappa-opioid receptor (KOR) in the treatment of addictive disorders such as alcohol dependence has been established. The extended amygdala is profoundly involved with the regulation of motivational and emotional systems in a manner that promotes personal survival and propagation of the species and is defined by functional connectivity between the central nucleus of the amygdala (CeA), the nucleus accumbens (Acb), and a third important brain structure: the bed nucleus of the stria terminalis (BNST). Until more information is established regarding the role of the BNST in alcohol dependence, a critical gap in our knowledge base will exist and prevent the development of comprehensive strategies to reduce the number of individuals suffering from alcohol dependence. That said, recent data heavily implicates the DYN/KOR system in the extended amygdala, including the BNST, as contributing to escalated alcohol self-administration and the emergence of negative affective states in dependent organisms during acute withdrawal and protracted abstinence. The current study evaluated KORs in the BNST for their contribution to escalated alcohol self-administration during acute

withdrawal in alcohol dependent rats. To this end, male Wistar rats were trained to self-administer alcohol, underwent stereotaxic intra-BNST cannula guide implantations and then were subjected to an alcohol-dependence induction procedure using intermittent alcohol vapor exposure (14 h alcohol exposure / 10 h alcohol withdrawal daily) or control air-exposure. Following the one-month of alcohol vapor exposure, animals were tested for alcohol self-administration at a time-point equivalent to six-hours into withdrawal until stable responding was achieved under conditions of intra-BNST sham and artificial cerebrospinal fluid infusions. Subsequently, infusion of a KOR antagonist into the BNST was shown to dose-dependently ameliorate escalated self-administration during acute withdrawal without altering non-dependent alcohol self-administration. The present results functionally confirm an important role of dysregulated DYN / KORs in the BNST and together with previous results showing recruitment of DYN / KOR system in the Acb and CeA during dependence, illustrate the importance of the extended amygdala in the maladaptive behavioral regulation observed in alcohol dependence.

Disclosures: C. Erikson: None. **B.M. Walker:** None.

Poster

826. Alcohol: Brain Circuitry II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 826.14/CCC5

Topic: G.08. Drugs of Abuse and Addiction

Support: T32AA007577

R00AA020839

Title: Dysregulation of hippocampal and frontocortical jnk signaling in alcohol dependence

Authors: *A. R. PAHNG, R. I. PAULSEN, M. A. FAROOQ, K. N. EDWARDS, S. EDWARDS;
Dept. of Physiol., LSU Hlth. Sci. Ctr., New Orleans, LA

Abstract: Alcohol dependence is a chronic, relapsing mental disorder that is characterized by the emergence of negative emotional states and the development of significant pain hypersensitivity (or hyperalgesia) during withdrawal. Accordingly, alcohol may be sought after and taken in excessive amounts to alleviate withdrawal-related symptoms. To develop more effective therapeutic treatments for alcohol dependence it is necessary to identify potential molecular targets that underlie the transition to dependence. In our rodent model of alcoholism, rats are made dependent on alcohol via chronic, intermittent ethanol vapor (CIEV) exposure. This

paradigm has previously been shown to reliably produce both somatic and motivational symptoms of dependence. In the present study, alcohol-dependent and non-dependent adult male Wistar rats were trained to self-administer alcohol. Following stable self-administration behavior whereby dependent rats consumed more alcohol than non-dependent rats, all animals were sacrificed during acute withdrawal (8 hours post-CIEV exposure). We found that c-Jun N-terminal kinase (JNK) phosphorylation was significantly decreased in the hippocampus and dorsomedial prefrontal cortex of alcohol-dependent rats relative to non-dependent controls. In contrast, in separate cohorts of rats, hippocampal JNK phosphorylation was increased following acute intraperitoneal administration of alcohol (1g/kg) compared to saline-injected controls. These data indicate that restoration of JNK activity in the hippocampus and dorsomedial prefrontal cortex following drinking could alleviate deficits produced by dependence and withdrawal. Based on the demonstrated efficacy of glucocorticoid receptor (GR) antagonism in reducing alcohol dependence-related behaviors, future studies will test our hypothesis that JNK-mediated regulation of glucocorticoid receptor activity in the hippocampus and dorsomedial prefrontal cortex mediates excessive alcohol seeking and hyperalgesia.

Disclosures: **A.R. Pahng:** None. **R.I. Paulsen:** None. **M.A. Farooq:** None. **K.N. Edwards:** None. **S. Edwards:** None.

Poster

826. Alcohol: Brain Circuitry II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 826.15/CCC6

Topic: G.08. Drugs of Abuse and Addiction

Support: Samuel C Johnson Genomics of Addiction Program Grant AA018779

Title: Hippocampal and striatal ENT1 regulates mitochondrial function to contribute to ethanol intoxication and withdrawal

Authors: ***D. R. LINDBERG**[1], D. HINTON[2], A. OLIVEROS[2], S. CHOI[2], D.-S. CHOI[2];
[1]Neurosci., Mayo Med. School, Mayo Clin., Rochester, MN; [2]Mayo Grad. Sch., Rochester, MN

Abstract: Mitochondrial dysfunction contributes to bioenergetic changes characteristic of numerous neurologic and neuropsychiatric disorders. Interestingly, purines, the biochemical substrates and endproducts of mitochondrial respiration have recently been demonstrated to play a critical role in regulating ethanol intake in mice. Mice lacking the type 1 equilibrative nucleoside transporter (ENT1) consume significantly more ethanol than wildtype littermates and display concomitant reductions in glutamate transport that lead to a pathological

hyperglutamatergic state. Here, we demonstrate that mice lacking ENT1 exhibit abnormal hippocampal and striatal mitochondrial morphology and localization, which are exacerbated by chronic ethanol exposure and persist during withdrawal. Furthermore, we demonstrate that similar changes in mitochondrial morphology and localization are induced in wildtype mice following chronic exposure to ethanol vapor and during withdrawal. Finally, we correlate these changes in mitochondrial morphology and location to reduced mitochondrial respiratory capacity in purified brain mitochondria in ENT1 null mice as well as in mice subjected to chronic ethanol exposure and withdrawal. These results suggest that ENT1 differentially regulates mitochondrial function during ethanol exposure and withdrawal and may contribute to the maintenance of an aberrant brain bioenergetic profile that manifests in the behavioral symptoms associated with ethanol addiction and withdrawal.

Disclosures: D.R. Lindberg: None. **D. Hinton:** None. **A. Oliveros:** None. **S. Choi:** None. **D. Choi:** None.

Poster

826. Alcohol: Brain Circuitry II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 826.16/CCC7

Topic: G.08. Drugs of Abuse and Addiction

Support: NIH/NIGMS COBRE: The Delaware Center for Neuroscience Research Grant 1P20GM103653 - 01A1

Title: Deficits in spatial and nonspatial memory following binge-like ethanol exposure in the early postnatal period suggest damage to hippocampal-prefrontal circuitry

Authors: *Z. GURSKY, K. E. BOSCHEN, A. Y. KLINTSOVA;
Dept. of Psychological & Brain Sci., Univ. of Delaware, Newark, DE

Abstract: Exposure to alcohol *in utero* can cause learning and memory deficits in humans on multiple spatial recall tasks (Hamilton et al., 2003; Uecker & Nadel, 1996). Similar spatial deficits are found following exposure of rats to ethanol (EtOH) on postnatal days (PD) 4 - 9 (Goodlett & Peterson, 1995; Thomas, Sather, & Whinery, 2008). EtOH administered during this time period can produce significant neurodegeneration in both the hippocampus (HPC) (Smith et al., 2015) and prefrontal cortex (Ikonomidou et al., 2015). We hypothesized that behaviors such as novel object recognition (NOR), object in place memory (OIP), and spatial memory - which are dependent on intact and properly functioning connectivity between the HPC and medial prefrontal cortex (mPFC) - would be affected by this model of developmental EtOH exposure in

rats.
On PD3, rats were assigned to one of three treatments: binge exposure of EtOH via intragastric intubation (AE; 5.25 g/kg/day), intubated without EtOH (SI), or left undisturbed (SC). Pups underwent their respective manipulation on PD4-9. Animals were weaned on PD23. Starting in early adulthood, male animals underwent behavioral testing for NOR, OIP, and spontaneous alternation (SA) tasks. A single NOR or OIP testing day consists of a habituation phase, an acquisition phase (initial exploration of objects), and a testing phase (exploration of novel and familiar objects (NOR) or familiar moved and unmoved objects (OIP)). A discrimination ratio was calculated for each animal on each task. To determine EtOH-specific effects, comparisons were run between SI and AE groups.
NOR revealed decreased preference for a novel object in AE relative to SI animals ($F_{(1,8)}$=5.6, p=0.045), while still being able to discriminate between the two objects ($t_{(4)}$=7.2, p=0.002). Differences were not due to the time spent exploring objects during acquisition or testing phases. OIP performance revealed a decreased preference for moved objects in AE relative to SI animals ($F_{(1,9)}$=6.0, p=0.037), which prevented AE animals from successfully discriminating between moved and unmoved objects ($t_{(3)}$=-1.1, p=0.346). Again, no differences in exploration during acquisition or testing were found. Data from SA indicate no effect of EtOH exposure on task performance ($F_{(1,6)}$=.01, p=0.935) or total number of arms entered ($F_{(1,6)}$=1.5, p=0.271). These data indicate an impairment in both nonspatial (NOR) and some (OIP), but not all (SA), forms of spatial memory. Additional research is currently targeting further mPFC-dependent behaviors following this EtOH exposure paradigm.
Supported by NIH/NIGMS COBRE: The Delaware Center for Neuroscience Research Grant 1P20GM103653 - 01A1 to AYK.

Disclosures: **Z. Gursky:** None. **K.E. Boschen:** None. **A.Y. Klintsova:** None.

Poster

826. Alcohol: Brain Circuitry II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 826.17/CCC8

Topic: G.08. Drugs of Abuse and Addiction

Support: NIH Grant R01 AA023410

NIH Grant R21 AA024036

Title: Low concentration ethanol impacts neural circuit function in the medial septum/diagonal band of Broca

Authors: *S. L. MILLER, H. H. YEH;
Dept. of Physiol. and Neurobio., The Geisel Sch. of Med. At Dartmouth, Lebanon, NH

Abstract: The medial septum/diagonal band of Broca (MS/DB) is implicated in cognitive and mnemonic functions often compromised following acute and chronic ethanol (EtOH) exposure. However, the cellular targets of EtOH within the operations of the MS/DB neural circuit await elucidation. Most prominent among neurons contributing to the operations of the MS/DB neural circuit are cholinergic neurons that maintain a muscarinic tone, as well as glutamatergic and GABAergic neurons that mediate excitatory and inhibitory neurotransmission, respectively. We previously reported that a relatively high concentration of EtOH (50mM) acutely increased cholinergic firing, heightening muscarinic tone that, in turn, augmented firing activity of non-cholinergic neurons. Here, we initiated a study, focusing on EtOH exposure at a low concentration (8mM or 0.03 g/dL equivalent), to re-examine the effect of acute EtOH on muscarinic tone, and extend investigation to testing whether glutamatergic and GABAergic neurotransmission in the MS/DB are also modulated. Cholinergic MS/DB neurons were identified for whole-cell patch clamp recording in live slices (200μm) obtained from postnatal day 28-40 adolescent transgenic mice generated using a BAC vector in which eGFP reported the expression of the ChAT gene (BAC-ChAT; GENSAT). Focal application of EtOH (8mM) consistently increased the firing activity of eGFP+ MS/DB cholinergic neurons monitored under current clamp. In the same slices, bath application of EtOH (8mM) also increased the firing rate of non-cholinergic (non-eGFP+) MS/DB neurons. These results are consistent with a low concentration of EtOH modulating muscarinic tone. In a separate series of voltage clamp experiments, focal application of EtOH (8mM) enhanced in cholinergic MS/DB neurons the frequency of glutamate-mediated spontaneous excitatory postsynaptic potentials (sEPSCs), monitored in isolation in the presence of bicuculline. Such an enhancement of sEPSCs points to EtOH targeting a presynaptic mechanism of glutamate release, and could in part account for the increased excitability of cholinergic neurons, leading to their increased firing rate. Our observations to date has identified the excitability of the adolescent MS/DB neural circuit as an exquisitely sensitive target for modulation by low concentrations of EtOH. Ongoing experiments are assessing whether EtOH also modulates GABAergic neurotransmission, including a GABA-mediated tonic current that we uncovered in the MS/DB. The working hypothesis is that EtOH increases the overall excitability of the MS/DB neural network by shifting the excitatory-inhibitory balance towards an hyperexcited state.

Disclosures: S.L. Miller: None. **H.H. Yeh:** None.

Poster

826. Alcohol: Brain Circuitry II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 826.18/CCC9

Topic: G.08. Drugs of Abuse and Addiction

Support: NIH Grant AA022408

NIH Grant AA022707

Title: Chronic intermittent ethanol alters CRF-dependent synaptic plasticity in the hypothalamus and HPA axis hormonal and behavioral responses to repeated stress

Authors: *V. N. MARTY, Y. MULPURI, D. H. TERRY, M. PEMPENA, S. YEE, I. SPIGELMAN;
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Abstract: Alcohol use disorders are associated with a persistently dysregulated hypothalamic-pituitary-adrenal (HPA) axis and corticotropin-releasing factor (CRF) signaling that leads to inappropriate stress responses, thereby increasing relapse susceptibility in abstinent alcoholics. Our goal is to identify the neuroadaptive mechanisms responsible for the dysregulation of the HPA axis. Using whole-cell patch-clamp recordings, we showed that stress induces a CRF-dependent depression of NMDAR function in parvocellular neurosecretory cells (PNCs) in the paraventricular nucleus of the hypothalamus (PVN), which allows for short-term potentiation (STP) of AMPAR-mediated evoked excitatory postsynaptic currents (eEPSCs) following high-frequency stimulation (HFS, 100Hz for 1sec, x4). This stress-induced STP can be evoked for several days and provides a mechanism by which the HPA axis responds adaptively to subsequent stressors. Here, we found that chronic intermittent EtOH (CIE, 30 doses, 5-6 g/kg EtOH, oral gavage) and >40 days of withdrawal potentiated NMDAR function in PNCs. As expected, stress (30 min restraint) unmasked HFS-induced STP of eEPSCs in vehicle-treated (CIV) rats. However, CIE impaired stress-induced STP. CRF-induced depression of NMDAR function was absent in CIE rats. NMDAR inhibition by intracellular MK-801 restored stress-induced STP suggesting that the loss of CRFR1-mediated NMDAR blockade in CIE rats may prevent stress-induced STP. To relate the expression of STP to the HPA axis hormonal response, we examined ACTH and CORT plasma levels in response to repeated (at 72hr-intervals) restraint stress. In CIE rats, the ACTH response to the 3rd stress was blunted, and the CORT response to the 3rd stress recovered faster to baseline compared to the 1st stress. In addition, hypothalamic mRNA expression of CRF, CRFR1, glucocorticoid receptor, and CRF-bp was increased in CIE rats 2h after the 3rd stress. Stress-induced increases in self-grooming behavior, an adaptive response involving the PVN that reflects the process of restoring behavioral homeostasis disturbed by stressors, were impaired in CIE rats. In an attempt to normalize the

increased NMDAR function observed in CIE rats, we used memantine (10mg/kg, i.p.), a non-competitive NMDAR antagonist. Preliminary data show that memantine reduced stress-induced increases in CORT plasma levels, and basal self-grooming in CIV and CIE rats. Stress increased self-grooming in memantine-injected CIV, but not CIE rats. These data implicate altered CRF and NMDAR signaling mechanisms in CIE-induced maladaptive HPA axis behavioral and hormonal responses to repeated stress.

Disclosures: V.N. Marty: None. **Y. Mulpuri:** None. **D.H. Terry:** None. **M. Pempena:** None. **S. Yee:** None. **I. Spigelman:** None.

Poster

826. Alcohol: Brain Circuitry II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 826.19/CCC10

Topic: G.08. Drugs of Abuse and Addiction

Support: NIH AA022292

NIH AA021657

Title: Electroacupuncture attenuates hyperalgesia in rats at withdrawal from chronic voluntary alcohol drinking involving habenula mu opioid receptors

Authors: *J. LI[1], H. LIU[2], C. FU[2], R. FU[2], J. H. YE[2];
[1]Anesthesiol., NJMS, NEWARK, NJ; [2]Anesthesiol., New Jersey Med. Sch., NEWARK, NJ

Abstract: Hyperalgesia that often occurs, in particular during abstinence in human alcoholics, is one of the major withdrawal symptoms that are believed to contribute significantly to relapse drinking. Acupuncture and electroacupuncture (EA) have been proven to be effective in various disorders, including pain, and substance abuse. Previous rat studies in our laboratory have observed hyperalgesia at withdrawal from chronic alcohol consumption, and EA at the acupoint Zusanli (ST36) significantly reduced excessive ethanol intake. However, whether EA can reduce pain during alcohol abstinence remain largely unknown. In the present study, we tested the effect of EA on the pain sensitivity in rats that chronically consumed high amount of ethanol. We trained Long-Evans rats (male, 250-330 g at the start of the experiment) to drink 20% ethanol in the intermittent access two-bottle free choice paradigm. After 8 week training, when rats achieved a stable baseline of ethanol consumption (5.6 ± 1.0 g/kg/24 h), we measured their paw withdrawal latencies (PWL) to radiation heat stimulation. PWL was significantly shorter at 24, 48, 72 h and 7 d after ethanol withdrawal compared to ethanol naïve rats. One time

administration of low frequency (2 Hz) EA for 20 min at Zusanli 30 min before PWL measurement significantly increased PWL at 24 h after ethanol withdrawal compared to sham (EA at the tail). Furthermore, the effect of EA was significantly attenuated by intra-habenula infusion of naltrexone. These results are consistent with our previous report that hyperalgesia occurs in rats that withdrawal from chronic ethanol exposure. Importantly, this hyperalgesia could be mitigated by 2 Hz EA via a mechanism involving mu opioid receptors in the habenula.

Disclosures: **J. Li:** None. **H. Liu:** None. **C. Fu:** None. **R. Fu:** None. **J.H. Ye:** None.

Poster

826. Alcohol: Brain Circuitry II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 826.20/CCC11

Topic: G.08. Drugs of Abuse and Addiction

Title: Neurons in the orbitofrontal cortex encode relative preference during alcohol and sucrose seeking

Authors: *J. HERNANDEZ[1], R. SIEGAL[2], D. E. MOORMAN[1,2];
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Abstract: Orbitofrontal cortex (OFC) activity is associated with reward valuation, preference and seeking. Despite a growing consensus that the OFC may be disrupted in addiction, few studies have examined the role of the OFC in alcohol use disorders. In alcohol-dependent individuals OFC is activated by alcohol cues, along with self-reported craving. Ethanol potently affects OFC neuron excitability in vitro, and OFC manipulation influences ethanol drinking in mice. No study has measured OFC neural activity during alcohol seeking or consumption, which would allow a mechanistic understanding of how OFC function encodes alcohol motivation. To address this issue, we recorded OFC neuron activity of neurons in the OFC during sucrose and/or alcohol seeking tasks. 16 Long-Evans rats received homecage intermittent access to 20% ethanol for 4 weeks. Rats were then trained on a cue-driven ethanol/sucrose seeking task. A sustained nosepoke (500 ms) triggered one of three reward-predicting tones: 20% ethanol (1 kHz), 10% ethanol (10 kHz), or sucrose (5 kHz). Rats were required to leave the nosepoke in less than 500 ms to retrieve the reward. Upon stable performance, we implanted 32 microwire arrays in the OFC to record from neurons during sucrose and alcohol seeking. OFC neurons were recorded in two session types: blocked and interleaved trials. In blocked trial sessions, only one type of tone and reward was presented (10% ethanol, 20% ethanol, or sucrose). In interleaved sessions, two

separate tones/reward trials (e.g., 20% ethanol and sucrose) were randomly interleaved. 140 neurons were recorded during blocked sucrose, 20% ethanol and interleaved sucrose/20% ethanol trials. 100 neurons were recorded during blocked 10% ethanol and interleaved 10%/20% ethanol trials. In blocked sucrose trials OFC activity was transiently suppressed during tone presentation, elevated during initiation of sucrose seeking, and suppressed again during sucrose consumption. During blocked 10% and 20% ethanol trials, activity also decreased during tones, but exhibited weaker rebound excitation during seeking and milder inhibition during consumption. During interleaved trials, similar patterns were observed, but changes in activity were strongest for sucrose vs. 10% ethanol and 20% ethanol vs. 10% ethanol. These patterns of activity matched behavioral preferences (sucrose>10% ethanol and 20% ethanol>10% ethanol), likely reflecting an innate preference for sucrose and a learned preference specifically for 20% ethanol. Thus OFC neuron activity reflected relative preferences, consistent with previous demonstrations using natural rewards, and extending this type of encoding to drug rewards.

Disclosures: **J. Hernandez:** None. **R. Siegal:** None. **D.E. Moorman:** None.

Poster

827. Addiction: Ethanol and Volatile Solvents

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 827.01/CCC12

Topic: G.08. Drugs of Abuse and Addiction

Support: National Institute on Alcohol Abuse and Alcoholism Intramural Program

Title: Association analysis of variants in the PIP5K1C gene and alcohol dependence

Authors: *A. D. ROSEN[1], C. MUENCH[1], M. L. SCHWANDT[1], E. A. TAWA[1], Z. A. KAMINSKY[2], F. W. LOHOFF[1];
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Abstract: Previous research has shown that 73% of individuals with Alcohol Dependence (AD) report comorbid chronic pain. Preclinical studies have implicated the gene Phosphatidylinositol-4-Phosphate 5-Kinase (PIP5K1C) as a potential key regulator of chronic pain. It produces Phosphatidylinositol 4,5-biphosphate (PIP_2), a protein signaling substrate that initiates pain signaling. The present study aimed to examine the association of PIP5K1C variants and AD in 927 subjects with AD and 461 healthy controls, who were dichotomized based on European ancestry (n=812) and African ancestry (n=564). Given the high comorbidity of AD and chronic pain, it was hypothesized that genetic variation in PIP5K1C would confer risk for AD. Sixteen

common PIP5K1C single nucleotide polymorphisms (SNPs) were extracted from genotype data generated using the Illumina Human OmniExpress-12 and Illumina Human OmniExpressExome v1.2 arrays. Exploratory χ^2 tests were performed using PLINK and the Benjamini-Hochberg procedure for false discovery rate was used to correct for multiple comparisons. In the African Ancestry group eight SNPs (rs4807493, rs10405681, rs2074957, rs10432303, rs8109485, rs1476592, rs10419980, and rs4432372) were significantly associated ($p<.05$ after correction) with AD, while no significant associations were found in the European ancestry group. Alcohol-related phenotypes, such as severity of AD, average number of drinks per day, and craving were not associated with any SNPs in either group. These results indicate a strong association between common PIP5K1C variants and AD in subjects of African ancestry that requires further investigation; specifically, clarification of additional neurobiological and genetic factors that may influence this relationship. Future research should replicate these results using a larger sample size and a haplotype analysis. Additionally, PIP5K1C variants should be examined in subjects with comorbid AD and chronic pain to translate previous preclinical findings on the role of PIP5K1C in chronic pain regulation to clinical populations and ultimately determine potential targets for treatment. Finally, future studies might explore this relationship and potential treatment targets across a variety of addiction phenotypes that are known to be associated with chronic pain, including opioid and cannabis dependence.

Disclosures: **A.D. Rosen:** None. **C. Muench:** None. **M.L. Schwandt:** None. **E.A. Tawa:** None. **Z.A. Kaminsky:** None. **F.W. Lohoff:** None.

Poster

827. Addiction: Ethanol and Volatile Solvents

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 827.02/CCC13

Topic: G.08. Drugs of Abuse and Addiction

Title: Early-ethanol exposure and vinpocetine treatment alter structural- and GTPase signalling-related proteins in the ventral hippocampus of Sprague-Dawley rats: A proteomic study

Authors: *P. C. SWART, V. A. RUSSELL, J. J. DIMATELIS;
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Abstract: Introduction: Early ethanol exposure may alter the expression and/or functionality of structural-, metabolic-, signalling-related and neurotrophic proteins in the developing brain which may play a role in the deleterious outcomes of exposure to alcohol in utero. Therefore, this study aimed to explore the long-term effects of early-ethanol exposure on behaviour and proteins in the brain using a rat model. Further, vinpocetine, a phosphodiesterase type 1 inhibitor was

tested to determine if it could reverse ethanol-induced changes in behaviour and neural proteins. **Methods:** Male Sprague-Dawley rats were administered 12 % ethanol solution (4 g/kg/day i.p.) or saline from postnatal day (P) 4 to P9. During adolescence, from P25 to P31, ethanol-exposed rats were injected with vinpocetine (20 mg/kg/day i.p.) or vehicle (DMSO) whereas saline-exposed rats were administered DMSO only. This resulted in 3 experimental groups for behavioural and biochemical analysis. Rats were sacrificed at P31. The ventral hippocampus (VH) was removed for proteomic analysis by iTRAQ labelling and quantification by liquid chromatography mass spectrometry (LC-MS). A change >20 % was used to identify differentially expressed proteins and a change >10 % in the same direction, indicated a supporting trend. **Results:** Early-ethanol exposure did not adversely affect behaviour in the open field. However, ethanol-exposed rats displayed thigmotaxis in the Morris Water Maze. Further, early ethanol exposure down-regulated myelin proteolipid protein, a structural protein, and eukaryotic translation initiation factor 3 subunit E (eIF3E) in the VH. Additionally, GTPase signalling-related proteins such as G protein couple receptor 21, ADP-ribosylation factor GAP 1 and GAP binding protein 2 were decreased in ethanol-exposed rats. Treatment of ethanol-exposed rats with vinpocetine increased levels (>10% change) of the above mentioned proteins compared to non-treated ethanol-exposed rats. In agreement with our previous findings NADH dehydrogenase [ubuiqione] 1 alpha subcomplex 9, an energy-related protein was decreased in ethanol-exposed rats. However, treatment with vinpocetine did not increase NADH dehydrogenase [ubuiqione] 1 alpha subcomplex 9 when compared to non-treated ethanol-exposed rats.**Conclusion:** The data suggests that early-ethanol exposure results in long-term alterations in structural-, GTPase signalling- and energy-related protein expression in the ventral hippocampus. Vinpocetine is able to increase levels of affected proteins in ethanol-exposed rat brains thereby providing possible means of treating early-ethanol exposure.

Disclosures: P.C. Swart: None. **V.A. Russell:** None. **J.J. Dimatelis:** None.

Poster

827. Addiction: Ethanol and Volatile Solvents

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 827.03/CCC14

Topic: G.08. Drugs of Abuse and Addiction

Support: T32 AA07471

NIAAA R01 AA020992

Title: Transgenerational effects of chronic ethanol treatment in *Caenorhabditis elegans*

Authors: *D. M. GUZMAN, D. SUCICH, J. T. PIERCE;
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Abstract: Alcoholism is a prevalent and often devastating disease, characterized by a psychological and physical dependence on alcohol consumption. Familial patterns of alcohol dependence, as well as human twin studies, suggest a heritable component to the susceptibility of this disease. However, simple genetic inheritance alone does not predict development of alcoholism. There is growing evidence that suggests that exposure to some drugs of addiction can lead to heritable changes in gene expression in the form of epigenetic alterations. In order to determine if chronic ethanol exposure alters alcohol response behaviors in progeny, we used the model nematode *C. elegans* for its unique advantages in transgenerational epigenetic studies. We treated parental generation (F_0) animals with either ethanol or control buffer, to generate the EtOH-line and Control-line, respectively. Three subsequent generations of these lines (F_1-F_3) were tested for sensitivity to acute intoxication displayed by these naïve animals. For each of the three generations, we found that the EtOH-line showed resistance to ethanol-induced locomotor inhibition relative to the Control-line. These results suggest that chronic exposure to EtOH confers resistance to intoxication in subsequent generations. This is particularly interesting because inherent resistance to the negative effects of alcohol consumption is thought to contribute to alcohol abuse susceptibility in humans. Further studies will focus on elucidating the neuronal and genetic mechanisms that may confer this apparent heritable resistance to alcohol.

Disclosures: D.M. Guzman: None. **D. Sucich:** None. **J.T. Pierce:** None.

Poster

827. Addiction: Ethanol and Volatile Solvents

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 827.04/CCC15

Topic: G.08. Drugs of Abuse and Addiction

Support: NIAAA Grant R37 AA016848

NIAAA Grant P50 AA017072

Title: The BDNF valine 68 to methionine polymorphism alters mouse reward sensitivity and anxiolytic effects of alcohol

Authors: *S. A. SAKHAI[1], N. MORISOT[2], D. RON[2];
[1]Neurol., [2]Univ. of California, San Francisco, San Francisco, CA

Abstract: The brain derived neurotrophic factor (BDNF) plays a major role in structural and functional neuronal plasticity, and we previously showed that corticostriatal BDNF gates alcohol intake in rodents [1]. The valine (Val) 66 to methionine (Met) substitution is a common genetic variant in the human BDNF gene, which is associated with multiple psychiatric disorders [2]. Using a transgenic mouse homologue of the human allele (Val68/Met68), we recently reported that mice carrying the Met68BDNF polymorphism exhibit increased excessive alcohol intake as compared to the wildtype Val68BDNF carriers [3]. Furthermore, we observed that the Met68BDNF mice consume alcohol despite negative consequences [3]. We hypothesized that the excessive and compulsive consumption of alcohol observed in Met68BDNF mice may be due to an alteration in the sensitivity to the rewarding and/or anxiolytic actions of alcohol. First, to determine if the Met68BDNF polymorphism alters alcohol reward sensitivity, we used a conditioned place preference (CPP) paradigm and found that Met68BDNF mice spend less time in the compartment associated with alcohol compared to Val68BDNF mice, suggesting reduced sensitivity to the rewarding properties of alcohol. Next, we tested whether the Met68BDNF polymorphism alters the anxiolytic actions of alcohol by using the elevated plus-maze task (EPM), which assesses anxiety-like behavior in rodents. We observed no basal differences in anxiety-like behavior between the Met68BDNF and Val68BDNF carriers. However, when given a moderate, anxiolytic dose (1.25 g/kg) of alcohol, we observed that Met68BDNF animals spend less time in the distal arm compared to Val68BDNF carriers suggesting reduced sensitivity to the anxiolytic actions of alcohol. To test whether this effect was specific to alcohol, we tested the effect of anxiolytic GABA modulator, diazepam (1.5 mg/kg) in both genotypes. We found no differences between the Met68BDNF and Val68BDNF, showing that the reduction in anxiolytic behavior observed in Met68BDNF mice is specific for alcohol. Taken together, these data suggest that excessive and compulsive alcohol intake spurred by a mutation in the BDNF gene, may be due, in part, to decreased sensitivity to the rewarding and anxiolytic actions of alcohol.
[1] M.L. Logrip, et al. *Brain Research (review)* (2015).
[2] M. Notaras, et al., *Mol. Psychiatry (review)*, (2015).
[3] V. Warnault, et al. *Biol. Psychiatry*, (2015).

Disclosures: **S.A. Sakhai:** None. **N. Morisot:** None. **D. Ron:** None.

Poster

827. Addiction: Ethanol and Volatile Solvents

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 827.05/CCC16

Topic: G.08. Drugs of Abuse and Addiction

Support: NIAAA P50 AA022538

NIAAA U01 AA016654

NIAAA U01 AA020912

Title: Modulation of alcohol reward, anxiety, & gene expression by the transcriptional regulator Lim-domain-only 3 (LMO3)

Authors: *A. M. SAVARESE[1], A. LASEK[2];
[2]Psychiatry, [1]Univ. of Illinois At Chicago, Chicago, IL

Abstract: LMO3 is a transcriptional regulator that has previously been implicated in several alcohol-related phenotypes; notably, *Lmo3* knockout (Lmo3KO) mice exhibit increased binge-like ethanol consumption. To further characterize Lmo3KO mice, we tested for the rewarding properties of ethanol, using the conditioned place preference test, and ethanol-induced anxiolysis, using the elevated plus maze test. In both tasks, we found a sex by genotype interaction, wherein female Lmo3KO mice exhibited attenuated ethanol preference and ethanol-induced anxiolysis, and male Lmo3KO mice exhibited greater baseline anxiety. In order to explore the mechanism by which LMO3 is regulating these behaviors, we compared the expression of several alcohol-related genes (*Crh*, *Crhr1*, *Gabra1*, *Gabra4*, and *Gabrd*) between Lmo3KO and wildtype (WT) mice. Gene expression was examined in the nucleus accumbens (NAc), central nucleus of amygdala (CeA), and basolateral amygdala (BLA) using qPCR. Lmo3KO mice had reduced *Gabra1* expression in the CeA and elevated *Gabra4* expression in the BLA relative to WT mice. A sex by genotype interaction was found for *Gabrd* – female Lmo3KO mice had significantly greater expression of *Gabrd* in the BLA than female WT mice. Finally, Lmo3KO mice had reduced expression of both *Crh* and *Crhr1* in the BLA, and reduced expression of *Crhr1* in the CeA. The dysregulated expression of GABA-A receptor subunits and the CRF system in the amygdala may account for the increased binge drinking in Lmo3KO mice, while changes in *Gabrd* expression in female Lmo3KO mice may drive the modulation of reward and altered anxiety-like behavior exhibited by these mice.

Disclosures: **A.M. Savarese:** None. **A. Lasek:** None.

Poster

827. Addiction: Ethanol and Volatile Solvents

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 827.06/CCC17

Topic: F.04. Stress and the Brain

Support: 1F30AA023696

AA018400

AA023305

Title: Role for corticotropin-releasing factor in the central amygdala in alcohol drinking after traumatic stress

Authors: *A. SCHREIBER, N. GILPIN;
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Abstract: Post-traumatic stress disorder (PTSD) affects 7.7 million Americans. Twenty percent of those affected also meet criteria Alcohol Use Disorder (AUD), making it the most common co-morbid mental health disorder in patients with PTSD. A possible chemical mediator for this co-morbidity is corticotropin-releasing factor (CRF), a pro-stress neuropeptide that is dysregulated in many anxiety disorders. CRF is highly expressed in the central amygdala (CeA), a brain region critical for mediating anxiety-like behavior. Both CRF and the CeA are known to be dysregulated by stress and alcohol use, making them potential mediators in this co-morbidity. Our lab has previously shown a role for CeA CRF signaling in traumatic stress-induced hyperalgesia. The purpose of this study was to determine the role of CRF in the CeA in mediating traumatic stress-induced escalation of alcohol drinking and to characterize avoidance behavior after repeated antagonism of CRF1 receptors (CRFR1). We hypothesized that predator odor stress would escalate alcohol drinking in rats that exhibit high avoidance of a predator odor-paired context and that this effect would be reversed by antagonism of CRFR1. Adult male Wistar rats were trained to self-administer alcohol on an FR1 schedule and were then implanted with bilateral cannula aimed at the CeA. After re-stabilization of baseline alcohol drinking and habituation to sham infusions, rats were exposed to predator odor stress in a 4-day conditioned place avoidance procedure and indexed for high (Avoiders) and low (Non-Avoiders) avoidance of predator odor-paired context, or were unstressed controls. On days 2, 5, 8, and 11 post-stress rats were infused with a CRFR1 antagonist of vehicle prior to self-administration sessions. Preliminary results suggest that intra-CeA CRFR1 antagonism does not reduce alcohol self-administration after traumatic stress. We are also using c-fos immunostaining to characterize the distribution and phenotypes of stress-induced neuronal activation in Avoiders, Non-Avoiders, and unstressed Controls.

Disclosures: A. Schreiber: None. **N. Gilpin:** F. Consulting Fees (e.g., advisory boards); Glauser Life Sciences.

Poster

827. Addiction: Ethanol and Volatile Solvents

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 827.07/CCC18

Topic: G.03. Emotion

Support: PAPIIT / IA203716

Title: Chronic orofacial pain induces cognitive and emotional alterations it leads to increase the predisposition to develop addiction

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Abstract: Since pain is a complex sensory modality, it turns to be essential for surviving. Nevertheless, chronic pain loses its protective function and it has emotional and cognitive implications that may lead to long-term changes in the central nervous system affecting welfare of those who suffer from it, above all their quality of life. These disturbances involve a failure from the subject to adapt to the requirements demanded by his environment, depression and it leads to addiction. The aim of the present study is to assess experimentally cognitive and emotional impairments induced by chronic neuropathic orofacial pain in a rodent model, evaluating motivation, adaptation, self-regulation, persistence and predisposition to increase the ethanol intake. 50 male Wistar rats (200-250g) were randomly divided in two groups, (1) chronic constriction injury of the mental nerve (mNC) a branch of the trigeminal and (2) sham surgery. In order to assess motivation, a method to measure motivation for sucrose (10%) consumption in a self-administration schedule was developed, in a fixed ratio schedule (FR), and then in a progressive ratio schedule (PR) in order to obtain sucrose solution. In order to evaluate persistence and adaptation, we used a variable of go/no-go task followed by a persistence trial; this way, learning, memory and self-regulation abilities were evaluated. In persistence trial a long time pressing the lever was taken as a sign of poor adaptation to environmental requests. Using the drink in darkness protocol (DID), we evaluated the ethanol intake after mNC. The mNC induces both mechanical and cold hyperalgesia. The mNC reduces the motivation for obtain a sucrose reward ($p<0.001$) in a FR and PR paradigm, but not the motor components of the task, reduces also the adaptation process and reversal learning in go no go/persistence task ($p<0.05$) and increase the ethanol intake in DID protocol. These results indicate, that the mNC not only affected the expectation and motivation to obtain a reward, also the individual's ability to adapt was disturbed and the susceptibility to develop ethanol addiction increased. These results support the hypothesis that persistent neuropathic orofacial pain causes cognitive and

emotional impairment, and could leads to addiction.This work was supported by PAPIIT / IA203716

Disclosures: **C. Sosa:** None. **N.E. Gutiérrez:** None. **C.D. Montes:** None. **J. Jimenez:** None. **I.O. Perez-Martinez:** None.

Poster

827. Addiction: Ethanol and Volatile Solvents

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 827.08/CCC19

Topic: G.08. Drugs of Abuse and Addiction

Support: NIH Grant T24GM008074

NIH Grant 8UL1GM118979-02

NIH Grant 8TL4GM118980-02

NIH Grant 8RL5GM118978-02

Title: Alcohol reward in male and female periadolescent rats: Effects of fixed vs. ascending dosing

Authors: *E. BATES[1], N. S. PENTKOWSKI[2], A. R. ZAVALA[1];
[1]Psychology, California State University, Long Beach, Long Beach, CA; [2]Univ. of New Mexico, Albuquerque, Albuquerque, NM

Abstract: Alcohol is the most commonly abused recreational substance that is first consumed during adolescence. Preclinical research examining the rewarding effects of alcohol in adolescence, as assessed using the conditioned place preference (CPP) paradigm, have resulted in weak or inconsistent results. The present study sought to examine whether ascending doses of alcohol during conditioning produces more robust alcohol-induced CPP compared to a fixed dosing regimen during conditioning. Support for this hypothesis is indicated by recent studies demonstrating more robust cocaine-induced CPP using ascending doses of cocaine during conditioning compared to fixed doses during conditioning. Beginning on postnatal day (PD) 23, male and female periadolescent rats underwent a 10-day alcohol CPP procedure. On days 1 and 10, rats were tested for their pre-conditioning and post-conditioning place preferences, respectively, during 15-min sessions. On days 2-9, rats were conditioned for 15-min with saline or alcohol on alternative days. During alcohol conditioning days, rats were randomly assigned to receive either ascending alcohol doses (0.125-2.0 mg/kg, intraperitoneally) or fixed alcohol

doses (0.5, 1.0, or 2.0 mg/kg, intraperitoneally). Results reveal differences in the strength of CPP in a dose dependent manner between fixed vs ascending dosing of alcohol during conditioning, with the latter produces a more robust CPP. Overall, these results suggest that the pattern of doses used during conditioning sessions may be play an important role in elucidating the rewarding effects of alcohol.

Disclosures: E. Bates: None. **N.S. Pentkowski:** None. **A.R. Zavala:** None.

Poster

827. Addiction: Ethanol and Volatile Solvents

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 827.09/CCC20

Topic: G.03. Emotion

Support: NIH Grant AA021657

NIH Grant AA022292

Title: Activation of 5-HT_2 receptors via CaMK II signaling in lateral habenula mediates pain at ethanol withdrawal in rats

Authors: *W. ZUO[1], L. WU, Female[2], R. FU, Male[3], A. BEKKER, Male[3], J.-H. YE, Male[3]; [1]Anesthesiol., Rutgers New Jersey Med. Sch., Newark, NJ; [2]Gynecology, The 2nd People's Hosp. of Guangdong Province, Guangzhou, China; [3]Anesthesiol., Rutgers, The State Univ. of New Jersey, New Jersey Med. Sch., Newark, NJ

Abstract: Pain symptoms often occurs at withdrawal from chronic ethanol consumption, yet the underlying cellular and molecular bases are unclear. Evidence has linked pain with disorders in the lateral habenula (LHb), central serotonin (5-HT) systems and Ca^{2+}/calmodulin-dependent kinase II (CaMK II). We have previously shown that ethanol withdrawal induced pain, and both acute ethanol and 5-HT type 2 receptor (5-HT_2R) agonists increase glutamate transmission and activity of LHb neurons. The present study tested the hypothesis that activation of 5-HT_2R via CaMKII signaling in LHb significantly contributes to the pain at ethanol withdrawal. We trained male Sprague Dawley rats to drink ethanol in an intermittent access two-bottle free choice paradigm for three months. *Ex vivo* electrophysiological recordings revealed that at 24 h ethanol withdrawal, basal glutamate transmission and spontaneous firing of LHb neurons in brain slices were enhanced, and the enhancement was attenuated by KN62, a CaMK II inhibitor. In addition, acute ethanol-induced facilitation of glutamate transmission and firings in LHb neurons of both ethanol-naïve and ethanol-withdrawn rats was attenuated by ritanserin and SB200646,

respectively 5-$HT_{2A/2C}$R and 5-$HT_{2B/2C}$R antagonists, and KN62. Conversely, this facilitation was mimicked by 5-$HT_{2A/2C}$R agonist DOI or 5-$HT_{2B/2C}$R agonist mCPP, but was reduced by KN62. More importantly, intra-LHb infusion of KN-62, ritanserin or SB200646 not only substantially reduced response to noxious stimuli in both ethanol-naïve and ethanol-withdrawn rats, but also reduced ethanol intake in ethanol drinking rats. Interestingly, LHb infusion of DOI or mCPP increased response to noxious stimuli in ethanol-naïve rats, and aggravated the pain in ethanol-withdrawn rats. Lastly, Quantitative real time PCR assay detected only the 5-HT 2A and 2C but not the 2B mRNA in LHb, and withdrawal from chronic ethanol did not significantly change 5-$HT_{2A/2C}$ mRNA level. Together, these data reveal that ethanol withdrawal-induced hyperactivity of LHb neurons via the activation of 5-$HT_{2A/2C}$Rs that is regulated by CaMKII signaling pathways, consequently results in neuropathic pain. LHb 5-$HT_{2A/2C}$Rs may therefore represent a potential therapeutical target for alcoholics. Key words: ethanol withdrawal, lateral habenula disorders, pain, serotonin.

Disclosures: **W. Zuo:** None. **L. Wu:** None. **R. Fu:** None. **A. Bekker:** None. **J. Ye:** None.

Poster

827. Addiction: Ethanol and Volatile Solvents

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 827.10/CCC21

Topic: F.04. Stress and the Brain

Support: UT's NeuroNET Research Center - Seed Grant

NIH R21 MH098190

Title: Ethanol use in mice differentially alters stress resilience in a modality-specific manner

Authors: ***A. GRIZZELL**[1], B. N. DULKA[1], J. LINDSAY[2], R. PROSSER[2], M. A. COOPER[1]; [1]Dept. of Psychology, [2]Dept. of Biochem. and Cell. and Mol. Biol., Univ. of Tennessee, Knoxville, TN

Abstract: Stress and alcohol use have been studied extensively but focus on chronic stress-induced changes in consumption levels predominate. Much less is known about the mechanisms by which ethanol (EtOH) alters behavioral processing of stressful events, including the expression of stress-resilient/susceptible phenotypes. In the current study, adult male c57bl/6 mice were provided daily *ad libitum* access to 15% EtOH in drinking water for the first four hours of the dark phase only (Drinking-In-Dark paradigm; DID). Upon stabilization of drinking behavior (7 days), mice were subjected to one of three acute stress conditions: 1) acute social

defeat - consisting of three, sequential, 2-minute defeats in the home cages of larger CD1 mice; 2*)* Acute Variable Stress (AVS) - consisting of 20 minutes of forced restraint, acute social defeat (as above), and 20 minutes of forced swim stress; or 3) handled/unstressed controls. Twenty-four hours after stress exposure, all mice were tested in light/dark transition and social interaction tests. Daily EtOH access via DID continued for one week following stress. Results indicate that neither social defeat alone nor AVS significantly altered EtOH self-administration, although general drinking behavior in H_2O control mice did increase following stress. General anxiety, as measured in the light/dark test, was also unchanged by EtOH. However, EtOH exposure did significantly alter behavior in the social interaction test in a stress modality-specific manner. Following social defeat, EtOH drinkers had a profound increase in social withdrawal whereas AVS-exposed, EtOH drinkers were statistically indistinguishable from non-stressed controls given EtOH or H_2O. Furthermore, we found that following either AVS or social defeat stress alone, 20% of H_2O exposed mice did not exhibit social avoidance, which is characteristic of a resilient phenotype. However, 58% of EtOH drinking mice exposed to AVS expressed a resilient phenotype (n=12). In contrast, exposure to social defeat stress alone eliminated the expression of a resilient phenotype in EtOH drinking mice (0%; n=20). Given that brain derived neurotrophic factor (BDNF) signaling in the nucleus accumbens (NAcc) regulates social avoidance following chronic social defeat and acute EtOH administration can upregulate BDNF mRNA in the NAcc, we are currently investigating whether stress and EtOH self-administration alter BDNF levels in the NAcc, thereby modulating stress resilience in a modality specific manner. Overall, these findings suggest that alcohol consumption can alter stress vulnerability and, perhaps, differentially influence the risk for stress-related psychopathology.

Disclosures: **A. Grizzell:** None. **B.N. Dulka:** None. **J. Lindsay:** None. **R. Prosser:** None. **M.A. Cooper:** None.

Poster

827. Addiction: Ethanol and Volatile Solvents

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 827.11/CCC22

Topic: F.02. Behavioral Neuroendocrinology

Support: NIH R21-AA020575

Title: Sex differences and hormone effects on ethanol-enhanced risky behavior with probability discounting in rats.

Authors: ***K. G. WALLIN**[1], J. R. CHESLEY[2], J. CASTRILLON[3], R. I. WOOD[1];
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Abstract: Ethanol (EtOH) intake correlates with increased risk-taking in male humans and rats. Compared to males, female rats exhibit greater preference for and higher voluntary intake of EtOH, but are also more risk averse. The influence of sex and gonadal hormones on risk taking under the influence of EtOH has not been determined. Adult Long-Evans rats (n=18 males and females) were gonadectomized; half received hormone replacement at physiologic levels (n=7-9/group). Males received testosterone (ORCHX+T) or blank (ORCHX) implants, and females received estrogen (OVX+E) or blank (OVX) implants. Risk-taking was assessed with a probability discounting task requiring rats to choose between a small/certain reward (1 sugar pellet), and a large/uncertain reward (3 pellets) delivered with decreasing probability (100, 66, 33, 0%) in 4 blocks of each daily session. 15 minutes before testing, rats received saline or EtOH (0.5 or 1.0 g/kg, 3 days/dose) ip. By RM-ANOVA, EtOH ($F_{2,129}$=5.40, $p<0.05$), hormone replacement ($F_{1,130}$=7.93, $p<0.05$) and male sex ($F_{1,130}$=13.92, $p<0.05$) significantly increased risk taking, measured by preference for the large/uncertain lever. After saline, hormone-treated rats (ORCHX+T and OVX+E) took significantly more risks than rats without hormone ($F_{1,30}$=14.46, $p<0.05$). After 1.0g/kg EtOH, males took significantly more risks than females ($F_{1,30}$=5.1, $p<0.05$), suggesting that EtOH interacts with sex to influence risk taking. Additionally, there were significant effects of Etoh and sex on choice latency, with males responding faster than females ($F_{1,55}$=7.12, $p<0.05$) and all rats choosing more quickly when treated with EtOH ($F_{1,55}$=4.94, $p<0.05$). This suggests that male sex and EtOH treatment increase impulsivity. Sensitivity to losses is measured by lose-shift behavior, when rats move to the small/certain lever after a loss on the large/uncertain lever. EtOH significantly decreased lose-shift behavior ($F_{1,49}$=7.15, $p<0.05$) in all rats. These results show that EtOH, sex, and hormones interact to influence decision making. EtOH increases risk-taking by increasing impulsivity and decreasing loss sensitivity. At baseline, the hormonal milieu is more important than sex for determining levels of risk taking. However, EtOH treatment reveals a sex difference in decision making, with males taking more risk under EtOH influence than females. This is relevant to understanding human behavior, particularly in adolescents who experience increased hormone levels and often engage in EtOH use and risk taking. Supported by NIH R21-AA020575 to RIW.

Disclosures: **K.G. Wallin:** None. **J.R. Chesley:** None. **J. Castrillon:** None. **R.I. Wood:** None.

Poster

827. Addiction: Ethanol and Volatile Solvents

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 827.12/CCC23

Topic: G.08. Drugs of Abuse and Addiction

Support: CONACyT grant No.736339

CONACyT grant No.2015-01465

CONACyT grant No.268062

SEP grant UDG-PTC-1115

Title: Cyclohexane affects sensitization, reward and incentive motivation in instrumental progressive-ratio schedules

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Abstract: Background: Cyclohexane (CHX) is a volatile solvent used as a substitute of dangerous organic solvents in several products utilized as drug of abuse, such as: paint thinners, adhesive, gasoline etc. Previous reports have found oxidative stress and glial reactivity in hippocampus after inhaling CHX. This drug also provokes temporal and biphasic behavioral disturbances that may be associated with motivational alterations and addiction. Instrumental conditioning and Progressive Ratio schedules used after exposure to psychoactive drugs help establish learning, motor or motivational deficits. **Objective:** To analyze the effects of cyclohexane inhalation on incentive motivation, learning and motor skills. **Method**: Male CD1 mice (P60) were divided in two groups: controls (n=3) and CHX (n=4). The CHX group was exposed to 30,000 ppm twice a day for 30 min per 30 days. After a food deprivation regimen (85% ad libitum weight), lever-press training was done with an auto-shaping procedure. The reward (25% sugar concentration) was presented every thirty seconds. One session with continuous reward (FR1) was given and followed by 10 Progressive Ratio (PR) test sessions. In this PR model the reward was obtained with an arithmetic progression. Hence, the first reward was obtained with one lever press, and the next ones were obtained by adding the number of lever presses of the previous reward plus two. The Mathematical Principles of Reinforcement (MPR) model was adjusted to the performance in PR, and motor skills and incentive motivation parameters were estimated for each subject. Statistical analysis were done with the Mann-Whitney ‘‘U’’ test and the Pearson correlation. **Results:** A negative significant correlation was found between body weight and behavioral breakpoint in PR, Pearson = -0.35, t (68) = -3.16; p = 0.002. In the auto-shaping procedure the CHX group had more responses (mean ± SD, 69 ± 30) than controls (29 ± 17). In FR test, CHX had more responses (105 ± 20) than controls (91 ± 68). Breakpoint in the last PR session was higher in CHX (26 ± 7) than controls (18 ± 3). Incentive motivation was also higher in the CHX group (296 ± 184) as compared to controls (219 ± 198). Motor skill was similar in the CHX (7 ± 1) and control groups (7 ± 3). However, we did not find statistically significant differences between groups. The sample size may affect the test

reliability. **Conclusion**: This preliminary analysis showed that CHX may produce deficits in learning and motivation but unaffected motor skill in an instrumental lever press task.

Disclosures: T.V. Campos Ordonez: None. **D. Zarate-Lopez:** None. **O. Gonzalez-Perez:** None. **J. Buritica:** None.

Poster

827. Addiction: Ethanol and Volatile Solvents

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 827.13/CCC24

Topic: G.08. Drugs of Abuse and Addiction

Support: Conacyt 182208

CIC-UMSNH 26.10

CIC-UMSNH 2.36

CIC-UMSNH 30.2

Title: Participation of voltage-gated sodium and calcium channels on toluene cardiac effects

Authors: D. GODINEZ-HERNANDEZ[1], M. CARREON-GARCIDUEÑAS[1], L. ORTEGA-VARELA[2], *M. Y. GAUTHEREAU[3];
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Abstract: Toluene is a volatile solvent that that shares several actions with CNS depressants and can be inhaled to achieve intoxicating states. It is found in thinner, paints and adhesives. In vitro studies indicate that toluene inhibits voltage-gated sodium and calcium channels and it is well known that these channels are important for cardiac function. On the other hand, several reports indicate that inhaling solvents can lead to the occurrence of cardiac arrhythmias and a phenomenon known as sudden sniffing death, but the mechanisms by which these effects are produced are not completely understood. However, there are some reports indicating that cardiac arrhythmias due to adrenergic sensitization of the heart are probably the most common cause of death. Based on this evidence, the purpose of this study was to investigate the effect of acute toluene exposure on the reactivity of the heart to epinephrine and the participation of voltage-gated sodium and calcium channels in this phenomenon. Male Wistar rats (250-300 g) were placed in a static exposure chamber and exposed to 6000 ppm of toluene or air (control) during 30 minutes. After exposure, rats were anesthetized with sodium pentobarbital (50 mg/kg), and

the hearts were isolated and perfused according to Langendorff method. Concentration-response curves to epinephrine (adrenergic agonist: 1 x 10^{-9} - 1 x 10^{-4} M) in the presence and absence of lidocaine (voltage-gated sodium channel blocker) and nifedipine (voltage-gated calcium channel blocker), were made and parameters such as perfusion pressure, heart rate and strength of ventricular contraction were measured. The results showed that acute toluene exposure produced an increase in perfusion pressure, in the strength of ventricular contraction and in heart rate, i.e., there were positive inotropic and cronotropic effects. In addition, those actions were inhibited in the presence of lidocaine and nifedipine. In conclusion, the results suggest that acute toluene exposure modify voltage-gated sodium and calcium channel function probably due to a cardiac adrenergic mechanism and these effects could be participating, at least in part, in the presence of cardiac arrhythmias.

Disclosures: D. Godinez-Hernandez: None. **M. Carreon-Garcidueñas:** None. **L. Ortega-Varela:** None. **M.Y. Gauthereau:** None.

Poster

827. Addiction: Ethanol and Volatile Solvents

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 827.14/CCC25

Topic: G.08. Drugs of Abuse and Addiction

Support: SIP-IPN 20160992

INPRFM NC103380.2

Estímulos Fundación Miguel Alemán

Title: Evaluation of the antioxidant capacity of environmental enrichment in animals exposed to toluene

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Abstract: Inhalants are substances widely used as recreational drugs. Toluene is the main chemical compound present in most inhalants used with these purposes. Previous studies have shown that repeated toluene exposure produces cellular death in the hippocampus and that this is maintained after several weeks of withdrawal. Furthermore, environmental enrichment was able to detain these responses. On the other hand, oxidative stress has been involved in the effects of

toluene however it is unknown if environmental enrichment rescue the alterations in oxidative stress induced by toluene. Therefore, in the first part of this study we evaluated oxidative stress in the hippocampus of mice exposed to toluene. In the second part we evaluated the antioxidant capacity of environmental enrichment in mice with history of toluene exposure. To fulfill both objectives young male mice were exposed to toluene during four weeks. In a group of animals the brains areas were dissected out, afterwards reactive oxygen species and glutathione levels were analyzed. Another group of mice were exposed to toluene and afterwards they were housed either on environmental enrichment or on standard conditions. Evaluation of oxidative stress was also conducted after four weeks of housing treatment. Results showed that toluene enhance reactive oxygen species in animals repeated exposed to toluene, while environmental enrichment reduces these levels. Additionally, toluene increase glutathione concentrations in hippocampus of mice exposed to toluene and environmental enrichment was able to reduce these concentrations. These data may suggest that regulation of the oxidative stress may be playing a role in the protective effects of environmental enrichment on cellular death in animals exposed to toluene.

Disclosures: **Y. Yee-Ríos:** None. **S. Montes:** None. **N. Paez-Martinez:** None.

Poster

827. Addiction: Ethanol and Volatile Solvents

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 827.15/CCC26

Topic: G.08. Drugs of Abuse and Addiction

Support: Psi Chi grant

Title: Decreased seizure threshold in mice following twenty-four hour exposure to toluene vapor

Authors: S. P. CALLAN[1], C. DAVIDSON[2], *S. E. BOWEN[2];
[1]Dept., [2]Psychology, Wayne State Univ., Detroit, MI

Abstract: The intentional misuse of volatile solvents is a persistent public health concern. Limited self-report data suggests that chronic inhalant abusers experience withdrawal symptoms including anxiety and seizure symptoms. However, these symptoms have never been explored in a preclinical model and are not considered part of the DSM-V criteria for an Inhalant Use Disorder. For this experiment, 76 young adult male Swiss Webster mice were exposed to either 5,000 ppm toluene vapor or air (0 ppm) for 24 consecutive hours beginning on postnatal day (PND) 30. Following the 24 hour exposure, mice were allowed to recover for 3 hours before behavioral testing began. In the 1st experiment, mice were tested for handling-induced seizure activity every hour for 6 hours (and again at 24 hours). As compared to controls, toluene-

abstinent animals showed persistent clonic seizure activity throughout the 6 hour period. In the 2nd experiment, mice were given a single i.p. injection of pentylenetetrazole (PTZ; 42 or 48 mg/kg) to induce seizure activity. Mice were observed for 30 min and seizure activity was scored for severity using criteria adapted from the Functional Observational Battery. As compared to air controls, toluene-abstinent mice displayed a significant increase in seizure symptoms. In the 3rd experiment, previously exposed toluene mice were re-exposed to toluene vapor for 30 min following the three hour abstinence period. Following toluene re-exposure, these mice were tested for seizure severity with 42 or 48 mg/kg PTZ. Toluene re-exposure significantly reduced the severity of the seizure response. Taken together, these results suggest that toluene abstinence lowers seizure threshold in mice and that toluene re-exposure raises it. These findings provide support for clinical reports of a physical withdrawal syndrome from inhalants, which has implications for the successful diagnosis and subsequent treatment of Inhalant Use Disorders.

Disclosures: S.P. Callan: None. **C. Davidson:** None. **S.E. Bowen:** None.

Poster

828. Alcohol: Cell Signaling

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 828.01/DDD1

Topic: G.08. Drugs of Abuse and Addiction

Support: R37AA009986

T32AA007474

P50AA010761

Title: Actions of alcohol in mice expressing ethanol-resistant GluN2 NMDA receptor subunits

Authors: P. ZAMUDIO-BULCOCK[1], J. BENEROFF[1], C. SMOTHERS[1], B. HUGHES[1], G. HOMANICS[3], *J. J. WOODWARD[2];
[2]Neurosciences, [1]Med. Univ. of South Carolina, Charleston, SC; [3]Univ. of Pittsburgh, Pittsburgh, PA

Abstract: Identification of ethanol sensitive residues is important in order to develop animal models that can be used to define the role of NMDA receptors in alcohol-mediated behaviors. Previous work by the Peoples and Woodward laboratories identified residues within transmembrane (TM) domains of the NMDA receptor that regulate its sensitivity to ethanol. For example, mutations introduced at phenylalanine (F) 639 within the TM3 of the GluN1 subunit or alanine (A) 825 of the GluN2A subunit markedly reduce ethanol inhibition of mutant receptors

expressed in HEK293 cells. In this study, we generated genetically modified mice that expressed ethanol resistant GluN2A(A825W) or GluN2B(G826W) receptors. GluN2A(A825W) mice were made using a gene targeting construct containing exons 11 and 12 and associated intronic sequences. CRISPR/Cas9 and a repair template oligonucleotide were used to generate the GluN2B(G826W) mice. GluN2A(A825W) mice were viable, bred normally and were used in subsequent experiments. In contrast, mice expressing the GluN2B(G826W) mutation were not viable and no further studies with these mice were conducted. In mPFC neurons from adult wild-type (WT) mice, ethanol (44 mM) inhibited NMDA-mediated EPSCs while those from GluN2A(A825W) mice were unaffected. In male and female adults of GluN2A(A825W) and WT mice, EtOH (2.5 g/kg, IP) impaired performance on the rotarod. However, male A825W mice recovered faster than their WT counterparts from EtOH-induced impairment in motor coordination while no difference in the recovery time was noted between WT and A825W females. EtOH (0.75 g/kg) increased locomotor activity in WT males but had no effect on locomotion in male A825W mice. At a higher dose of EtOH (1.5 g/kg) A825W mice showed enhanced locomotor activity. At the highest dose tested (2 g/kg) EtOH did not have a significant effect in locomotion in either group. There were no differences in the locomotor responses after EtOH (0.75, 1.5, 2 g/kg) injections in mutant and WT females. In the elevated zero-maze, EtOH (1.25 g/kg) produced a similar anxiolytic response in WT and GluN2A(A825W) males and females. This anxiolytic response differed from the blunted response that we previously reported for GluN1(F639A) mice suggesting that receptors expressing the GluN2A subunit do not participate in EtOH-induced anxiolytic responses. Studies evaluating EtOH metabolism and consumption as well as further characterizing NMDAR-mediated currents in GluN2A(A825W) mice are currently underway. Supported by T32AA007474, R37AA009986 and P50AA010761.

Disclosures: **P. Zamudio-Bulcock:** None. **J. Beneroff:** None. **C. Smothers:** None. **B. Hughes:** None. **G. Homanics:** None. **J.J. Woodward:** None.

Poster

828. Alcohol: Cell Signaling

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 828.02/DDD2

Topic: G.08. Drugs of Abuse and Addiction

Support: NIH Grant AA020960

NIH Grant AA021667

Title: Dysregulated signaling pathways in alcohol self-administering rats

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Abstract: We used Gene Set Enrichment Analysis (GSEA) to identify biologic pathways dysregulated in gene expression profiles of rats self-administering alcohol under non-dependent or dependent conditions, in RNA from brain regions associated with alcohol's reinforcing actions. GSEA is a computational method to determine whether a defined gene set shows significant concordant expression difference when comparing gene expression profiles of two biological states. Pathways from the Broad Institute Molecular Signatures Database (MSigDB) were used. Among differentially expressed signaling pathways was the mTOR pathway, a well characterized target of alcohol's actions (KEGG MTOR SIGNALING_PATHWAY); genes regulated by glutamatergic kainate receptors, which have been shown to be sensitive to low alcohol concentrations (REACTOME ACTIVATION OF KAINATE RECEPTORS UPON GLUTAMATE BINDING); the ALK signaling pathway (BIOCARTA_ALK_PATHWAY), CREB-mediated gene expression (MCCLUNG CREB1 TARGETS), and signaling by G proteins and in particular the G beta-gamma complex and PLC-beta (REACTOME G PROTEIN ACTIVATION, REACTOME G BETA GAMMA SIGNALLING THROUGH PLC BETA). Both non-dependent and dependent alcohol drinking induced several pathways involved in inflammation such as TNF-alpha and interferon (IFN)-alpha signaling, and signaling by the P2Y12 purinergic receptor, which is involved in microglial activation (representative gene sets included HALLMARK TNFA SIGNALING VIA NFKB; HALLMARK INTERFERON ALPHA RESPONSE, REACTOME ADP SIGNALLING THROUGH P2RY12). Additional significant changes were seen in genes involved in oxidative phosphorylation (HALLMARK OXIDATIVE PHOSPHORYLATION). GSEA analyses also revealed that oligodendrocyte gene expression is a significant target of alcohol as a considerable number of genes related to oligodendrocytes previously associated with psychiatric disorders showed a predominantly reduced expression, even in non-dependent alcohol self-administering rats in comparison to control rats (e.g., ALL DISORDERS OLIGODENDROCYTE NUMBER CORR UP).

Disclosures: V.R. Canonigo: None. **B. Zorman:** None. **P. Sumazin:** None. **P. Sanna:** None.

Poster

828. Alcohol: Cell Signaling

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 828.03/DDD3

Topic: G.08. Drugs of Abuse and Addiction

Support: U01AA016658

Title: Role of the orphan GPCR, GPR88, in ethanol-associated behaviors

Authors: *S. BEN HAMIDA[1], S. MENDONÇA-NETTO[2], L. BOULOS[1], R. MALDONADO[2], B. KIEFFER[1,3];
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Abstract: The orphan G protein-coupled receptor, GPR88, is a G protein coupled receptor with no known endogenous ligand. This receptor is highly enriched in the striatum modulating dopaminergic transmission (Ghate et al., 2007, Neuroscience ; Massart et al., 2009, Eur J Neurosci) and the Gpr88 gene has been associated with psychiatric disorders in humans (Del Zompo et al., 2014, Mol Genet Genomic Med). Using a gene expression study, we previously showed that GPR88 is upregulated in the extended amygdala following 4 weeks of abstinence to several drugs of abuse, including ethanol (Le Merrer et al., 2012, Addict Biol). The role of GPR88 in the neurobiology of addiction remains unclear, however. Here we report that GPR88 knockout mice display enhanced home cage ethanol drinking and binge-like drinking compared to wild-type mice. Importantly, no alterations in water, saccharine, or quinine intake were observed in these mice. Moreover, mice lacking the *Gpr88* gene show enhanced motivation for ethanol-taking and seeking behaviors and decreased rewarding value of ethanol as shown by place preference test. This increased vulnerability to ethanol is accompanied by decreased dopamine response to ethanol in the nucleus accumbens, suggesting a compensatory response to decreased ethanol reward in GPR88 knockout mice. These findings suggest that GPR88 deletion increases vulnerability to ethanol, and that reduced GPR88 availability in the brain may constitute a risk faction for the development and expression of alcohol dependence.

Disclosures: S. Ben Hamida: None. **S. Mendonça-Netto:** None. **L. Boulos:** None. **R. Maldonado:** None. **B. Kieffer:** None.

Poster

828. Alcohol: Cell Signaling

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 828.04/DDD4

Topic: G.08. Drugs of Abuse and Addiction

Support: NIH-NIAAA P50 AA017072 (DR)

Title: Prosapip1- a novel mediator of alcohol abuse disorder

Authors: *S. LAGUESSE, N. MORISOT, F. LIU, D. RON;
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Abstract: We previously reported that excessive consumption of alcohol activates the H-Ras/PI3K/AKT signaling in the nucleus accumbens (NAc) of rodents, which ultimately leads to the activation of the mechanistic target of rapamycin complex 1 (mTORC1). mTORC1 is localized in dendrites and plays an important role in synaptic plasticity by promoting the translation of synaptic proteins. We therefore hypothesized that mTORC1-dependent mRNA translation contributes to neuroadaptations that underlie excessive alcohol consumption. We utilized the high throughput RNA sequencing (RNA seq) approach to identify novel genes whose mTORC1-dependent translation is induced in the NAc in response to excessive alcohol consumption. Among the 12 identified candidates was ProSAP-interacting protein 1 (Prosapip1), a synaptic protein whose function is not well understood. We first determined Prosapip1 expression profile in the brain and found that the protein is highly expressed in the striatum. Next, we confirmed the RNAseq data and showed that the translation of Prosapip1 but not the transcription was induced in response to excessive alcohol drinking in an mTORC1-dependent manner. The increase in Prosapip1 protein in the NAc in response to alcohol drinking was localized to the synaptic fraction and was maintained even after 24 hours of withdrawal. Prosapip1 levels were not altered in brain regions where mTORC1 is not activated by alcohol. Next, we elucidated the potential cellular consequences of mTORC1-dependent increase in Prosapip1 levels in the NAc. Prosapip1 has been indirectly linked to actin cytoskeleton regulation, and we found that the overexpression of Prosapip1 in the NAc as well as binge drinking of alcohol leads to increased F-actin content. Conversely, shRNA-mediated knockdown endogenous *Prosapip1* reduced the amount of actin filaments. Next, we determined whether Prosapip1 contributes to mechanisms underlying alcohol drinking behaviors. To do so, Prosapip1 was knocked-down in the NAc and alcohol intake was evaluated using an operant-self administration paradigm. We found that a reduction of Prosapip1 expression in the NAc lead to an attenuation of operant self-administration of alcohol. The decrease in alcohol self-administration by Prosapip1 knockdown was not due to non-specific changes in locomotion. We further showed that decreasing Prosapip1 levels in the NAc reduces alcohol place preference. Together, our data suggest that alcohol-mediated mTORC1-dependent translation of Prosapip1 in the NAc contributes to increase in F-actin content and drives the motivation to seek and consume alcohol.

Disclosures: S. Laguesse: None. **N. Morisot:** None. **F. Liu:** None. **D. Ron:** None.

Poster

828. Alcohol: Cell Signaling

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 828.05/DDD5

Topic: G.08. Drugs of Abuse and Addiction

Support: JSPS KAKENHI Grant Number JP16K08913

Title: Chronic ethanol consumption and withdrawal affect the expression of microRNAs in mouse brain

Authors: *K. MIZUO, R. MURAKAMI, S. OKAZAKI, S. WATANABE;
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Abstract: Several microRNAs (miRs) have been considered to be implicated in the action of abused drugs. We previously reported that acute ethanol administration caused the long-lasting increase in the expression of miR-124 in mouse brain. In the present study, we investigated the expression of miRs in mouse ethanol dependence and withdrawal model. Mice were treated with liquid diet containing ethanol for 10 days. Using the escalating ethanol dosage schedule, the mice were fed the ethanol diet as follows: 1st day: 1 w/v%; 2nd and 3rd day: 3 w/v%; 4th to 10th day: 4 w/v% ethanol diet, respectively. The control mice were given the same volume of ethanol-free liquid diet with sucrose substituted in isocaloric quantities for ethanol. The mice chronically treated with ethanol revealed severe withdrawal signs after discontinuation of ethanol. The mice were killed by decapitation and the limbic forebrain (containing nucleus accumbens), lower midbrain (containing ventral tegmental area) and amygdala were dissected. RT-PCR analysis for detection of miRs in the brain was performed. The expression of miR-124 was significantly increased in limbic forebrain following chronic treatment of ethanol. On the other hand, miR-132, miR-212 and miR-146a were decreased in lower midbrain following chronic treatment of ethanol. It has been reported that miR-146a regulates toll-like receptor 4 (TLR4) expression. TLR4 has been implicated in the development of alcohol-induced liver disease and osteonecrosis. Our findings suggest that the decrease in miR-146a in lower midbrain may affect the development of ethanol dependence via TLR4 signaling. We next investigated the changes in the miR expression in ethanol withdrawal state. We observed a significant decrease in miR-124 and miR-29a, miR-146a in lower midbrain at 9 hrs after ethanol withdrawal. It has been reported that loss of miR-29a results in neuronal cell death. These findings suggest that the decrease in miR-29a may cause neuronal death in ethanol withdrawal. In conclusion, we clarified that changes in the expression of miRs during ethanol dependence and withdrawal state.

Disclosures: **K. Mizuo:** None. **R. Murakami:** None. **S. Okazaki:** None. **S. Watanabe:** None.

Poster

828. Alcohol: Cell Signaling

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 828.06/DDD6

Topic: G.08. Drugs of Abuse and Addiction

Support: NIH Grant P50AA017823

Title: Potentiation of stress-induced corticosterone release during ethanol withdrawal is associated with upregulation of corticosterone synthesis in the adrenals

Authors: *T. L. DOREMUS-FITZWATER, A. S. VORE, A. GANO, T. DEAK; Psychology, Binghamton Univ., Binghamton, NY

Abstract: Previously, we have demonstrated that both male and female adult and adolescent rats exhibit an exacerbated corticosterone (CORT) response to mild or moderate stressors experienced during withdrawal from an acute ethanol challenge (Buck et al., 2011). As we have not yet identified a potential mechanism by which acute withdrawal might increase responsiveness of the HPA axis to stress exposure, the purpose of this experiment was to more fully examine central and peripheral changes in gene expression related to HPA axis activation during a state of ethanol withdrawal, as well as measurement of plasma CORT and its precursor, progesterone (PROG). Male and female adult Sprague-Dawley rats (N = 32) were given either saline (n = 16) or an acute ethanol injection (4 g/kg; intraperitoneally; n = 16). Approximately 3 h after ethanol clearance (18 and 13.5 h post-injection for males and females, respectively), all rats were exposed to a mild stressor, restraint, in size-appropriate tubes. Trunk blood, brains, pituitary and adrenal glands were collected 15 min after stress onset. PVN, pituitary, and adrenal expression of HPA axis activation-related genes was analyzed using real time RT-PCR. Similar to our prior studies, results demonstrated that ethanol-withdrawn rats exhibited significantly higher stress-induced elevations in plasma CORT when compared to vehicle controls. No withdrawal-related differences in PROG concentrations were observed in response to restraint. While ethanol withdrawal elicited few (if any) significant alterations in expression of the genes examined in the PVN or pituitary in response to restraint stress, the adrenal gland was dramatically altered by acute withdrawal. More specifically, restraint-induced increases in mRNA expression of *Star* (cholesterol transport protein), as well as *Cyp11B1* and *Cyp21A2* (CORT synthesis enzymes), in the adrenals were approximately 3-4 times higher in rats experiencing acute withdrawal at the time of stress exposure. A withdrawal-related suppression of stress-induced *C-fos* and *Cox-2* activation in the adrenal would suggest that these increases in CORT synthesis factors were not merely due to a more general withdrawal-induced activation of gene expression in this organ. Together, these findings provide evidence that withdrawal-related enhancement of the HPA axis response to stress is not evident at the level of the hypothalamus or

pituitary, but instead points toward the adrenal glands as the primary site of withdrawal-related sensitization of the HPA axis. Future studies will be necessary to identify the mechanism by which ethanol withdrawal potentiates CORT release in the adrenals in response to stress.

Disclosures: T.L. Doremus-Fitzwater: None. **A.S. Vore:** None. **A. Gano:** None. **T. Deak:** None.

Poster

828. Alcohol: Cell Signaling

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 828.07/DDD7

Topic: G.08. Drugs of Abuse and Addiction

Title: Novel role of glyoxalase 1 in stimulant response to ethanol

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Abstract: Alcohol (ethanol) can produce both stimulating and sedative effects. Sensitivity to ethanol stimulation is associated with greater reported ethanol reward and drug liking. Furthermore, heavy social drinkers show higher ethanol stimulation and higher ethanol stimulation can also predict future alcohol use disorder symptom severity and binge drinking frequency. We have previously identified glyoxalase 1 (Glo1) as a possible target for reducing binge-like drinking in mice. In the present studies, we investigated whether Glo1 inhibition could block the locomotor stimulating effects of ethanol. Male C57BL/6J mice were pretreated with one of two doses of a Glo1 inhibitor that has been shown to reduce ethanol binge-like drinking (pBBG; 6.25 or 50 mg/kg) or vehicle. Immediately before testing, mice received an injection of 2 g/kg ethanol or vehicle and were placed into locomotor chambers to record activity for 50 minutes. N=13-14 mice per each of the following treatment groups: 6.25 mg/kg pBBG alone, 50 mg/kg pBBG alone, 2 g/kg ethanol alone, 6.25 mg/kg pBBG + 2 g/kg ethanol, 50 mg/kg pBBG + 2 g/kg ethanol, and pBBG vehicle+saline. Ethanol alone produced significant locomotor stimulation compared to the vehicle+saline group. This effect was blocked by pretreatment with 50 mg/kg pBBG, and 6.25 mg/kg pBBG showed a trend toward significantly reducing locomotor stimulation as well. Neither dose of pBBG alone significantly altered locomotor activity as compared to the vehicle+saline group. These findings suggest that Glo1 inhibition can attenuate the stimulating effects of ethanol, which may be related to Glo1 inhibitor reduction of ethanol drinking. Glo1 therefore represents a potentially promising novel therapeutic target for alcohol use disorders.

Disclosures: **A.M. Barkley-Levenson:** None. **K.M.J. McMurray:** None. **A.A. Palmer:** None.

Poster

828. Alcohol: Cell Signaling

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 828.08/DDD8

Topic: G.08. Drugs of Abuse and Addiction

Support: DA026356

Title: Targets of low dose alcohol in the rat brain

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Abstract: The legal limit of alcohol consumption refers to its subsequent blood ethanol concentration (BEC) of 80 mg/dL or 17.4 mM. The physiological effects of alcohol are dose-dependent. Studies have focused on the effects and mechanisms underlying consumption of high dose of hard liquor with a high ethanol (EtOH) concentration (e.g. >40% w/v), but little has been done to elucidate the targets and actions of low dose alcohol. By mapping EtOH-induced FOS immunoreactivity (FOSir), we previously identified several brain nuclei as sites of action of high dose (3.0 g/kg) EtOH, whereas only the central nucleus of the amygdala (CeA) and Edinger-Westphal nucleus (EW) appear to be affected by low dose (0.75 g/kg) EtOH. The CeA, a nucleus within the amygdala, innervates several brain areas, including the nucleus accumbens (NAc), which plays a key role in the rewarding system. Recently, we found that treatment of F344 rats with 1.0 g/kg EtOH (16% w/v), resulting in a peak blood EtOH concentration (pBEC) of 5.31 ± 0.75 mM (24.46 ± 3.46 mg/dL), for 13 d significantly alters the expression of an array of genes related to addiction in the NAc. We then used the Library of Integrated Network-Based Cellular Signatures (LINCS), a database that utilizes gene profile signatures to suggest probability outcomes in terms of drug mimics and effects, to analyze the gene expression profile in the NAc of rats given EtOH. We found that knock-down gene expression of GABRG1, GABRB3, and GABRA5, three subunits of the $GABA_A$ receptor, mimics the effects of EtOH, indicating that the $GAGA_A$ receptor in the CeA is a target for low dose EtOH (1.0 g/kg) in the brain. To test our hypothesis, we randomly assigned F344 rats (7-8 wks old) into 4 groups: two groups were pre-treated with 1.0 mg/kg (i.p.) of the $GAGA_A$ receptor antagonist, bicuculline and two groups received saline 15 min prior to being administered either 1.0 g/kg (52% w/v) EtOH or water via oral gavage. EtOH at 52% w/v was chosen to mimic hard liquor and this treatment results in a pBEC of 7.63 ± 1.25 mM (35.15 ± 5.76 mg/dL). The rats were sacrificed 2 h after treatment, and

the CeA was microdissected from each animal. Using qRT-PCR and PCR array, we found that treatment with EtOH significantly increased *c-fos* mRNA expression, which was reversed by pre-treatment with bicuculline. In conclusion, these data support our hypothesis that the $GAGA_A$ receptor in the CeA is a target for low dose alchol in the rat brain (partially supported by DA026356).

Disclosures: W. Huang: None. **A. Dieterich:** None. **X. Qin:** None. **M.D. Li:** None. **S.L. Chang:** None.

Poster

828. Alcohol: Cell Signaling

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 828.09/DDD9

Topic: G.08. Drugs of Abuse and Addiction

Support: COBRE Grant 5P20GM103642

USDE Title V Cooperative Agreement Grant P031S130068

NIH Grant G12MD 007600

Title: Alcohol molecular tolerance of BK channels via beta-catenin gene regulation

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Abstract: The development and retention of alcohol tolerance has long been associated to neural mechanisms related to learning and memory. We have found a persistent component of alcohol molecular tolerance; internalization of BK channels, in both striatal and hippocampus neurons. It is further characterized by increases in ß-catenin in response to physiologically relevant concentrations of alcohol, which are necessary for BK channel internalization. Accumulation of ß-catenin was impaired in the presence of general protein synthesis inhibitors cyclohexamide and emetine, which further blocked ethanol-induced BK channel internalization in heterologous expression system. Interestingly, BK channel dissociation from lipid raft fractions in response to ethanol exposure was not significantly affected by protein synthesis inhibition. Translational regulation of EtOH was evaluated via tandem mass spectrometry (MS/MS) and Western Blot analysis of *de novo* synthesized proteins in heterologously expressed hSloα HEK293 preparations. Results indicated that ß-catenin is increased 2.5 fold in response to alcohol

compared within a subset of over seven hundred proteins assayed. Transcriptional regulation of EtOH in striatal tissue has been further studied suggesting changes in miRNA profile in response to duration of EtOH exposure. These findings suggest the canonical Wnt/ß-catenin signaling pathway plays a critical role in mediating a persistent form of BK channel molecular alcohol tolerance regulating BK channel surface distribution, and potentially mediating transcriptional regulation in response to EtOH.

Disclosures: J.O. Garcia: None. **A. Burgos:** None. **J. Soto:** None. **K. Cordero:** None. **S. Jimenez:** None. **S.N. Treistman:** None. **C. Velazquez-Marrero:** None.

Poster

828. Alcohol: Cell Signaling

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 828.10/DDD10

Topic: G.08. Drugs of Abuse and Addiction

Title: Effects of glucagon-like peptide-1 (glp-1) receptor stimulation on alcohol consumption in alcohol-preferring vervet monkeys

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Abstract: Glucagon-like peptide-1 (GLP-1) is an incretin hormone, which is secreted from endocrine L-cells of the small intestine in response to nutrients in the gut lumen, and GLP-1 analogues are used for the treatment of type 2 diabetes. The well-established effect of GLP-1 analogues on food reward seems to be centrally mediated and GLP-1 is believed to play a role in reward, thus important for the development of alcohol use disorders. In addition, pre-clinical studies have demonstrated inhibitory effects of the GLP-1 receptor agonist Exendin-4 on alcohol-mediated behaviour in rodents. However, the effects of GLP-1 receptor agonists on alcohol consumption have to our knowledge not been investigated in primates. To this end, we studied the effects of the GLP-1 receptor agonist Exenatide (Bydureon©, S.C. injection once weekly) on 10 days alcohol consumption (limited access drinking 4 hours daily) in alcohol-preferring vervet monkeys in a placebo-controlled trial.Twenty-four alcohol-preferring monkeys

were divided into 2 groups, balanced with respect to alcohol consumption, so that each group included monkeys with high and moderate alcohol intake levels. Following ten days of drug-free alcohol consumption all monkeys were treated in the absence of ethanol with Exenatide or placebo for a period of 5 weeks in order to obtain steady state drug levels. Thereafter, alcohol consumption was resumed for ten days (4 hours daily) during which time Exenatide or placebo treatment was continued. Water and alcohol consumption were measured daily after 4 h ethanol exposure. Plasma levels of Exenatide were measured at the end of the experiment.Exenatide significantly reduced alcohol consumption in the first half of the Exenatide / placebo testing period without causing signs of emesis. The present study suggests that the GLP-1 receptor is involved in voluntary alcohol consumption in non-human primates. The possibility that GLP-1 analogues might be useful in the medical treatment of alcohol use disorder mandates further evaluation.

Disclosures: **A. Fink-Jensen:** None. **A. Molander:** None. **J.J. Holst:** None. **M. Ptito:** None. **R. Palmour:** None.

Poster

828. Alcohol: Cell Signaling

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 828.11/DDD11

Topic: G.08. Drugs of Abuse and Addiction

Support: NIH Grant

WSU ADARP

Title: Chronic intermittent alcohol exposure alters negative affect and endocannabinoid-related mRNA expression in ovariectomized female rats

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Abstract: Alcohol dependent individuals experience significant negative physiological, cognitive, and psychological symptoms during withdrawal. Considerable sex differences exist with respect to the symptoms of alcohol use disorders. The endocannabinoid (ECB) system, which is intimately linked to female sex hormones (most notably estradiol; E_2), also influences both the motivation to consume alcohol and the negative affective symptoms of withdrawal. Our laboratory has recently shown that, following chronic intermittent alcohol (CIA) exposure, male

rats display enhanced negative affective behaviors and deficits in ECB-related mRNA in the basolateral amygdala (BLA), ventromedial prefrontal cortex (vmPFC), and nucleus accumbens (NAc) during acute withdrawal. However, these changes were not observed in female rats, suggesting a protective role of ovarian hormones on these endpoints. We therefore examined the effects of ovariectomy (OVX) with or without E_2 replacement on anxiety-like behavior in the elevated plus maze (EPM) and ECB-related genes (CNR1, NAPE-PLD, DAGLα, MAGL, and FAAH) in the BLA, vmPFC, and NAc following CIA vapor exposure. E_2 replacement significantly increased the number of entries and time spent in the open arms of the EPM in female OVX rats, however, this anxiolytic effect of E_2 was abolished in female rats exposed to CIA vapor. We also observed a hypolocomotor effect of CIA exposure independent of hormone status, reflected by significantly less distance traveled in the EPM in all CIA-exposed female rats. In the BLA, CIA-exposed female rats experienced reductions in NAPE-PLD and MAGL mRNA expression that were not rescued by E_2 replacement, thus indicating a potential impairment in the biosynthesis of anandamide (AEA) and degradation of 2-arachidonoylglycerol (2-AG), respectively. Within the vmPFC, CIA exposure significantly decreased the expression of all ECB-related genes in OVX female rats, which was similarly not rescued by E_2 replacement. In the NAc, E_2 treatment significantly decreased the expression of DAGLα and MAGL, but only in alcohol-dependent female rats. These results indicate that CIA exposure abrogates the anxiolytic properties of E_2, yet E_2 replacement in OVX rats is insufficient to prevent CIA-induced alterations in ECB-related genes in the BLA and vmPFC, whereas in the NAc, CIA exposure and E_2 interact to influence 2-AG synthesis and metabolism. These data provide insight into the neurobiological and hormonal mechanisms that may contribute to the induction of alcohol dependence and withdrawal in female rats, which can be leveraged to identify novel therapeutic strategies for treating alcohol use disorders in women.

Disclosures: **L. Baxter-Potter:** None. **A. Henricks:** None. **A. Berger:** None. **J. Lugo:** None. **R. McLaughlin:** None.

Poster

828. Alcohol: Cell Signaling

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 828.12/DDD12

Topic: G.08. Drugs of Abuse and Addiction

Support: NIAAA 5UO1AA17875

DPI20140008

Title: Glycine receptor alpha1 subunit regulates consumption and conditioned preference to ethanol

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Abstract: Introduction
Ethanol affects brain regions that are part of the reward system. One region, the nucleus Accumbens (nAc), receives several inputs from different brain areas including the ventral tegmental area (VTA). Activation of VTA neurons causes dopamine (DA) release into nAc and reinforces ethanol consumption. Glycine receptors (GlyR) are expressed in upper brain regions including nAc, where they have a role in DA release and can also regulate the consumption of ethanol. However, the mechanisms on how GlyRs regulate these effects are largely unknown. Previous studies from our laboratory showed that α1 GlyR is highly sensitive to ethanol, thus to evaluate the role of α1 GlyR in consumption and preference to ethanol we used a KI mice bearing an ethanol insensitive GlyR.
Results
We found the presence of GlyR synaptic currents (IPSCs) in nAc in WT and KI mice, both insensitive to ethanol effects. We also found the presence of GlyR-mediated tonic currents in nAc. The amplitude of this current in WT and KI was increased when a glycine transporter inhibitor (Org24598) was used (-14 ± 6 pA and -14 ± 3 pA, respectively); In addition, these current shifts were inhibited by 1 μM strychnine in both genotypes (3 ± 2 pA WT and 3 ± 1 pA KI). Interestingly, only the tonic current in WT mice was sensitive to ethanol (10 mM). To evaluate the role of α1 GlyR in the excitability of neurons from the nAc, we performed current clamp recordings to analyze action potential (AP) firing. In the presence of ethanol, AP firing was reduced to about 25% during a 200 pA depolarizing pulse. This effect was inhibited by co-application of 1 μM of strychnine in WT neurons. On the other hand, the firing in neurons from nAc of KI mice was not affected by ethanol. Finally, we evaluated the role of α1 GlyR in consumption and preference to ethanol using drinking in the dark (DID) and conditioned-place preference (CPP) protocols. The results indicate that KI mice consume higher amounts of ethanol during the first days of testing (WT: 1.6 ± 0.4 g/kg, n=15; KI: 5.1 ± 0.5 g/kg, n=13), and achieved a faster ethanol-conditioned preference than the WT mice.
Conclusion
This study shows the presence of synaptic and tonic glycine currents in nAc. Only the tonic current was sensitive to ethanol and regulated neuronal excitability. Because ethanol did not affect the responses in KI mice, we postulate that the loss of neuronal firing regulation causes a higher increase in consumption and ethanol-conditioned preference than the WT mice. These findings suggest a role for α1 GlyR in the regulation of reinforcement and addictive properties of ethanol.
Supported by NIAAA 5UO1AA17875 and DPI20140008

Disclosures: **S.S. Gallegos:** None. **B. Munoz:** None. **P. Murath:** None. **D.M. Lovinger:** None. **G.E. Homanics:** None. **L.G. Aguayo:** None.

Poster

828. Alcohol: Cell Signaling

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 828.13/DDD13

Topic: G.08. Drugs of Abuse and Addiction

Support: P50 AA0225338

U01 AA016654

U01 AA020912

Title: Estrogenic enhancement of ethanol reward requires activation of both ERα and ERβ.

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Abstract: Current alcohol use disorder (AUD) treatments are based on studies conducted primarily in male animals, and little is known about sex differences in the brain's response to ethanol. As the prevalence of AUDs in women continues to rise, the need to identify mechanisms that promote ethanol abuse in women is pressing. Here we investigated the role of estrogen receptors (ERs) as a modulator of ethanol reward in ovariectomized (OVX) female mice. Using the conditioned place preference (CPP) paradigm, we examined the effects of three ER agonists on preference for an ethanol-paired compartment. We also tested for effects of the steroid hormone estradiol on ethanol metabolism. Adult female C57BL/6J mice were OVX and allowed to recover for two weeks before the start of all experiments. For ethanol CPP, mice were administered 2.0 g/kg ethanol (20% v/v in saline) by intraperitoneal (IP) injection and confined to their initially non-preferred chamber of the CPP apparatus for 5 min. On alternate days, they received IP saline and were confined to the opposite chamber. A total of eight conditioning sessions (four ethanol, four saline) were used. Five treatment groups were examined: control (vehicle), estradiol benzoate (EB; 0.2 μg), the ERα agonist PPT (1 mg/kg), the ERβ agonist DPN (1 mg/kg), and a combined treatment of PPT and DPN together (1 mg/kg each). For the metabolism study, OVX mice were given vehicle or EB (0.2 μg) for a total of three days (one injection/day). On the third day, mice received IP ethanol (2.0 g/kg, 20% v/v in saline), and serial blood samples were collected from each animal at seven time points post-injection. Blood ethanol concentrations were measured using the alcohol dehydrogenase (ADH) assay. EB

treatment significantly enhanced preference for the ethanol-paired compartment. Neither PPT nor DPN alone was able to replicate this effect. When both agonists were administered together, however, we again observed a significant enhancement of ethanol CPP. EB treatment did not alter ethanol metabolism. Our findings demonstrate that estradiol enhances the rewarding effects of ethanol in female mice. Estradiol binds with approximately equal affinity to both of the classical ERs, ERα and ERβ. The effect of estradiol is replicated by co-administration of PPT and DPN, suggesting that concurrent activation of ERα and ERβ is necessary for estrogenic enhancement of ethanol reward. Supported by P50 AA0225338, U01 AA016654, and U01 AA020912 to AWL.

Disclosures: E.R. Hilderbrand: None. **A.W. Lasek:** None.

Poster

828. Alcohol: Cell Signaling

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 828.14/DDD14

Topic: G.08. Drugs of Abuse and Addiction

Support: NIHAA 018779

Title: Enhanced transition from impulsive to compulsive ethanol seeking behavior is associated with increased ERK-ΔFosB activity during ethanol extinction

Authors: *P. A. STARSKI[1], A. OLIVEROS[1], A. CUI[2], S. CHOI[1], D. CHOI[1];
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Abstract: Alcohol use disorder (AUD) represents a global risk factor for disease and premature mortality. Individuals affected by AUD exhibit a propensity for excessive risk-taking, resulting in maladaptive impulsive and compulsive behaviors. However, the behavioral models and molecular mechanisms underlying the transition between impulsive-to-compulsive ethanol seeking behaviors remains largely unexplored. Using the 5-choice serial reaction time task (5-CSRTT) for a sucrose (S-mice) or sucrose-ethanol (SE-mice) reward, we sought to investigate behavioral responses to ethanol during reward acquisition and extinction. First, we found that SE mice emitted higher numbers of positive ultrasonic vocalizations (USVs) during 5-CSRTT pre-training and 5-CSRTT testing, suggesting increased positive affective state during ethanol seeking. Interestingly, SE-mice displayed exacerbated impulsivity during early 5-CSRTT testing. In contrast, during extinction, SE-mice exhibited aberrant compulsive seeking in the absence of ethanol reward. Since both ERK1/2 and ΔFosB have been implicated in reward seeking mediated by the amygdala (AMY) and nucleus accumbens (NAc), we examined protein expression of

ERK1/2 and ΔFosB in these brain regions. Our results indicate that increased phosphorylation of ERK1/2 and higher expression of ΔFosB in the AMY are associated with prolonged compulsive reward seeking during extinction. Taken together, our behavioral and molecular studies provide novel insights underlying the transition from impulsive to compulsive ethanol seeking behavior.

Disclosures: **P.A. Starski:** None. **A. Oliveros:** None. **A. Cui:** None. **S. Choi:** None. **D. Choi:** None.

Poster

828. Alcohol: Cell Signaling

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 828.15/EEE1

Topic: G.08. Drugs of Abuse and Addiction

Support: NIH/NIAAA R03AA022479

Title: Effects of chronic alcohol in an animal model of depression: role of cortical alpha-2 adrenoceptors

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Abstract: Alcoholism is commonly associated with depression. A role for alpha-2 adrenoceptors in depression and drug dependence has been suggested. However, very little information on a direct interaction between alcohol and these receptors is available. In this study adult female Wistar-Kyoto (WKY) rats, a putative animal model of depression, were exposed daily to alcohol via inhalation chambers such that a blood alcohol concentration of approximately 150 mg% was achieved each day. The animals were exposed 4 hrs daily for 10 days with and without post-treatment with an antidepressant drug. These drugs included nomifensine, a selective norepinephrine/dopamine (NE/DA) uptake inhibitor, or imipramine, a selective NE/serotonin (NE/5HT) uptake inhibitor. The drugs (10 mg/kg, each) or saline were injected intraperitoneally immediately after removal from the inhalation chamber. The animals were tested on day 11 (approximately 18 h after the last alcohol exposure) for their open field locomotor activity (OFLA) as well as their performance in the forced swim test (FST). Each test was carried out for 5 min. FST was performed immediately after the OFLA. Two hours after the behavioral tests the aimals were sacrificed for measurements of alpha-2 receptor densities in discrete brain regions using [3H]RX 821002 as the specific ligand. Chronic alcohol treatment inccreased the immobility in the FST, suggesting an exacerbation of the depressive-like characteristic in WKY rats. Open field activity was not affected. Both nomifensine and imipramine noramlized the

behavior in the FST. The behavioral effects of alcohol were correlated with a decrease in cortical but not hippocampal alpha-2 receptor densities. The reductions in the receptor densities induced by chronic alcohol were also normalized by both antidepressant drugs. The results suggest a role for cortical alpha-2 adrenoceptors in alcohol exacerbation of the depressive-like behavior and reversal of these effects by antidepressant drugs. Further elucidation of the specific alpha-2 adrenoceptor subtype(s) involvement in behavioral effects of alcohol and/or antidepressants may provide novel targets for intervention in alcoholism-depression co-morbidity. Supported by: NIH/NIAAA R03AA022479

Disclosures: **B. Getachew:** None. **Y. Tizabi:** None.

Poster

828. Alcohol: Cell Signaling

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 828.16/EEE2

Topic: G.08. Drugs of Abuse and Addiction

Support: NIH Grant AA016179

NIH Grant MH096463

NIH Grant NS076517

Title: Involvement of GABA-A receptors expressing the alpha5 subunit in the reinstatement of alcohol seeking in rats

Authors: C. CHANDLER[1,2], J. REEVES-DARBY[2], S. JONES[2], G. LI[3], J. COOK[3], *D. M. PLATT[2,1];
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Abstract: Relapse to heavy alcohol drinking following a period of abstinence is a prevalent feature of alcohol use disorders. Patients in alcohol recovery report that both re-exposure to alcohol, as well as environmental cues associated with heavy alcohol use, can trigger a relapse episode. While pharmacotherapies exist that aid in relapse prevention, they are not universally effective. Therefore, a need exists for pharmacotherapies specific for relapse prevention that exhibit a broader effectiveness than those currently in use. The GABA-A receptor is a primary target for alcohol, and the function of this receptor is enhanced in alcohol's presence. Our lab and others have shown a key role for GABA-A receptors expressing the alpha5 subunit (i.e., alpha5GABA-A receptors) in both the reinforcing effects of alcohol (and the

subjective/interoceptive effects of alcohol. This specific GABA-A receptor subtype also may play a critical role in alcohol relapse due to their primary location, the hippocampus, a brain region involved in the reward circuitry that is responsible for the formation of memories associated with alcohol use. At present, the potential role of the alpha5GABA-A receptor in relapse to alcohol use is unknown. Here, we investigated the role of alpha5GABA-A receptors in the reinstatement of alcohol seeking in rats. Adult male Sprague Dawley rats were trained to press a lever for the delivery of a sucrose/alcohol solution paired with an ethanol-associated cue light using a standard sucrose-fading procedure. Once rats reached criteria for stable responding (consistent intake at pharmacologically-relevant doses, i.e., >0.5 g/kg), lever pressing behavior was extinguished by omitting deliveries of alcohol and the alcohol-paired cues. We then determined the degree to which re-exposure to alcohol and/or the alcohol-paired cues reinstated extinguished alcohol-seeking behavior. In contrast to the alcohol prime and the alcohol prime + cue conditions, re-presentation of the alcohol-paired cues produced significant alcohol-seeking behavior compared to extinction. Therefore, we utilized cue-induced reinstatement for subsequent drug testing. In tests, the alpha5GABA-A receptor-selective inverse agonist L-655,708 inhibited the cue-induced reinstatement of alcohol seeking, whereas the alpha5GABA-A receptor-selective agonist QH-ii-066 augmented to a small degree the cue-induced reinstatement of alcohol seeking. These results support the hypothesis that alpha5GABA-A receptors have a mechanistic involvement in environmental cue-induced alcohol relapse, and may serve as a target for pharmacotherapies specific for the prevention of alcohol relapse.

Disclosures: **C. Chandler:** None. **J. Reeves-Darby:** None. **S. Jones:** None. **G. Li:** None. **J. Cook:** None. **D.M. Platt:** None.

Poster

828. Alcohol: Cell Signaling

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 828.17/EEE3

Topic: G.08. Drugs of Abuse and Addiction

Support: Plan Nacional sobre Drogas grant 2012I102

Ministerio de Economia y Competitividad grant SAF2013-46135-P

CONACyT grants 234965, 263473 and 236778

Title: Modulating properties of Ethanol on dopamine levels, rewarding and psychostimulant effects of 3, 4-methylenedioxypyrovalerone (MDPV)

Authors: *M. H. BUENROSTRO-JAUREGUI[1,2], R. LÓPEZ-ARNAU[2], P. MUÑOZ-VILLEGAS[2], A. CIUDAD-ROBERTS[2], D. PUBILL[2], E. ESCUBEDO[2], J. CAMARASA[2]; [1]Univ. Enrique Díaz De León, Guadalajara, Mexico; [2]Univ. of Barcelona, Barcelona, Spain

Abstract: The 3, 4-methylenedioxypyrovalerone (MDPV) is a cathinone derivative with cocaine-like properties. As ethanol (EtOH) is a constant feature in most psychostimulant consumers, the aim of this study was to test the effect of EtOH on the psychostimulant and reinforcing effects of MDPV, when administered concomitantly in rats.
Saline, MDPV (0.3 or 3.0 mg/kg SC), EtOH (1g/kg IP) or both (MDPV SC + EtOH IP) were administered to male rats. To test the psychostimulant effect, horizontal locomotor activity (HLA) was registered during 120/360 min. A conditioned place preference (CPP) test was performed to assess the effect of EtOH on the rewarding properties of MDPV, using an EtOH dose that did not produce CPP on its own. Microdialysis experiments were carried out to quantify extracellular dopamine (DA) in the nucleus accumbens, as well as its main metabolites: 3,4-dihydroxyphenylacetic acid (DOPAC) and homovanillic acid (HVA). Finally, we measured MDPV levels in the striatum and in blood samples collected through a jugular catheter. Cathinone concentration, DA levels, and its metabolites were quantified by LC-MS/MS.
MDPV alone increased HLA at all tested doses, compared to the saline group. Interestingly, EtOH induced a significant decrease in hyperlocomotion elicited by a low dose of MDPV (0.3 mg/kg), but not when testing the highest doses of MDPV. MDPV-treated animals showed CPP with a score of 3.5 at the 0.3 mg/kg dose and of 6 at the 3 mg/kg dose, without EtOH influence. MDPV at both doses caused a rapid and dose-dependent increase in DA levels and a decrease of those of DOPAC and HVA, as expected from its mechanism of action. According to CPP data, EtOH did not modify DA levels in either time or tested dose of MDPV, probably due to its own effect on DA levels. In order to assess a possible pharmacokinetic interaction causing the EtOH influence on MDPV psychostimulant effect, the cathinone levels in plasma and striatum were determined after SC or IV administration of 0.3 mg/kg MDPV with or without EtOH (IP). Cathinone levels significantly decreased by EtOH only when testing MDPV by SC route, pointing to an interaction in the absorption process.
Our results suggest that EtOH decreases the MDPV psychostimulant properties affecting its absorption, and not the blood-brain-barrier crossing, as expected. Therefore, combining EtOH with low-moderate MDPV doses could reduce the psychostimulant effect without affecting the rewarding properties of the cathinone. This could lead to increase the dosage in order to attain the same effect, but increasing its addictive potential. This should be taken into consideration in future studies concerning the risks associated with MDPV and EtOH use.

Disclosures: M.H. Buenrostro-jauregui: None. **R. López-Arnau:** None. **P. Muñoz-Villegas:** None. **A. Ciudad-Roberts:** None. **D. Pubill:** None. **E. Escubedo:** None. **J. Camarasa:** None.

Poster

828. Alcohol: Cell Signaling

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 828.18/EEE4

Topic: G.08. Drugs of Abuse and Addiction

Support: NIH Grant U01 AA020913

NIH Grant P60 AA006420

NIH Grant R21 AA024198

NIH Grant R01 AA021491

NIH Grant T32 AA007456

NIH Grant R01 AA020608

Title: Ethanol dependence and the Cdk5 signaling pathway

Authors: *S. P. GOULDING, G. DE GUGLIELMO, O. GEORGE, C. CONTET;
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Abstract: The opioid system is hijacked by drugs of abuse, which contributes to the acute rewarding effects and the activation of stress and habit-forming circuits during the development of drug dependence and in drug-seeking during abstinence. Thus, transcriptional changes that occur downstream of chronic opioid receptor activation likely mediate some of the neuroplastic adaptations that drive addictive behaviors. In support of this possibility, we identified a subset of mu-opioid receptor regulated genes that are differentially expressed in the extended amygdala of ethanol-dependent mice and gene network analysis further revealed that the Cdk5 pathway is significantly impacted. Therefore, we hypothesize that Cdk5 may contribute to the morphological and functional plasticity associated with the escalation of ethanol self-administration. To test this hypothesis, we measured the phosphorylation levels of seven Cdk5 substrates involved in dendritic spine remodeling, neurotransmitter release, and postsynaptic signaling in three extended amygdala subregions from ethanol-dependent, nondependent, and naïve rats. Animals were trained to lever press for ethanol and water oral self-administration during twelve, 30 min daily sessions and divided into two groups: one group was subjected to chronic intermittent exposure to ethanol vapor (dependent group), while the other group only inhaled air (nondependent group). Operant self-administration sessions were resumed four weeks later, every-other-day, for four to seven additional weeks, until dependent rats significantly escalated their ethanol intake compared to the nondependent rats. Naïve rats were age-matched and handled, but never exposed to ethanol. Punches of the bed nucleus of the stria terminalis,

basolateral amygdala, and central amygdala were collected from snap-frozen brains and processed by western blotting to quantify Cdk5 and p35/25, as well as total and phosphorylated levels of seven known Cdk5 effectors: DARPP-32, Dynamin 1, NMDAR2B, p27KIP1, PAK1, PSD-95, and Synapsin-1. Our data indicate that ethanol dependence alters the phosphorylation state of Cdk5 effectors in a brain region-dependent manner. Furthermore, systemic administration of (S)-CR8, a potent and selective inhibitor of cyclin-dependent kinases, reduced voluntary ethanol consumption in dependent rats, but it did not affect intake in nondependent rats. Thus, our data will help identify the cellular process through which Cdk5 may facilitate ethanol drinking escalation.

Disclosures: S.P. Goulding: None. **G. de Guglielmo:** None. **O. George:** None. **C. Contet:** None.

Poster

828. Alcohol: Cell Signaling

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 828.19/EEE5

Topic: G.08. Drugs of Abuse and Addiction

Support: NIDA K08 DA030439-01A1

Robert Wood Johnson 70638

Title: Chronic alcohol use enhances vulnerability to compulsive cocaine self-administration by promoting degradation of HDAC4 and HDAC5

Authors: *E. A. GRIFFIN, JR[1], P. MELAS[5], R. ZHOU[2], Y. LI[2], K. KEMPADOO[3], L. COLNAGHI[3], K. TAYLOR[2], E. KANDEL[3], D. KANDEL[4];
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Abstract: Addiction to cocaine is commonly preceded by experiences with legal and decriminalized drugs, such as alcohol, nicotine and marijuana. The biological mechanisms by which these gateway drugs contribute to cocaine addiction are only beginning to be understood. Here we report that in the rat, chronic alcohol consumption results in enhanced addictive behaviors to cocaine, including continued cocaine use despite aversive consequences. Conversely, cocaine self-administration has no effect on alcohol preference. Long-term, but not short-term, alcohol consumption promotes proteasome-mediated degradation of the nuclear histone deacetylases HDAC4 and HDAC5 in the nucleus accumbens, a brain region critical for

reward-based memory. Decreased nuclear HDAC activity results in global H3 acetylation, creating a permissive environment for cocaine-induced gene expression. We also find that selective degradation of HDAC4 and HDAC5, facilitated by the class II specific HDAC inhibitor MC1568, enhances compulsive cocaine self-administration. These results parallel our previously reported findings that nicotine enhances the behavioral effects of cocaine via HDAC inhibition. Taken together, our findings suggest a shared mechanism of action for the gateway drugs alcohol and nicotine, and reveal a novel mechanism by which environmental factors may alter the epigenetic landscape of the reward system to increase vulnerability to cocaine addiction.

Disclosures: **E.A. Griffin:** None. **P. Melas:** None. **R. Zhou:** None. **Y. Li:** None. **K. Kempadoo:** None. **L. Colnaghi:** None. **K. Taylor:** None. **E. Kandel:** None. **D. Kandel:** None.

Poster

829. Cocaine: Behavioral Studies I

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 829.01/EEE6

Topic: G.08. Drugs of Abuse and Addiction

Support: National Institute on Drug Abuse DA011064

Title: Effects of a 5-HT_{1B} receptor agonist on locomotion and reinstatement of cocaine-conditioned place preference after abstinence from repeated injections in mice

Authors: *T. DER-GHAZARIAN[1], S. BRUNSWASSER[2], K. DAI[1], K. STEFANCO[1], T. CALL[1], S. SCOTT[1], S. NOUDALI[1], R. GARCIA[1], J. NEISEWANDER[1];
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Abstract: We previously reported that the 5-HT_{1B} receptor (5-HT_{1B}R) agonist CP94253 enhances cocaine self-administration and seeking in rats tested during daily self-administration sessions, but inhibits these behaviors when tested after a period of forced abstinence. This study investigated whether a similar pattern of effects occurs in mice given 21 daily cocaine (15 mg/kg, IP) injections followed by testing for effects of CP94253 on locomotion and reinstatement of cocaine conditioned place preference (CPP) either 1 or 21 days after the last injection. In the CPP experiment, mice underwent conditioning procedures while receiving their daily injections of cocaine or saline either during or ≥2 h after CPP procedures. The procedural timeline consisted of baseline preference testing (days 12-13 of the chronic regimen), conditioning (days 14-19, 2 daily 30-min sessions separated by 5 h), CPP test (day 21), extinction (days 22-39), CPP extinction test (day 40), and reinstatement test (day 41). On test

day, mice were pretreated with either saline or CP94253 (10 mg/kg, IP) and 30 min later they were primed with either saline or cocaine (15 mg/kg, IP) and then immediately tested. We found that CP94253 initially increased locomotion in mice receiving repeated administrations of either saline or cocaine, but after the 21-day abstinence period from the repeated injections, CP94253 had no effect on spontaneous locomotion but did attenuate expression of cocaine sensitized locomotion. In noninjected, drug-naïve mice, CP94253 had no effect on locomotion. Mice reinstated cocaine-CPP when given a cocaine prime and showed a trend toward CP94253 attenuation of reinstatement. We are adding n/condition to further examine this trend. The findings suggest that CP94253 attenuates effects of cocaine after a period of abstinence from a chronic administration regimen, consistent with its effects in rats. This study supports the idea that 5-HT_{1B}R agonists may be useful for treating cocaine dependence.

Disclosures: **T. Der-Ghazarian:** None. **S. Brunswasser:** None. **K. Dai:** None. **K. Stefanco:** None. **T. Call:** None. **S. Scott:** None. **S. Noudali:** None. **R. Garcia:** None. **J. Neisewander:** None.

Poster

829. Cocaine: Behavioral Studies I

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 829.02/EEE7

Topic: G.08. Drugs of Abuse and Addiction

Support: NIH Grant R01 DA037897

NIH Grant K01 DA030445

Title: Activation of central glucagon-like peptide-1 (GLP-1) receptors is sufficient to reduce cocaine seeking in rats

Authors: *N. S. HERNANDEZ, C. A. TURNER, J. D. WOLFHEIMER, H. D. SCHMIDT; Univ. of Pennsylvania, Philadelphia, PA

Abstract: A growing body of literature indicates that administration of glucagon-like peptide-1 receptor (GLP-1R) agonists reduces drug-associated behaviors in rodents. GLP-1Rs are expressed throughout the brain including the ventral tegmental area (VTA) and nucleus accumbens (NAc), areas that mediate cocaine reinforcement. Previously, our lab showed that GLP-1R activation in the VTA decreases cocaine taking in rats. However, the role of central GLP-1Rs in the reinstatement of cocaine seeking, an animal model of relapse, is not clear. The present study tested the hypothesis that systemic administration of a GLP-1R agonist would

attenuate the reinstatement of cocaine-seeking behavior. Initially, rats were allowed to self-administer cocaine (0.25 mg/infusion i.v.) for 21 days on a fixed-ratio 5 schedule of reinforcement. Cocaine self-administration was then extinguished by replacing cocaine with saline. Once cocaine taking was extinguished, rats received an acute priming injection of cocaine (10 mg/kg i.p.) to reinstate drug-seeking behavior. During subsequent reinstatement test sessions, rats were pretreated with the fluorescent GLP-1R agonist fluoro-exendin-4 (3.0 µg/kg i.p.) prior to a priming injection of cocaine. Fluoro-exendin-4 attenuated cocaine seeking and colocalized with neurons and astrocytes in the VTA and NAc. Based on these findings, we next determined the role of VTA and NAc GLP-1Rs in cocaine seeking. During reinstatement test sessions, rats were pretreated with intra-cranial infusions of the GLP-1R agonist exendin-4 (0, 0.005 and 0.05 µg) prior to a priming injection of cocaine. To determine if the suppressive effects of exendin-4 in the VTA and NAc on cocaine seeking were due to drug-induced motor impairments, we conducted parallel studies of sucrose reinstatement. We show that administration of exendin-4 directly into the VTA, NAc core or NAc shell dose-dependently attenuated cocaine reinstatement and had no effect on sucrose reinstatement. To determine if VTA GLP-1Rs are required for the effect of systemic exendin-4 on cocaine seeking, rats were pretreated with intra-VTA infusions of the GLP-1R antagonist exendin-(9-39) (10.0 µg) and a systemic injection of exendin-4 (3.0 µg/kg i.p.) prior to a priming injection of cocaine. We show that the ability of systemic exendin-4 to attenuate cocaine seeking was prevented by an infusion of exendin-(9-39) directly into the VTA. Taken together, these results indicate that GLP-1Rs in the VTA and NAc play a critical role in cocaine-seeking behavior and support re-purposing GLP-1R agonists, which are FDA-approved for treating diabetes type II and obesity, for the treatment of cocaine addiction.

Disclosures: **N.S. Hernandez:** None. **C.A. Turner:** None. **J.D. Wolfheimer:** None. **H.D. Schmidt:** None.

Poster

829. Cocaine: Behavioral Studies I

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 829.03/EEE8

Topic: G.08. Drugs of Abuse and Addiction

Support: National Institute on Drug Abuse Intramural Research Program

Title: Behavioral effects of dietary zinc manipulation and methods for brain zinc assessment

Authors: *L. A. RODRIGUEZ, J. L. GOMEZ, R. ELLIS, M. MICHAELIDES, K. M. DALY; Neuroimaging Res. Br., Natl. Inst. On Drug Abuse, Baltimore, MD

Abstract: Zinc imbalances are associated with psychiatric and brain disorders, such as depression, autism, ADHD, and neurodegenerative disorders, like Alzheimer's disease. Zinc is the second most abundant trace metal in the body and is found in high concentration in the brain where it exists in two forms: about 90% of it is static and found on metalloproteins, while the remaining labile zinc acts on a variety of biological processes and is predominantly found in zinc-containing glutamatergic neurons. In terms of its distribution in the brain, the highest concentrations of zinc are found in the hippocampus, amygdala, cortex and striatum. Prior studies have shown that zinc interacts with brain dopamine and glutamate systems but precise mechanisms are unknown. Here we evaluated behavioral effects of dietary zinc manipulations in mice and examined *in vitro* and *in vivo* imaging assays for detection of zinc levels and activity in the brain. We believe that these studies will facilitate advancement of our understanding of the effects of zinc on dopamine- and glutamate-related neurobiology and behavior.

Disclosures: L.A. Rodriguez: None. **J.L. Gomez:** None. **R. Ellis:** None. **M. Michaelides:** None. **K.M. Daly:** None.

Poster

829. Cocaine: Behavioral Studies I

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 829.04/EEE9

Topic: G.08. Drugs of Abuse and Addiction

Support: R01DA027811

TRDRP Award 24RT-0023

Title: Effects of a series of novel nociceptin opioid receptor (NOPr) agonists on the rewarding actions of cocaine

Authors: *K. LUTFY[1], P. MARQUEZ[1], A. HAMID[1], N. ZAVERI[2];
[1]Pharmaceut. Sci., Western Univ. of Hlth. Sci., Pomona, CA; [2]Astraea Therapeutics, LLC., Mountain View, CA

Abstract: Orphanin FQ/Nociceptin (OFQ/N), the endogenous ligand of the nociceptin opioid receptor (NOP, also known as the opioid receptor-like receptor), has been shown to reduce the rewarding action of cocaine and other addictive drugs, suggesting that the NOP receptor could be a potential target to develop medications to treat drug addiction. To this end, we developed a series of NOP receptor agonists and tested their effects on cocaine-induced conditioned place preference (CPP), widely used as an animal model of drug reward. Using mice lacking NOP

receptor, we also examined the selectivity of these compounds. Mice lacking NOP receptor and their wild-type littermates were tested for baseline place preference on day 1, in which mice were placed in the central neutral chamber of the CPP apparatus, and allowed to freely explore the CPP chambers for 15 min. The amount of time that mice spent in each chamber was recorded. The next day, mice were treated with vehicle or one of the NOP agonists (AT-202, AT-312 or AT-328) followed, 5 min later, by cocaine (15 mg/kg) and then confined to one of the conditioning chambers for 30 min. In the afternoon, mice were injected with the alternate treatment, and confined to the opposite chamber. Mice received additional conditionings on days 3 and 4, and were tested for postconditioning place preference on day 5. On this test day, mice were tested for 15 min, as described for day 1. Our results showed that cocaine induced a robust CPP response in control mice, i.e., those treated with vehicle prior to cocaine conditioning. Although AT-202 failed to alter cocaine-induced CPP, AT-312 and AT-328 each abolished the CPP response in wild-type mice. In contrast, none of the compounds altered cocaine-induced CPP in mice lacking NOP receptor, suggesting that these compounds reduced the rewarding action of cocaine via the NOP receptor. Although it is not clear why AT-202 failed to alter cocaine CPP, our in vitro data indicate that AT-312 and AT-328 each exhibits a better selectivity profile toward the NOP receptor over the other opioid receptors compared to AT-202. Taken together, the present data suggest that the NOP receptor may be a potential target to develop medications to treat cocaine addiction.

Disclosures: **K. Lutfy:** None. **P. Marquez:** None. **A. Hamid:** None. **N. Zaveri:** None.

Poster

829. Cocaine: Behavioral Studies I

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 829.05/EEE10

Topic: G.08. Drugs of Abuse and Addiction

Support: This work is supported by NIDA IRP

Title: Prior exposure to alcohol has no effect on cocaine self-administration and relapse: evidence from a rat model against the gateway hypothesis

Authors: *I. FREDRIKSSON[1,2], S. ADHIKARY[3], P. STEENSLAND[1], L. VENDRUSCOLO[4], Y. SHAHAM[3], A. BONCI[2,5,6], J. M. BOSSERT[3];
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Abstract: Background and objectives: The gateway hypothesis posits that initial exposure to legal drugs promotes subsequent addiction to illicit drugs. However, epidemiological studies are correlational and cannot rule out the alternative hypothesis of shared addiction vulnerability to legal and illegal drugs. We tested the gateway hypothesis using established rat alcohol exposure procedures and cocaine self-administration and reinstatement (relapse) procedures. **Methods:** We gave Wistar or alcohol-preferring (P) rats intermittent access to water or 20% alcohol in their home-cage for 7 weeks (three 24-h sessions/week). We also exposed Wistar rats to intoxicating levels of alcohol or air (control condition) in vapor chambers for 14-h/day for 7 weeks. We then tested the different groups of rats for acquisition of cocaine self-administration using ascending doses of cocaine (0.125, 0.25, 0.5, 1 mg/kg/infusion) followed by a dose-response curve after acquisition of cocaine self-administration. Next, after extinction of lever-pressing, we tested the rats for reinstatement of drug seeking induced by cocaine-paired cues and cocaine priming (0, 2.5, 5 and 10 mg/kg, i.p.). **Results:** Wistar rats consumed moderate amounts of alcohol (4.6 g/kg/24 h), P rats consumed higher amounts of alcohol (7.6 g/kg/24 h), and Wistar rats exposed to alcohol vapor had a mean blood alcohol concentration of 176.2 mg/dl during the last week of alcohol exposure. Alcohol pre-exposure had no effect on cocaine self-administration, extinction responding, and reinstatement of drug seeking. **Conclusions:** Pre-exposure to moderate, high, or intoxicating levels of alcohol had no effect on cocaine self-administration and relapse to cocaine seeking. Our data do not support the gateway hypothesis.

Disclosures: I. Fredriksson: None. **S. Adhikary:** None. **P. Steensland:** None. **L. Vendruscolo:** None. **Y. Shaham:** None. **A. Bonci:** None. **J.M. Bossert:** None.

Poster

829. Cocaine: Behavioral Studies I

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 829.06/EEE11

Topic: G.08. Drugs of Abuse and Addiction

Support: 2R25GM061151-13

FIPI120051574

Title: Nutritional omega-3 fatty acid deficiency intensifies anxiety- and depression-like behaviors after withdrawal in rats subjected to incubation of cocaine-craving.

Authors: *S. SERRANO, N. RODRIGUEZ-SOSA, J. R. GESTE, C. S. MALDONADO-VLAAR;
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Abstract: In recent years, n-3 polyunsaturated fatty acids (PUFAs)—more commonly known as omega-3 (ω-3)—have been gaining attention due to their ability to modify the physiology of several neurotransmitter systems; and thus supporting a potential involvement with cognitive and emotional processes. These PUFA-induced modulatory neurotransmissions may have a direct impact on addictive-related behaviors, drugs' addictive potential, and/or withdrawal symptoms severity. To address this issue, we evaluated whether nutritional ω-3 deprivation from pre-puberty to adulthood would lead to changes in cocaine addictive behaviors. In addition, emotional behavioral alterations of early and late withdrawal after chronic cocaine self-administration were investigated. Male Sprague-Dawley rats (P21) were fed either a standard rodent lab chow (CON) or deficient ω-3 rodent lab chow (DEF). Animals were trained to self-administer cocaine (6 h/day with 0.5 mg.kg/ infusion) paired with a tone-light cue for 8 days. We observed incubation of cue reactivity between ID1 (Incubation Day 1) and ID40 of forced abstinence. Also, anxiety-like and depression-like behaviors were evaluated after 10 weeks of food/only consumption (FO), WD1 (Withdrawal Day 1) and WD35; using the elevated plus maze test (EPM) and the Forced Swimming Test (FST). Interestingly, dietary ω-3 depletion reduced lever pressing activity during the first two days, and diminished movement episodes throughout the self-administration sessions. On ID40, the DEF group had lower cue-induced cocaine-seeking behavior compared to the CON group. Conversely, there was a significant robust incubation of cocaine seeking in CON group at ID40 vs. ID1, in contrast to the DEF group, which was not significant. In the EPM, starting from WD1, the DEF group showed a gradual reduction in the time spent on the open-arm and an increased time spent in the closed-arms. Lastly, during the FST test, the DEF group demonstrated greater immobility time on WD1 compared to the CON group, whereas no difference was observed in FO or WD35. This study demonstrated that dietary absence of ω-3 could intensify the symptoms of anxiety and depression during withdrawal periods after an extended access of cocaine self-administration. Furthermore, it also suggests that this deficiency can modify sensitivity to the rewarding effects of cocaine. We can speculate that these dietary-induced perturbations in PUFA homeostasis can deregulate the dopaminergic and serotoninergic systems, leading to mood behavioral changes and impaired responsiveness to positive events. Future molecular experiments will address this assumption to achieve a more definite conclusion.

Disclosures: S. Serrano: None. **N. Rodriguez-Sosa:** None. **J.R. Geste:** None. **C.S. Maldonado-Vlaar:** None.

Poster

829. Cocaine: Behavioral Studies I

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 829.07/EEE12

Topic: G.08. Drugs of Abuse and Addiction

Support: NIH Grant P30GM103398-05

Title: Early life exposure to dietary high-salt induces neuroadaptations that facilitate increased cocaine seeking

Authors: *P. M. DINGESS[1], F. W. FLYNN[2], T. E. BROWN[2];
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Abstract: Dietary salt, though important for many homeostatic processes, is widely overconsumed yet understudied in contexts outside of osmoregulation and cardiovascular function. There is evidence to suggest that excess salt consumption during pregnancy has the potential to significantly impact offspring behavior and physiology, evidenced in part by reports that maternal salt consumption elicits an increase in offspring reward sensitivity to glucose, salt, and amphetamine. Despite these findings, the influence of early salt exposure on brain reward circuitry and drug-seeking behavior has not been studied. To investigate this, we utilized adult male Sprague-Dawley offspring from dams fed a high-salt (4% NaCl) or control (1% NaCl) diet during gestation and lactation (perinatal). Our results show that dietary perinatal salt exposure induces alterations in dendritic spine type and density within the prefrontal cortex (PFC) and nucleus accumbens (NAc) that mimic changes observed following early life stress. Additionally, high-salt offspring exhibit a heightened stress-induced reinstatement to cocaine in a conditioned place preference (CPP) paradigm and exhibit behavioral responses in a cold forced swim test (FST) similar to offspring exposed to early life stress. Utilizing structural and functional analyses with DiI staining and electrophysiology, we will further characterize cellular plasticity in key reward circuit regions as well as measure behavioral reward sensitivity using cocaine CPP and self-administration. By examining this novel form of plasticity and the associated behavioral responses, our findings may have direct clinical relevance for both prenatal nutritional guidelines and drug addiction more broadly.

Disclosures: **P.M. Dingess:** None. **F.W. Flynn:** None. **T.E. Brown:** None.

Poster

829. Cocaine: Behavioral Studies I

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 829.08/EEE13

Topic: G.08. Drugs of Abuse and Addiction

Support: NIH Grant R01DA007315

NIH Grant T32DA007268

Title: A buprenorphine analog attenuates drug-primed and stress-induced cocaine reinstatement

Authors: T. M. HILLHOUSE[1,2], J. E. HALLAHAN[1], E. M. JUTKIEWICZ[1], S. M. HUSBANDS[3], *J. R. TRAYNOR[1];
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Abstract: Cocaine and opioid pain relievers are highly abused drugs. Moreover, ~70% of cocaine and opiate addicts are poly-drug users that also abuse other substances. Current treatments for addiction leave much to be desired as the majority of drug users relapse within the first year of treatment. The opioid system has emerged as a viable target for relapse prevention in drug addicts. For example, buprenorphine effectively decreases the number of positive drug tests in poly-drug users. Buprenorphine is a mu-opioid receptor (MOPr) and nociceptin receptor (NOPr) partial agonist, and a delta-opioid receptor (DOPr) and kappa-opioid receptor (KOPr) antagonist. Ultimately, there are concerns surrounding prolonged buprenorphine treatment due to physical dependence and addiction liability associated with MOPr agonists. To combat this issue, we developed BU10119 which has similar *in vitro* pharmacological properties to buprenorphine, but lacks agonist action at MOPr and has improved activity at NOPr. Here, we confirm that this *in vitro* pharmacological profile of BU10119 translates to *in vivo* behavioral assays in mice. BU10119 completely blocked the antinociceptive effects of the MOPr agonist morphine and KOPr agonist ethylketocyclazocine (EKC) in the warm water tail withdrawal assay, attenuated the antinociceptive effects of the DOPr agonist SNC80 in acid-stimulated stretching and caused a hyperalgesic response consistent with its NOPr agonism. A conditioned place preference mouse model of reinstatement was used to determine the ability of BU10119 to prevent drug seeking behavior. BU10119 dose dependently attenuated both cocaine- and stress-primed reinstatement, but did not alter cocaine-induced locomotor activity. The nonselective opioid antagonist naloxone, which has no pharmacological effects at NOPr, and the NOPr agonist SCH221510 were used for comparison to determine the receptor mechanisms involved in the anti-reinstatement effects of BU10119. When administered alone, naloxone and SCH221510 failed to attenuate cocaine-primed reinstatement. These results suggest that mixed efficacy activity at all opioid receptors (MOP, DOP, KOP, and NOP) might be necessary for the effects of BU10119 on cocaine seeking behaviors.

Disclosures: **T.M. Hillhouse:** None. **J.E. Hallahan:** None. **E.M. Jutkiewicz:** None. **S.M. Husbands:** None. **J.R. Traynor:** None.

Poster

829. Cocaine: Behavioral Studies I

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 829.09/EEE14

Topic: G.08. Drugs of Abuse and Addiction

Support: NIH Grant DA023924

DoD Grant PR141230

DoD Grant PR141230P1

Title: Delta-opioid receptor (DOR) antagonism introduced by tryptophan substitution in CJ-15,208 prevents opioid antinociceptive tolerance and stress-induced reinstatement of extinguished drug-conditioned place preference

Authors: *J. P. MCLAUGHLIN[1], S. O. EANS[2], J. M. MEDINA[2], K. A. HYMEL[2], S. N. SENADHEERA[4], T. F. MURRAY[5], J. V. ALDRICH[3];
[2]Pharmacodynamics, [3]Medicinal Chem., [1]Univ. of Florida, Gainesville, FL; [4]Medicinal Chem., Univ. of Kansas, Lawrence, KS; [5]Pharmacol., Creighton Univ., Creighton, NE

Abstract: Aims: The macrocyclic tetrapeptide natural product CJ-15,208 (*cyclo*[Phe-D-Pro-Phe-Trp]) and its D-Trp isomer exhibit short lasting kappa opioid receptor (KOR) antagonism which prevents stress-induced reinstatement of extinguished cocaine-conditioned place preference (CPP). During exploration of structure-activity relationships to improve these two lead peptides, alanine analogs exhibited unexpected changes in opioid activity. Therefore, we performed a conservative substitution of the Trp and D-Trp residues to examine potential changes in opioid activity, antinociceptive tolerance and the ability to prevent relapse to extinguished drug-CPP.
Methods: Several analogs were synthesized using a combination of solid phase and solution synthesis. We evaluated the analogs for opioid receptor affinity *in vitro* using competition binding assays, and for opioid efficacy and selectivity *in vivo* with the mouse 55^{o}C warm-water tail-withdrawal assay. We then determined the effect of analogs on the reinstatement of extinguished cocaine-place preference in a CPP assay.
Results: Substitutions resulted in little change in KOR affinity, but significantly increased affinity for mu-opioid receptors (MOR) *in vitro*. *In vivo,* the CJ-15,208 analogs demonstrated antinociception activity, although the potencies varied over a 1000-fold range and the mediating opioid receptors differed depending on the substitution. Although KOR antagonism was greatly reduced, two analogs demonstrated delta-opioid receptor (DOR) antagonism. Introduction of DOR antagonism reduced acute opioid antinociceptive tolerance, and prevented stress-induced reinstatement of extinguished cocaine-CPP.
Conclusions: Overall, these data suggest that even conservative substitutions for Trp or D-Trp

had profound effects on the opioid activity profile of the analogs, in some cases eliminating KOR antagonism and in two cases introducing DOR antagonism. The demonstration that DOR antagonism prevents opioid antinociceptive tolerance and stress-induced reinstatement of extinguished cocaine-CPP suggests these analogs may have promise in treating both pain and substance abuse.

Disclosures: J.P. McLaughlin: None. **S.O. Eans:** None. **J.M. Medina:** None. **K.A. Hymel:** None. **S.N. Senadheera:** None. **T.F. Murray:** None. **J.V. Aldrich:** None.

Poster

829. Cocaine: Behavioral Studies I

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 829.10/FFF1

Topic: G.08. Drugs of Abuse and Addiction

Support: NIDA-IRP

Title: Effects of sigma receptor ligands on the discriminative-stimlus effects of cocaine in rats

Authors: *T. HIRANITA[1,2], J. L. KATZ[2];
[1]Neurotoxicology, NCTR/FDA, Jefferson, AR; [2]Psychobiology Section, NIDA-IRP/NIH/DHHS, Baltimore, MD

Abstract: Previous studies demonstrated that sigma receptor (σR) antagonists block various effects of cocaine, though other studies demonstrated a lack of their effects on cocaine self administration (SA). Subsequently other studies found that σR antagonists dose-dependently blocked cocaine SA when administered in combination with dopamine transporter (DAT) inhibitors. Thus the present study assessed effects of σR ligands alone and combined with DAT inhibitors in rats trained to discriminate cocaine (10 mg/kg, IP) from saline injections. DAT inhibitors (WIN 35,428: 0.1—3.2 mg/kg, IP; methylphenidate: 0.32—3.2 mg/kg, IP) dose-dependently substituted for cocaine, while neither σR agonists (DTG: 3.2—17 mg/kg, IP; PRE 084: 10—56 mg/kg, IP) nor σR antagonists (BD 1008, BD 1047, BD 1063: 1.0—56 mg/kg IP, each) fully substituted, up to doses that markedly decreased response rates. As with DAT inhibitor pretreatments (0.1, 0.32 mg/kg, each), σR agonists (DTG: 3.2, 10 mg/kg; PRE 084: 10, 32 mg/kg) dose-dependently shifted the cocaine dose-effect curve (DEC) leftward. Unexpectedly, σR antagonists (10, 17 mg/kg, each) also shifted the cocaine DEC leftward, though the shifts were not dose related. Further, the σR antagonists (10, 17 mg/kg, each) failed to block leftward shifts produced by 32 mg/kg PRE 084. Additionally, the σR antagonists (10 mg/kg, each) enhanced the leftward shifts in the cocaine DECs induced by DAT inhibitors (0.1,

0.3 mg/kg), whether the latter were at active or inactive doses. The effects of DAT inhibitors were similar to those found with SA: both fully substituted for cocaine and shifted the cocaine DEC leftward when administered as pretreatments. In contrast, σR agonists substituted in rats self-administering cocaine but not in rats discriminating cocaine. Both σR agonists left shifted DECs under both procedures, though the potency relation of the two σR agonists in doing so were opposite in the two procedures, and the PRE 084-induced leftward shifts in the cocaine discrimination DECs were not blocked by σR antagonists. These results suggest that the effects of σR agonists on cocaine discrimination were not mediated by σRs. In contrast, the effects of σR agonists on cocaine SA appear to be mediated by σRs. Further, the dual DAT and σR inhibition that attenuates cocaine SA only enhanced the discriminative effects of cocaine. This outcome is not inconsistent with the interpretation that dual DAT/σR inhibition on cocaine SA may be due to an enhancement of cocaine effects that create a satiation-like alteration in cocaine SA that is similar to effects of excess food on food-reinforced responding. Supported by NIDA-IRP.

Disclosures: T. Hiranita: None. **J.L. Katz:** None.

Poster

829. Cocaine: Behavioral Studies I

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 829.11/FFF2

Topic: G.08. Drugs of Abuse and Addiction

Support: DA007237

DA031767

Title: The role of hypocretin (orexin) and dynorphin in reward and anxiety following chronic cocaine administration and withdrawal

Authors: *T. A. GENTILE[1], S. SIMMONS[2], J. MUSCHAMP[2];
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Abstract: Lateral hypothalamic orexins (hypocretins) have a role in arousal, reward processing, attention, and impulsivity. Dynorphin, the endogenous ligand of the kappa opioid receptor (KOR), co-localizes with orexin, and has critical roles in producing negative affective states through interactions with brain stress circuits. Orexin-dynorphin neurons project to structures that govern motivated behavior, including the bed nucleus of the stria termanalis (BNST), amygdala, locus coeruleus and ventral tegmental area (VTA). Orexin and dynorphin

transmission modulates cell excitability through opposing signaling mechanisms; while orexins bind predominantly excitatory orexin-1 and -2 G_s- coupled receptors, dynorphins bind inhibitory G_i-protein coupled kappa opioid receptors (KORs). Several mental illnesses, including anxiety and substance abuse disorders, may be due in part to alterations in orexin-dynorphin signaling. The present experiments were conducted to explore the role of orexin and dynorphin activity in models of cocaine reward as well as the negative effects associated with cocaine withdrawal. To accomplish this we measured alterations in lateral hypothalamic orexin and dynorphin content in response to chronic cocaine administration and withdrawal using enzyme-linked immune-sorbent assays and cfos immunohistochemistry. Further, effects of chronic cocaine administration on reward and anxiety were assessed in using intracranial self-stimulation, conditioned place preference, and the elevated plus maze. Collectively, these studies will provide a comprehensive evaluation of how endogenous orexin and dynorphin peptide content becomes altered within substrates known to regulate positive and negative mood states at various phases of cocaine addiction.

Disclosures: **T.A. Gentile:** None. **S. Simmons:** None. **J. Muschamp:** None.

Poster

829. Cocaine: Behavioral Studies I

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 829.12/FFF3

Topic: G.08. Drugs of Abuse and Addiction

Support: Ministério da Saúde/ CNPq/SESAU-AL/FAPEAL

Title: Citrus limon essential oil blocks the psychostimulant effect and increase the threshold of epileptic seizures in mice submitted to a new model of crack-cocaine inhalation

Authors: *O. W. CASTRO[1], C. CAVALCANTE[2], N. TAVEIROS-SILVA[1], F. SOUZA[1], I. SANTANA[1], A. PACHECO[1], J. SANTOS-NETO[1], M. AMARAL[1], M. ARAÚJO[1], D. PIMENTEL[1], M. DUZZIONI[1];
[2]Physiol., [1]Federal Univ. of Alagoas, Maceio, Brazil

Abstract: Background: Crack-cocaine is a psychostimulant drug associated with comorbidities such as anxiety, depression and epilepsy. Mice exposed to a new model of crack-cocaine inhalation showed psychostimulant effects and reduced threshold of epileptic seizures. Citrus limon essential oil promotes sedative, anxiolytic, and anticonvulsant effects in rodents. Objective: This study aimed to evaluate the influence of essential oil from Citrus limon (EOCL) on the psychostimulant and epileptic activity induced by crack-cocaine inhalation. Methods:

Experimental procedures were approved by the Ethical Committee for Animal Research of UFAL (protocol number: 48/2013). Male Swiss mice were individually exposed to the smoke from 100, 200, 400 or 800 mg of crack-cocaine, 10 minutes/day for 5 consecutive days. After that, the animals were submitted to the open field test (OFT) for 10 minutes. To evaluate the influence of EOCL on the psychostimulant effect of crack-cocaine inhalation, animals were pretreated with EOCL (300 mg/kg, v.o.) 60 minutes before smoke from 200 or 400 mg of drug, and then submitted to the OFT. To analyze the influence of EOCL on the epileptic activity induced by crack-cocaine inhalation, animals were pretreated with EOCL (300 mg/kg, v.o.) and, after 20 minutes, with scopolamine methyl bromide (1mg/kg s.c.). After 30 minutes, animals were exposed to crack-cocaine smoke (400 mg, 10 minutes) and then with pilocarpine (75mg/kg, i.p.). Behavioral analysis of seizures was performed for 90 minutes during of SE, according to Racine's scale (1972). Results: Our results showed that crack-cocaine subchronic inhalation produces a dose-dependent psychostimulant effect and tolerance in mice as evaluated in the OFT. Pretreatment with EOCL (300 mg/kg, v.o.) blocked the psychostimulant effect of crack-cocaine in the OFT (118.9±21.35). In model of pilocarpine-induced seizures, the group pretreated with EOCL developed milder seizures when compared to the group without pretreatment. Conclusion: Our results showed that the EOCL blocked the psychostimulant effect of and reduced the severity of seizures induced by crack-cocaine inhalation. However, more studies are necessary to confirm these results and suggest that the EOCL can be an adjuvant in the clinical treatment for crack-cocaine addiction.

Disclosures: O.W. Castro: None. **C. Cavalcante:** None. **N. Taveiros-Silva:** None. **F. Souza:** None. **I. Santana:** None. **A. Pacheco:** None. **J. Santos-Neto:** None. **M. Amaral:** None. **M. Araújo:** None. **D. Pimentel:** None. **M. Duzzioni:** None.

Poster

829. Cocaine: Behavioral Studies I

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 829.13/FFF4

Topic: G.08. Drugs of Abuse and Addiction

Support: The Dorothea Dix Fellowship Fund

the Dr. Miriam and Sheldon G. Adelson Medical Research Foundation

Title: Acute administration of a short acting kappa antagonist reduces signs of withdrawal from extended access cocaine self-administration

Authors: *M. VALENZA, E. R. BUTELMAN, M. KREEK;
The Rockefeller Univ., New York, NY

Abstract: Stress is one major trigger of relapse to specific addictive disease. Stress upregulates Kappa opioid receptor (KOPr) signaling tone, largely through upregulation of transcription of KOPr and its endogenous agonists, the dynorphins, leading to depressive-like and relapse-like behaviors. While KOPr agonists can induce dysphoria and aversion-like behaviors, antagonists has received considerable attention as a novel anti-depressant and anti-relapse pharmacotherapeutic approach. However, most of the current knowledge on the pharmacotherapeutic potential of KOPr antagonism is based on drugs (e.g. norBNI, JTDic) with unusual pharmacokinetic and pharmacodynamic properties, including delayed onset of KOPr selectivity, very slow onset and extended durations of action. These features have limited experimental designs, interpretation and translation of results into the clinic. We characterized *in vivo* the pharmacotherapeutic-like effectiveness of systemic administration of LY 2444296 (also known as FP3FBZ), a novel short-acting KOPr antagonist, which is a close structural analog of CERC-501 (formerly LY2456302) that has reached clinical investigation stage. Results collected in outbred rats showed that acute administration of the short-acting KOPr antagonist LY2444296 prevented behavioral and neuroendocrine effects induced by acute administration of KOPr agonist U69,593 confirming its specificity of action. Then we tested LY 2444296 potential effect in reducing signs of withdrawal in a rodent model of cocaine addiction. Acute LY 2444296 reduced anxiety-like and depressive-like behaviors (tested by Elevated Plus Maze and Forced Swim Test, respectively) provoked by early withdrawal (30h) from a novel paradigm of extended access cocaine self-administration (18 h /day for 14 days; 0.5mg/kg/infusion, FR1). This effect was selective since it was not observed either in cocaine naïve rats stressed by being socially isolated for 8 weeks, either in control no-stressed group-housed rats.

Disclosures: **M. Valenza:** None. **E.R. Butelman:** None. **M. Kreek:** None.

Poster

829. Cocaine: Behavioral Studies I

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 829.14/FFF5

Topic: G.08. Drugs of Abuse and Addiction

Support: NIH Grant GM083883

Title: Role of D1 and D2 receptors for the induction and expression of cocaine-induced behavioral sensitization in preweanling rats

Authors: K. N. RUDBERG, A. VELIZ, L. C. ROMERO, A. E. GONZALEZ, A. MOHD-YUSOF, *S. A. MCDOUGALL;
Dept. of Psychology, California State Univ., San Bernardino, CA

Abstract: Behavioral sensitization is an animal model of drug addiction that is useful for studying age-dependent differences in incentive salience. Because of the translational relevance of early ontogenetic drug studies, our purpose was to determine whether D1 and/or D2 receptor stimulation is necessary for the induction and expression of cocaine-induced behavioral sensitization in preweanling rats. To this end, selective D1 and/or D2 receptor antagonists were administered either before cocaine pretreatment (induction) or cocaine challenge (expression). These experiments employed a one-trial sensitization procedure in order to minimize the effects of tolerance and dependence, while permitting an unbiased measure of induction and expression. Briefly, preweanling rats (PD 20) were injected with saline, raclopride, or SCH23390+raclopride 15 min before a single injection of cocaine (30 mg/kg, ip). One day later (PD 21), rats were challenged with cocaine (20 mg/kg, ip) and locomotor sensitization was assessed across a 120 min testing session. In a second experiment, rats were treated identically except that raclopride, SCH23390, or SCH23390+raclopride was injected 15 min before a test day injection of cocaine. In a separate study, the nonselective irreversible receptor antagonist *N*-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline (EEDQ) was administered 24 h before the induction or expression of cocaine sensitization. To determine the relative involvement of dopamine receptors, selective dopamine antagonists were used to protect D1 and/or D2 receptors from EEDQ-induced inactivation. Results showed that neither D1 nor D2 receptor antagonists prevented the induction of behavioral sensitization in preweanling rats. EEDQ disrupted the induction process, however, suggesting that another receptor type (e.g., 5-HT_{2A}, α1b-adrenergic, etc.) sensitive to EEDQ alkylation is necessary for the induction of cocaine sensitization. Expression of the sensitized response was prevented by the acute administration of SCH23390, but not raclopride, indicating that D1 receptor stimulation is necessary for the expression of cocaine sensitization in preweanling rats. Overall, the pattern of antagonist-induced effects just described is similar to what is observed in adult rats. In some ways these findings are surprising since the characteristics of cocaine sensitization differ substantially between young and adult rats (e.g., strength and longevity of the sensitized response, importance of contextual associations, etc.), yet it now appears that these age-dependent differences are not caused by maturational changes in dopamine receptor systems.

Disclosures: K.N. Rudberg: None. **A. Veliz:** None. **L.C. Romero:** None. **A.E. Gonzalez:** None. **A. Mohd-Yusof:** None. **S.A. McDougall:** None.

Poster

829. Cocaine: Behavioral Studies I

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 829.15/FFF6

Topic: G.08. Drugs of Abuse and Addiction

Support: DA023957

Title: Effect of a dopamine D3 receptor partial agonist on cocaine-induced locomotion and self-administration

Authors: *J. P. BONADONNA[1], G. L. POWELL[1], A. K. CARLSON[1], R. MENDOZA[1], R. H. MACH[2], R. R. LUEDTKE[3], K. XU[2], J. L. NEISEWANDER[1];
[1]Sch. of Life Sci., Arizona State Univ., Tempe, AZ; [2]Perelman Sch. of Med., Univ. of Pennsylvania, Philadelphia, PA; [3]Hlth. Sci. Ctr., Univ. of North Texas, Fort Worth, TX

Abstract: Compounds selective for dopamine D3 receptors (D3R) may have therapeutic effects for cocaine dependence. We have previously shown that D3R partial agonists are effective in decreasing cocaine self-administration (SA) on a high, but not a low, effort schedule of reinforcement. Here, we investigated the effects of a 168-fold selective partial D3R agonist, LS-3-134 (LS) on locomotor activity; cocaine and sucrose reinforcement rates on a low-effort, multiple variable-interval (VI) 60-second schedule; extinction of responding as a measure of cocaine seeking; and, cocaine reinforcement rates on a high-effort progressive ratio (PR) schedule. Male Sprague Dawley rats (N=15) were injected on separate days with either LS (0, 1.0, 3.2, 5.6 mg/kg) or LS+cocaine (15 mg/kg IP). 5 min post injection, locomotor activity was recorded for 1 hr. Rats were then trained on a VI-60 schedule that alternated components of cocaine (0.75 mg/kg/0.1 mL IV) and sucrose reinforcement. Once reinforcement rates were stable, rats underwent repeated tests, each 5 min after pretreatment with varying doses of LS. The cocaine dose available during the testing phase was reduced to 0.375 mg/kg, IV and stable reinforcement rates were reestablished between tests. Rats were then injected with either LS (5.6 mg/kg) or vehicle 5 min prior to a 60-min extinction test during which reinforcement was not available. Finally, rats were trained with cocaine (0.375 mg/kg/0.1 mL IV) reinforcement on a PR schedule and twice tested, once with LS (5.6 mg/kg) and once with vehicle pretreatment. The highest dose of LS tested (5.6 mg/kg) reversed cocaine-induced locomotion but had no effect on spontaneous locomotion nor on cocaine or sucrose reinforcement rates on the low effort multiple schedule of reinforcement. Under extinction, LS reduced response rates on the sucrose lever, but not on the cocaine lever. LS also reduced both active lever response rates and number of cocaine infusions on the PR schedule. The findings that LS reduced cocaine seeking behavior and reinforcement under the high effort PR schedule are consistent with the selective effects of other D3R drugs on motivation for cocaine.

Disclosures: **J.P. Bonadonna:** None. **G.L. Powell:** None. **A.K. Carlson:** None. **R. Mendoza:** None. **R.H. Mach:** None. **R.R. Luedtke:** None. **K. Xu:** None. **J.L. Neisewander:** None.

Poster

829. Cocaine: Behavioral Studies I

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 829.16/FFF7

Topic: G.08. Drugs of Abuse and Addiction

Title: Effects of sub-chronic anabolic steroids exposure on cocaine conditioning and anxiety-like behaviors in adult male rats.

Authors: *J. R. GESTE[1], M. POMPILUS, 00931[2], S. SERRANO-TORRES[2], G. MOLINA[2], A. LOYOLA[2], T. ORTIZ-LINARES[2], M. DUQUE-OSORNO[2], E. COLON-MORALES[2], C. S. MALDONADO-VLAAR[2];
[1]Biol. Dept., Univ. of Porto Rico, San Juan, PR; [2]Biol., Univ. of Puerto Rico-Rio Piedras, San Juan, PR

Abstract: Androgenic anabolic steroids (AAS) are a broad and rapidly increasing group of synthetic androgens used both clinically and illicitly. Several clinical studies have demonstrated its efficacy and benefit in treatment of anemia, osteoporosis, HIV and neoplasia. AAS are usually utilized at supraphysiological doses by bodybuilders, athletes to ameliorate performance, non-athlete for the euphoric and aesthetic effects or recreational purposes. Several studies revealed that AAS potentiate aggressive behavior and cocaine intake in current users. Misuse and abuse may contribute to the wide spectrum of AAS-induced effects reported on physical and mental health. The present set of experiments aimed at investigating the effects of sub-chronic AAS exposure on environment-elicited cocaine conditioning and anxiety in adult male rats. Animals were divided in two treatment groups which received subcutaneous injections of either: nandrolone (ND) or sesame oil (SO) for ten consecutive days (P68-78). At the P84 animals were tested in the elevated plus maze (EPM). On P85, both groups were exposed to a multimodal environment within activity chambers that signaled cocaine (cocaine-paired) or saline (controls, cocaine-unpaired) injections. Prior to placing the animals in the chambers, rats received systemic intraperitoneal injections of saline or cocaine for 10 consecutive sessions. In the test session (D12), animals were exposed to the multimodal environment without any cocaine or saline pre-treatment. At the end of the D12 session each animal was exposed to EPM testing. Our findings showed that pre-treatment with AAS (a) potentiated cocaine conditioned locomotion when compared to controls (b) induced anxiogenic-like behavior after exposure to the conditioning paradigm (c) promoted cardiac hypertrophy and adrenal atrophy (d) upregulated androgen

receptor (AR) and dopamine 1 receptor (D1) within the heart and brain of AAS-cocaine treated animals. Taken together, these results demonstrate for the first time a motivational and emotional vulnerability of animals with a history of AAS-cocaine use.

Disclosures: **J.R. Geste:** None. **M. Pompilus:** None. **S. Serrano-Torres:** None. **G. Molina:** None. **A. Loyola:** None. **T. Ortiz-Linares:** None. **M. Duque-Osorno:** None. **E. Colon-Morales:** None. **C.S. Maldonado-Vlaar:** None.

Poster

830. Cocaine: Behavioral Studies II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 830.01/FFF8

Topic: G.08. Drugs of Abuse and Addiction

Support: Psi Chi Spring 2015-16 Undergraduate Research

Title: The long term effects of repeated cocaine exposure on impulse inhibition: a pilot study

Authors: ***N. MACK**, C. COWAN, K. PONDER, D. HOLT, M. SHOUP-KNOX, J. DYCHE; Psychology, James Madison Univ., Harrisonburg, VA

Abstract: Cocaine use has been correlated to impulsivity, but the causal relationship between the two remains unclear. Are addicts innately more impulsive, or does repeated drug use lead to heightened impulsivity? Impulsivity is a multifaceted construct and the purpose of this experiment is to extend previous literature on the long-term effects of cocaine on impulsive choice to impulse inhibition. This is the first study to use differential reinforcement of low rates (DRL) of responding methodology to study impulsivity during cocaine withdrawal. Male Sprague Dawley (n=8) rats received two daily IP injections of 15mg/kg cocaine HCl or saline for 14 days. Rats were tested on a DRL-20 during withdrawal days 7, 14, and 21-28. Efficiency on the DRL task during withdrawal was analyzed using a 2x4 between-groups ANCOVA, with baseline efficiency measures as the covariate. There was a significant main effect of drug condition on impulsivity during withdrawal, $F(1,5) = 6.72$, $p = 0.49$, $\eta^2 = 0.57$. Thus, 57% of the variance in impulse inhibition during withdrawal can be explained by drug treatment. Immunohistochemistry is currently underway to analyze dopamine subtype 2 receptors (D2R) in the nucleus accumbens, and it is hypothesized that D2R will be significantly down regulated in rats repeatedly exposed to cocaine. Although cocaine rats preformed significantly worse during withdrawal compared to controls, it appears all rats return to their individual baseline efficiency. Replication of this experiment with more stringent baseline stabilization criteria and a larger

sample size is currently underway and will better determine if repeated cocaine exposure has long term effects on impulse inhibition.

Disclosures: **N. Mack:** None. **C. Cowan:** None. **K. Ponder:** None. **D. Holt:** None. **M. Shoup-Knox:** None. **J. Dyche:** None.

Poster

830. Cocaine: Behavioral Studies II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 830.02/FFF9

Topic: G.08. Drugs of Abuse and Addiction

Support: P50DA037844

Title: Ultrasonic vocalizations in sign-tracker vs. goal-trackers: no difference in food cue responses, but larger acute and sensitized responses in sign-trackers

Authors: *J. A. TRIPI, M. L. DENT, P. J. MEYER;
Psychology, Univ. at Buffalo, Buffalo, NY

Abstract: There is a partial overlap between the neurobehavioral substrates underlying responsivity to food-associated stimuli ("cues") and the response to drugs and drug cues (Robinson and Berridge, 2008). In rats, drug-induced ultrasonic vocalizations (USVs) are associated with patterns of drug self-administration and have been proposed as a "self-report" of drug craving, as well as an expression of reward anticipation (Mahler et al., 2013; Burgdorf and Panksepp, 2006). Therefore, drug-induced USVs and the response to food cues may reflect common underlying psychological processes that are associated with patterns of drug-taking behavior. To test this, we measured responsivity to food cues and cocaine-induced 50kHz USVs in two experiments.
In Exp. 1, adult male Sprague Dawley rats (n=48) were tested using a Pavlovian conditioned approach (PavCA) paradigm, in which they learned to associate a lever cue with the delivery of a food pellet into a food cup. Based on their approach to the lever cue and food cup entries, subjects were categorized as sign-trackers (intense approach to the lever cue), or goal trackers (approach to food cup). Sign and goal trackers (n=10 and n=14, respectively) subsequently underwent nine 30-minute testing days in which they were then administered an intraperitoneal injection of saline (day 1-2) or cocaine (10 mg/kg; day 5, 7, 9, 12, 14, 16, 23), and then placed into a locomotor chamber where distance travelled and USVs were recorded. While no difference was found in locomotor activity, repeated measures ANOVA indicated a significant difference between sign- and goal-trackers in cocaine-induced USVs ($p < 0.001$). Additionally,

USV response to cocaine sensitized in STs ($p < 0.05$), but not GTs.
For Exp. 2, the order of testing was reversed to evaluate whether cocaine-induced USVs could predict PavCA performance. In this, subjects (n=48) were tested in the locomotor chambers for one saline-treated day followed by one cocaine-treated day. Analysis revealed that sign-trackers again produced significantly more cocaine-induced USVs when compared to goal-trackers ($p < 0.001$). USV were recorded in a subset of rats (n=31) during the 25 trails of PavCA to determine if the food cue would elicit USVs. We analyzed the eight-second periods prior to, during, and after the lever cue (CS) and found a significant difference between sign- and goal -trackers only during the pre-CS period of the first 5 trials ($p < 0.001$). Further, the cue presentation did not increase USVs in either sign- or goal-trackers. Taken together, cocaine-induced USVs may index the neurochemical differences underlying the behavioral differences in food cue responsivity.

Disclosures: J.A. Tripi: None. **M.L. Dent:** None. **P.J. Meyer:** None.

Poster

830. Cocaine: Behavioral Studies II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 830.03/FFF10

Topic: G.08. Drugs of Abuse and Addiction

Support: NIH Grant GM083883

NIH Grant DA033877

Title: Persistence of one-trial and ten-trial cocaine-induced conditioned activity in adult rats

Authors: *A. E. MORAN, V. REAL, G. J. KAPLAN, S. A. MCDOUGALL;
Dept. of Psychology, California State Univ., San Bernardino, CA

Abstract: The neural mechanisms mediating conditioned activity are poorly understood, although the nucleus accumbens, amygdala, and hippocampus have been implicated. In a typical experimental design, adult rats are given five to ten cocaine-environment pairings and conditioned activity is assessed a few days later. Interestingly, rats will also show conditioned activity when a single injection of cocaine is administered in a novel chamber 24 h before testing. The purpose of the present study was to determine the strength and persistence of one-trial and ten-trial cocaine-induced conditioned activity in adult rats. On postnatal day (PD) 71-80 or PD 80, rats in the 'Paired' group were injected with cocaine (30 mg/kg, ip) before being placed in the test chamber and then injected with saline 30 min after being returned to the home cage. In the 'Unpaired' group, rats were injected with saline before being placed in the test

chamber and then injected with cocaine 30 min after being returned to the home cage. Rats in the 'Saline Control' group were given two injections of saline, whereas rats in the 'Non-Habituated' group were injected with cocaine and immediately returned to the home cage. After 60 days (i.e., on PD 140), rats were injected with saline and placed in the test chamber where locomotor activity was measured for 90 min. Immediately after behavioral testing, brains were removed and processed for Fos IR. Overall, rats in the 'Paired' group exhibited significantly more locomotor activity (i.e., conditioned activity) than the three control groups on PD 140. This effect was most evident in rats receiving ten drug-environment pairings, although rats given a single injection of cocaine in the test chamber on PD 80 also showed a significant conditioned locomotor response on PD 140. In the one-trial condition, the non-habituated controls also exhibited elevated locomotor activity on the test day, suggesting that nonassociative processes may have affected behavior. In summary, the present results extend the findings of past studies by showing that a single cocaine exposure during early adulthood can induce a conditioned locomotor response when testing occurs 60 days later. Consistent with Pavlovian learning principles, increasing the number of drug-environment pairings enhances the strength of the conditioned locomotor response.

Disclosures: **A.E. Moran:** None. **V. Real:** None. **G.J. Kaplan:** None. **S.A. McDougall:** None.

Poster

830. Cocaine: Behavioral Studies II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 830.04/FFF11

Topic: G.08. Drugs of Abuse and Addiction

Support: NIH Grant DA-039952

University of Michigan Medical School Host Microbiome Initiative

Title: Sex differences in the gut microbiome during cocaine self-administration in rats

Authors: *J. B. BECKER[1], H. KERVER[2], R. HEIN[3], C. M. BASSIS[3];
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Abstract: Men currently constitute the majority of cocaine users; however, use among women is rapidly increasing and in the 13-18 year age range there is no difference. Furthermore, women begin using cocaine and enter treatment at earlier ages than men and have more severe cocaine use at intake. Thus, the progression to dependence may differ between the sexes, with women progressing from initial use to dependence at a faster rate. Part of this difference relates to sex

differences in the reinforcing effects of cocaine and the loss of interest in natural rewards. Using a novel choice self-administration paradigm, in which animals develop a preference for either cocaine or tasty food pellets, we have previously demonstrated that a greater proportion of females develop cocaine preferences (CP) compared to males. CP's were associated with increased motivation for cocaine and reduced motivation for food in both sexes (Perry et al., 2013, 2015). In the current experiment, male and female rats were tested in the choice paradigm and control animals were given cocaine and/or pellets on a non-contingent schedule. The feces were collected at the end of each week to analyze changes in the microbiome across preference formation. From the feces, DNA was isolated and the V4 region of the bacterial 16S rRNA gene was amplified and sequenced. The sequences were processed and analyzed using the software package mothur. After clustering the sequences into operational taxonomic units (OTUs) based on sequence similarity, θ_{YC} distances between communities, based on relative abundances of both shared and non-shared OTUs, were calculated. Analysis of molecular variance (AMOVA) on θ_{YC} distances was used to test for significant differences between the microbiota of different groups. By AMOVA the fecal microbiota communities of CP and pellet-preferring (PP) male rats were significantly different from each other (AMOVA p-value: 0.002; OTU6 (Clostridium sensu stricto) was identified by linear discriminant analysis and effect size to be significantly greater in CP males). This increase may be the result of changes from PP to CP preference, or may be driving the change in preference. Non-self-administering control groups did not differ. The female CP and PP rats did not differ from each other, but did differ from the non-self-administering rats overall. The fecal bacteria communities of males and females were significantly different from each other. Thus, there are sex differences in the microbiota of rats. Furthermore, males exhibit a shift in fecal bacterial communities with CP, but females do not.

Disclosures: **J.B. Becker:** None. **H. Kerver:** None. **R. Hein:** None. **C.M. Bassis:** None.

Poster

830. Cocaine: Behavioral Studies II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 830.05/FFF12

Topic: G.08. Drugs of Abuse and Addiction

Support: NIDA/NIH DA033533 (N.S)

NIDA/NIH DA037294 (N.S.)

NIAAA/NIH AA023183 (N.S.)

NIDA/NIH DA035865 (M.W.B.)

NIDA/NIH DA032898 (T.C.J.)

NIDA/NIAAA AA022082 (F.W.)

NIDA/NIH DA0398210 (F.W.)

Title: Addiction-linked drug history results in compulsive appetite via disruption in non-homeostatic control of food intake

Authors: A. LAQUE[1], A. MATZEU[1], M. W. BUCZYNSKI[1], G. DE GUGLIELMO[1], G. DE NESS[1], G. E. WAGNER[1], T. KERR[1], A. M. GREGUS[1], T. C. JHOU[2], R. C. RITTER[3], F. WEISS[1], *N. SUTO[1];
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Abstract: Obesity and pathological overeating have received increasing recognition as disorders of "food addiction". While the applicability of this nosology remains controversial, striking similarities in behavioral manifestations and neurobiological underpinnings do exist between certain forms of maladaptive eating habits and drug addiction. We hypothesized that addiction-linked drug history, known to result in addiction-like brain changes and drug motivation, would result in similar addiction-like motivation for food. We first tested this hypothesis in rats with an extensive history of cocaine intake (6 hr/day or "long access [LgA]") - a well-established animal model of cocaine addiction. As a measurement of addiction-like food motivation, all rats were tested for their willingness to self-administer sweetened condensed milk despite an adverse consequence (foot-shock punishment). LgA cocaine history resulted in a heightened resistance to punishment without significantly affecting routine feeding and bodyweight gain. This lack of overeating and excess weight gain suggests that addiction-like food motivation or "compulsive appetite" is due to dysregulation in the non-homeostatic rather than homeostatic control of food intake. Accordingly, LgA cocaine history resulted in compulsive appetite for non-caloric saccharin (motivation solely under the control of non-homeostatic brain system) and upregulated mGluR2/3 in medial prefrontal cortex (mPFC) and amygdala (brain sites implicated in non-homeostatic control of food intake). These receptors negatively modulate neural excitability, possibly contributing to the impaired functional connectivity between mPFC and amygdala observed in addicts. Extensive but passive administration of cocaine also resulted in compulsive appetite for saccharin. Thus, the pharmacological action of cocaine, rather than the act of cocaine intake or maladaptive learning per se, likely triggers addiction-linked brain changes that result in compulsive appetite. Moreover, addiction-linked history of alcohol and obesogenic diet both resulted in a similar compulsive appetite for saccharin. In contrast, an extensive history of caffeine (a substance with low addiction liability and putative anti-obesity properties) did not. Taken together, the nosology of food addiction is most applicable to the phenotypes of eating disorders characterized by compulsive appetite such as binge-eating disorder and bulimia nervosa. Overlapping neurobiological dysregulations in the non-homeostatic brain system likely mediate compulsive appetite - a shared ramification of addiction-linked drug and obesogenic diet history.

Disclosures: **A. Laque:** None. **A. Matzeu:** None. **M.W. Buczynski:** None. **G. de Guglielmo:** None. **G. De Ness:** None. **G.E. Wagner:** None. **T. Kerr:** None. **A.M. Gregus:** None. **T.C. Jhou:** None. **R.C. Ritter:** None. **F. Weiss:** None. **N. Suto:** None.

Poster

830. Cocaine: Behavioral Studies II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 830.06/FFF13

Topic: G.08. Drugs of Abuse and Addiction

Support: CONICET PIP 0249

Title: Prenatal stress and pubertal anxiety are related with adult vulnerability to cocaine-induced conditioning place preference

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Abstract: Increasing evidences point to the influence of early life adversity on the development of substance use disorders, suggesting that drug addiction could be considered a developmental disorder. Nonetheless, no studies today have focused on the relationship between pubertal behavioral traits and adult vulnerability to drug reward in prenatally stressed rats. We designed the present study to determine if anxiety or novelty-induced locomotor activity during puberty have any relationship with individual differences to cocaine-induced conditioned place preference (CPP) during adulthood and the influence of prenatal stress on CPP vulnerability. Pregnant dams were randomly assigned to either the non-prenatal stress (NPS) or the prenatal stress (PS) group. Male offspring were tested for anxiety and novelty response during puberty (P35) and left undisturbed until P90, when we trained them in a 4-trial CPP with cocaine (20 mg/kg). Cocaine-treated animals were classified based on their CPP score in LowCPP or HighCPP (i.e., a CPP score below or above the mean of the sample, respectively). Notably, HighCPP group was further represented by PS (71%) than NPS rats (29%) supporting the notion that prenatal stress is a risk factor for cocaine vulnerability. The analysis of behavioral traits during puberty showed that novelty response was the same in LowCPP and HighCPP and no differences were found between NPS and PS groups neither in novelty response nor in rearing or grooming behaviors. Interestingly, for NPS group, HighCPP animals were more anxious than LowCPP animals during puberty. In contrast, in PS group, HighCPP animals were less anxious than LowCPP animals, evidenced not only by the total time spend in open arms but also by the number of entries to open arms in the elevated plus maze. These results indicate, that adult

Wistar rats differed in their CPP score, with some exhibiting a greater preference than others (HighCPP and LowCPP). Moreover, HighCPP and LowCPP differed in their anxiety traits during puberty in an opposite way in NPS *vs.* PS rats; suggesting that the relationship between adolescent anxiety and adult vulnerability to cocaine reward assessed by CPP depends on the exposure of the offspring to gestational stress. Our findings also emphasize the importance of using animal models based on differential individual behavioral profiles as an effective strategy for identifying genes and molecular mechanisms that can promote vulnerability to drug addiction.

Disclosures: V. Pastor: None. **M.E. Pallarés:** None. **S. Olszevicki:** None. **M.C. Antonelli:** None.

Poster

830. Cocaine: Behavioral Studies II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 830.07/FFF14

Topic: G.08. Drugs of Abuse and Addiction

Support: NIMH Grant R01MH100241

NIDA Grant RO1DA023690

Title: Characterization of collaborative cross mouse strains with extreme initial locomotor sensitivity to cocaine

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Abstract: Substance use disorders (SUDs) are highly prevalent and result in a significant burden to the affected individual, their family and society as a whole. Despite the staggering prevalence and financial toll of SUDs, very few effective treatments exist. This is due, in large part, to the complexity of SUDs and our lack of understanding about underlying etiology. Studies have shown that individual predisposition to develop a SUD exists, both in propensity to initiate drug use and the switch from drug use to drug dependence. Predisposing factors include an individual's genetic background, various environmental exposures and gene by environment

interactions. Studying SUDs in humans is challenging due to the complexity of the human genome, inability to control for environmental exposures, lack of access to drug naïve patients prior to prolonged drug exposure and other logistical and ethical hurdles. Animal models of specific aspects of SUDs have been developed to overcome these challenges. Novelty-induced locomotion in rodents has been used to predict drug self-administration and initial sensitivity to psychostimulants - a model of initial drug sensitivity that in humans predicts future use and abuse. However, among existing models, the link between these behaviors has varied across studies and identification of common and distinct underlying mechanisms has been challenging. We identified two Collaborative Cross (CC) Recombinant Inbred Intercross (CC-RIX) mouse lines that showed significantly high (CC-RIX^{high}) and low (CC-RIX^{low}) locomotor response to novelty. We predicted and confirmed that initial locomotor response to cocaine is higher in CC-RIX^{high} animals compared to CC-RIX^{low}. We are using these two strains as models of high and low predisposition for initial drug sensitivity and have designed a set of experiments to study the relationship among animal models of addiction and elucidate the underlying mechanisms responsible for phenotypic differences. These studies include investigation of stress response, brain levels of dopamine and cocaine pharmacokinetics as well as brain gene expression analysis.
The CC is a genetically stable, inbred mouse population that combines the genomes of 8 different inbred strains from 3 *Mus musculus* subspecies. The CC has been designed to maximize both phenotypic and genetic diversity and provide a platform on which to study complex systems genetics. We are using the unique genetic makeup of CC lines to map candidate regions underlying divergent cocaine responses.

Disclosures: S. Schoenrock: None. **J. Farrington:** None. **P. Kumar:** None. **S. Khan:** None. **F.P. Manuel de Villena:** None. **W. Valdar:** None. **L.M. Tarantino:** None.

Poster

830. Cocaine: Behavioral Studies II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 830.08/FFF15

Topic: G.08. Drugs of Abuse and Addiction

Support: VA BLR&D Grant 1IK2BX002531

Title: Acute sleep deprivation enhances conditioned place preference

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Abstract: Drug abuse is a major problem worldwide with upwards of 23.2 million people suffering from an addiction at a cost of roughly 180.9 billion dollars in the US. Additionally, relapse is a common occurrence with nearly half of those seeking treatment unable to remain continually abstinent. One factor that has been linked to an increase in relapse is insomnia or difficulty falling asleep or maintaining sleep. Insomnia is also thought to be a risk factor for developing abuse patterns. Furthermore, drugs of abuse (including both stimulants and depressants) can cause long-lasting changes in sleep/waking architecture and amount. Thus, there is evidence of a bidirectional relationship between sleep loss and drug use. However, it is unknown whether sleep loss alters the rewarding properties of a substance with abuse potential in drug naïve animals, which could influence the development of an addiction; therefore, we tested the hypothesis that sleep deprivation would alter preference to cocaine.
Adult male mice underwent conditioned place preference (CPP) training using an unbiased design. Mice exhibiting a side bias during a 20 min pretest were excluded from the study as were mice that spent the majority of time in the center compartment, while all other mice were divided into control and experimental groups. The CPP protocol consisted of 4, 30 min trials with the cocaine (8 mg/kg) paired trials on days 1 and 3 and the saline (vehicle control) paired trials on days 2 and 4. A 20 min post-test was conducted on day 5. For CPP acquisition testing, experimental mice were sleep deprived for 4 hours immediately prior to the cocaine conditioning trials while control mice were sleep deprived for 4 hours immediately prior to the saline conditioning trials. For CPP expression testing, experimental mice were sleep deprived for 4 hours immediately prior to the post-test, while control mice were not sleep deprived. Mice were housing in individual cages atop a treadmill belt throughout the study; to prevent sleep, the treadmill belt was turned on at a speed of 3cm/sec which enforces a slow walk to maintain waking.
For both CPP acquisition and expression, control mice showed preference for the cocaine-paired side as expected with this reinforcing dose of cocaine. Acute sleep deprivation further significantly increased preference for the cocaine-paired side for both CPP acquisition and expression, with increases of roughly 4.5 and 3.5 min, respectively, in the cocaine-paired side compared to controls.
Overall, these results suggest that acute sleep deprivation enhances the rewarding properties of a substance with abuse potential.

Disclosures: **T.E. Bjorness:** None. **R.W. Greene:** None.

Poster

830. Cocaine: Behavioral Studies II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 830.09/FFF16

Topic: G.08. Drugs of Abuse and Addiction

Support: National Institutes of Health Grant R01DA020654

American Recovery Reinvestment Act grant R01DA020654-04S1

Start up funds to Dr. Michela Marinelli from the University of Texas at Austin

Title: Adolescents don't fear punishment in the face of reward: possible role of dopamine

Authors: *A. MUTTI[1], W. WONG[2], V. S. RAMACHANDRA[1], M. MARINELLI[1,2];
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Abstract: Background: In humans, adolescence is a period of increased risk taking and experimental drug use. There is controversy as to whether punishing adolescents could be an effective deterrent for subsequent drug use.
We used male rats and tested if punishment (in the form of electric footshock) disrupts self-administration for cocaine differentially in adults vs. adolescents. We also examined the possible role of dopamine neuron activity in these effects. Thus, dopamine neurons of the ventral tegmental area show a brief pause in their activity when presented with an adverse event (footshock), which has been suggested to help making associations with adverse events.
Methods: Adolescent (postnatal day 42-50) and adult (postnatal day >85) male rats were trained to nose poke for cocaine (1.2 mg/kg). Once reliable responding for the reward was established, we paired the reward with an electric footshock for one self-administration day. Self-administration behavior was monitored before, during, and after this "punishment day".
In a separate group of rats, we examined the response of dopamine neurons to footshock, using in vivo single unit extracellular recordings in anesthetized conditions. The firing rate of dopamine neurons in the ventral tegmental area was recorded before, during, and after trains of footshocks.
Results: All rats suppressed responding for cocaine on the day of the footshock. However, adolescents resumed baseline responding levels the day after the footshock, whereas adults maintained suppressed responding.
This effect did not depend on inability of adolescent rats to condition to an adverse event in the absence of rewards. In fact, both adolescent and adult rats showed similar freezing behavior in a fear conditioning procedure.
In response to footshock, 54% of dopamine neurons showed a pause in activity in adults, whereas only 12% showed a pause in activity in adolescents. We are currently testing if manipulations of dopamine neuron activity modifies the behavioral consequences of footshock punishment.
Conclusions: Punishing adolescents is not likely to be an effective deterrent for subsequent drug use. Indeed, adolescent rats are less sensitive to punishment compared with their adult counterparts. This is likely explained by an inability of adverse events to inhibit dopamine neuron activity at this age. These results highlight how adolescence is a period of heightened

vulnerability to rewards and less reactivity to punishment; they also provide insight on possible role of dopamine neurons underlying these effects.

Disclosures: **A. Mutti:** A. Employment/Salary (full or part-time): University of Texas at Austin. B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution; Start up funds to Dr. Michela Marinelli from the University of Texas at Austin, National Institutes of Health Grant R01DA020654, American Recovery Reinvestment Act grant R01DA020654-04S1. **W. Wong:** None. **V.S. Ramachandra:** A. Employment/Salary (full or part-time): University of Texas at Austin. **M. Marinelli:** A. Employment/Salary (full or part-time): University of Texas at Austin.

Poster

830. Cocaine: Behavioral Studies II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 830.10/FFF17

Topic: G.08. Drugs of Abuse and Addiction

Support: NIDA/INSERM

Title: Context-induced relapse to cocaine seeking after punishment-imposed abstinence in a rat model.

Authors: *Y. PELLOUX, S. ADHIKARY, J. BOSSERT, Y. SHAHAM;
Behavioral Neurosci. Br., NIDA IRP, Baltimore, MD

Abstract: Background and objective: We recently developed a punishment-based procedure of context-induced relapse to alcohol seeking in rats to model human relapse to alcohol after self-imposed abstinence due to adverse consequences of drug use (Marchant et al., 2013). Here, we extended this procedure to relapse to cocaine seeking after punishment-imposed abstinence. **Methods:** We trained rats to self-administer cocaine (0.75 mg/kg/infusion, 6-h/d) in context A under continuous reinforcement and 30-s variable interval (VI30) reinforcement schedules (6 d on each schedule). Next, the rats continued to self-administer cocaine in context B under the VI30 reinforcement schedule. For half of the rats, 50% of the reinforced lever presses were paired with intermittent footshock (contingent group) and for the other rats, shock exposure was unpaired with cocaine infusions (non-contingent group). We increased the shock intensity daily from 0 to 0.7 mA. We then tested the rats for cocaine seeking under extinction conditions in contexts A and B (counterbalanced) without footshock for 1 h. Next, we retrained the rats (VI30s, 6 d), re-exposed them to shocks and re-tested for context-induced relapse. **Results:**

Cocaine self-administration in context B was suppressed by contingent (punishment) but not non-contingent footshock. In both relapse tests, extinction responding was higher in context A than in context B in the contingent group (context-induced relapse). In contrast, extinction responding was high in contexts A and B in the non-contingent group. **Conclusions:** Context-induced relapse to cocaine seeking after intermittent punishment is a promising procedure for characterizing mechanisms underlying relapse to cocaine use after self-imposed abstinence. This study was supported by a NIDA/INSERM fellowship.

Disclosures: **Y. Pelloux:** None. **S. Adhikary:** None. **J. Bossert:** None. **Y. Shaham:** None.

Poster

830. Cocaine: Behavioral Studies II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 830.11/FFF18

Topic: G.08. Drugs of Abuse and Addiction

Support: NIH Grant F32 DA038383

NIH Grant P01 DA031656

Title: The development of addiction-like behavior does not require DLS-dependent habitual drug-seeking.

Authors: *B. F. SINGER, M. M. FADANELLI, A. B. KAWA, M. B. SCHWEIR, C. W. CARTER, T. E. ROBINSON;
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Abstract: Drug self-administration procedures in the rat often use schedules of reinforcement that encourage the development of habitual drug-seeking behavior. However, drug-seeking may not be habitual in humans. People have to actively search out drugs, problem-solving and adjusting their behavior according to unpredictable circumstances. Once a drug is obtained, rather than continuously administering the substance for hours on end, research has shown that experienced users tend to titrate their dosing, taking large doses of drug to “spike” blood levels intermittently during a binge. In order to model these patterns of drug-seeking and -taking, we developed a procedure in which rats solved puzzles to get intermittent access to cocaine. These puzzles changed daily and required rats to complete specific sequences of lever presses, nose pokes, and wheel turns. Correct responding on a puzzle was guided by tone cues, and incorrect responses resulted in the rats having to restart the puzzle sequence. If these tone cues were removed, then rats ceased puzzle-solving, indicating that drug-seeking was controlled by

motivated action-outcome associations. Once rats successfully finished a puzzle, the animals gained access to a cocaine-taking lever for five minutes (FR1 schedule), which was then followed by a 25-minute timeout period. On a single day, rats learned one puzzle and improved their performance over ten drug-seeking/taking trials. In contrast, because rats needed to learn how to solve a new puzzle every day, there was no opportunity for them to develop habitual drug-seeking behavior. Indeed, inhibition of dopamine receptors in the dorsolateral striatum (DLS), which has previously been shown to reduce habitual drug-seeking, had no effect on non-habitual drug-seeking in our puzzle-solving rats. Furthermore, after weeks of training, rats showed several behavioral phenotypes of addiction, including increases in Pmax, a behavioral economic measure of motivation to take cocaine. Under extinction, rats demonstrated potentiated cocaine-primed reinstatement of responding and enhanced susceptibility to the conditioned reinforcing properties of drug-paired cues. Thus, sensitized motivation to take drug may not require the development of automatic or habitual drug-seeking behavior.

Disclosures: **B.F. Singer:** None. **M.M. Fadanelli:** None. **A.B. Kawa:** None. **M.B. Schweir:** None. **C.W. Carter:** None. **T.E. Robinson:** None.

Poster

830. Cocaine: Behavioral Studies II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 830.12/FFF19

Topic: G.08. Drugs of Abuse and Addiction

Support: Neuroscience Institute at Georgia State University

Title: Effects of an aversive white noise stimulus on cocaine self-administration, extinction, and reinstatement in adolescent and adult male rats

Authors: *G. J. SUESS[1], J. N. DAVE[1], A. C. WHITE[1], R. G. WILLIAMS[2], B. A. DANIEL[1], B. F. WILLIAMS[1], K. J. FRANTZ[1];
[1]Neurosci. Inst., Georgia State Univ., Atlanta, GA; [2]Neurosci., Univ. of Washington, Seattle, WA

Abstract: Compulsive drug use is a characteristic of clinical substance use disorder, defined as continued drug-seeking and drug-taking in the face of adverse consequences. Despite reports that adolescence is a period of high recreational drug use, investigations of adolescent compulsive drug seeking are lacking. To fill this void, we compared drug taking behavior between adolescent and adult rats under a “conflict model” of cocaine self-administration using white noise as an aversive stimulus. We then examined extinction and reinstatement behavior after

varying lengths of abstinence. Based on lower sensitivity among adolescents to aversive stimuli, we predicted that adolescents would have less attenuation of cocaine intake than adults during conflict, extending to higher rates of reinstatement. Adolescent and adult male Wistar rats were allowed to acquire lever-pressing that was reinforced by the removal of a constant white noise stimulus. In this case, white noise acted as a negative reinforcer. Next, cocaine infusions were paired with the removal of white noise to facilitate a transition to cocaine self-administration. We then switched the role of white noise, making it act as a positive punisher by presenting a burst of white noise only in conjunction with a cocaine infusion. This defined our "conflict model" of cocaine seeking. Response-contingent removal of white noise was effective as a reinforcer of lever pressing for both age groups, although a higher percentage of adults acquired stable lever pressing. During the conflict model, lever pressing declined dramatically, similarly for both age groups, failing to support our prediction. In extinction and reinstatement tests after 1, 14, or 30 days of abstinence, adolescents showed less lever pressing than adults, independent of abstinence length, also failing to support our prediction. Incubation of cocaine seeking was observed in that extinction responding at 14- and 30-days abstinence was higher than at 1-day, regardless of age group. Although these results did not support the current hypothesis, lower levels of drug-seeking after abstinence among adolescent-onset groups are consistent with previous reports from our laboratory. In combination with regional analysis of neural activation during reinstatement, this study may ultimately contribute to targeted treatment of substance use disorder depending on the subject's age.

Disclosures: **G.J. Suess:** None. **J.N. Dave:** None. **A.C. White:** None. **R.G. Williams:** None. **B.A. Daniel:** None. **B.F. Williams:** None. **K.J. Frantz:** None.

Poster

830. Cocaine: Behavioral Studies II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 830.13/FFF20

Topic: G.08. Drugs of Abuse and Addiction

Support: NIDA U54DA039002

Commonwealth of Pennsylvania Department of Health - CURE Addiction Center of Excellence

NIDA R01DA010241

NIDA R33DA026114

Title: The vulnerable brain "persists": undiminished responding to 33 msec drug cues predicts cocaine relapse.

Authors: *A. R. CHILDRESS[1], K. JAGANNATHAN[1], P. REGIER[1], S. DARNLEY[1], T. FRANKLIN[1], D. LANGLEBEN[1,2], Z. MONGE[1], J. J. SUH[1], K. YOUNG[1], R. WETHERILL[1], K. KAMPMAN[1,2], R. EHRMAN[1,2], M. GAWRYSIAK[1], R. SZUCS-REED[1], C. P. O'BRIEN[1]; [1]Dept Psychiat, Univ. PENN Perelman Sch. Med., Philadelphia, PA; [2]VA Med. Ctr., Philadelphia, PA

Abstract: Aims: The healthy brain generally “learns to ignore” incoming signals that are repeated over and over again without consequence - even if these stimuli are initially novel or have learned significance. In fear-driven disorders (e.g., anxiety, phobias, PTSD), a core pathology is the “persistent”, non-extinguishing response to learned cues for danger. We propose that a parallel vulnerability exists in reward-driven disorders (i.e., the addictions): individuals with a “pathological persistence” of the brain response to repeated reward cues may be at greater risk for relapse - even if the cues themselves occur completely outside conscious awareness. We tested this hypothesis by measuring whether the “pathological persistence” of the brain response to “unseen” 33 msec cocaine cues could predict future cocaine use, in an accrued cohort of cocaine patients.
Methods: In a "fast" event-related BOLD fMRI paradigm, cocaine inpatients (n=49) were exposed to cocaine-related and to comparison (sexual, aversive and neutral) cues of 33 msec duration. Each cue (48 presentations of each cue category) was “backward-masked” by a 467 msec neutral stimulus to prevent conscious recognition. Pre-planned contrasts to characterize “persistence” (e.g., drug2-drug1; drug2-neut2) were calculated within SPM 8 for each cue category. A cocaine use score for each individual (% urines cocaine positive or missing, across 8 outpatient treatment weeks) was used as a continuous regressor within each contrast.
Results: As hypothesized, cocaine patients with a “persistent” brain response in *a priori* limbic regions to 33 msec cocaine cues in the **second** half of the task ($2<t<5$; peak t, in amygdala, 3.18) had more cocaine use during the outpatient treatment phase. The persistence was reflected in the amygdala and hippocampus (both contrasts), as well as the ventral tegmental area, v. pallidum, and striatum (drug2-neut2 contrast).
Conclusions: These findings highlight the relapse relevance of a “persistent” limbic brain response to drug cues, even when these cues occur completely outside awareness. These new results in a larger, accrued cocaine cohort suggest that “persistence” may indeed be a sensitive predictor of relapse - and an important, druggable target for relapse-prevention. Our cue paradigms can be used both to screen candidate anti-relapse medications, and to identify the patients with a “persistent” vulnerability-- who will need these medications to achieve a sustained recovery.

Disclosures: A.R. Childress: None. **K. Jagannathan:** None. **P. Regier:** None. **S. Darnley:** None. **T. Franklin:** None. **D. Langleben:** None. **Z. Monge:** None. **J.J. Suh:** None. **K. Young:** None. **R. Wetherill:** None. **K. Kampman:** None. **R. Ehrman:** None. **M. Gawrysiak:** None. **R. Szucs-Reed:** None. **C.P. O'Brien:** None.

Poster

830. Cocaine: Behavioral Studies II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 830.14/FFF21

Topic: G.08. Drugs of Abuse and Addiction

Support: NIDA T32 Translational Addiction Research Fellowship 400-4413-4-564440-5043-2810-1870

Title: The vulnerable brain 'persists': Lifetime emotional, physical, and/or sexual abuse is associated with increased responding across a 500 msec cue task

Authors: *P. S. REGIER, K. JAGANNATHAN, T. FRANKLIN, D. LANGLEBEN, J. SUH, R. EHRMAN, C. P. O'BRIEN, A. R. CHILDRESS;
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Abstract: Introduction: Individuals with substance-use disorders have consistently exhibited a robust limbic response to drug-specific cues. Previously, we have reported that those with a history of emotional, physical, and/or sexual abuse have a heightened limbic response compared to those without abuse. Interestingly the ventral striatum and other surrounding ventral limbic regions, typically activated by drug cues, were not detected with the standard fMRI subtraction approach (i.e., drug cues minus a 'neutral' comparator). We suspected that activation of the ventral striatum to the evocative cues might be obscured by "carry-over" of arousal from the (repeated) evocative cues into the neutral comparator cue condition. We used an analysis approach that could intentionally reveal the "persistence" of arousal to repeated cues, with the hypothesis that "carry-over" arousal in limbic regions (including ventral striatum) would be even more prominent in cue-vulnerable subgroup with a history of abuse.
Methods: Sixty-nine cocaine-dependent individuals were scanned with BOLD fMRI during 24 pseudo-random presentations of 500 msec cues in each of 4 categories (e.g., drug, sex, aversive, neutral) in the first half of an event-related task; the cues were then repeated. Within SPM8, we compared the limbic response for each cue category (e.g., drug) across the two halves of the task.
Results: All reported results met or exceeded cluster correction of $p < 0.05$. The brain response in striatum, including ventral striatum, increased to the drug cues (peak $t = 3.40$) across the task. Similar "persistence" effects were found in the neutral cues (peak $t = 3.33$). Individuals with a history of abuse (vs. no prior abuse) had greater increases to drug cues across the task in ventral regions, including striatum (peak $t = 2.50$), caudal (peak $t = 2.78$) and lateral (peak $t = 2.83$) oribitofrontal cortex.
Conclusion: In a group of participants with lifetime emotional, physical, and/or sexual abuse, the response to drug cues increased across the task, and a similar effect was found for the neutral cues. As the healthy brain typically shows dramatic reductions (habituation; extinction) in the

response to repeated stimuli, the “persistence” of cue responding by the cocaine patients with prior abuse may reflect a vulnerable brain that is less able to manage evocative stimuli, including drug cues linked to relapse (see Childress, et al. SFN 2016 poster). To our knowledge, this is the first study linking a prior history of abuse to the brain’s “persistence”.

Disclosures: **P.S. Regier:** None. **K. Jagannathan:** None. **T. Franklin:** None. **D. Langleben:** None. **J. Suh:** None. **R. Ehrman:** None. **C.P. O'Brien:** None. **A.R. Childress:** None.

Poster

830. Cocaine: Behavioral Studies II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 830.15/FFF22

Topic: G.08. Drugs of Abuse and Addiction

Title: The effects of cocaine self-administration on social bonds in the prairie vole

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Abstract: Addiction is a disease primarily characterized by compulsive drug seeking and taking; however, equally devastating is the dissolution of important social relationships. Cocaine addicts have smaller social networks, reduced empathy and are more “self-serving” than non-users. Cocaine addicts also show reduced activation of brain reward systems during social interactions. Thus, cocaine use alters the way the brain processes social signals, which may lead to social detachment and loss of social support. Social support and the composition of drug users’ social networks can in turn impact their frequency of drug use, duration of abstinence, overall health and engagement in other high risk behaviors. Thus, it is essential to understand how abused drugs alter the processing of social information and disrupt important relationships. Prairie voles (*Microtus ochrogaster*) display selective affiliation towards family members and other familiar individuals, which affords the opportunity to examine how voluntary drug self-administration affects these highly valued and structured relationships. Adult male and female prairie voles were fitted with indwelling jugular catheters. Voles self-administered cocaine (0.4 mg/kg/inf) and banana-flavored food pellets (10 mg, BioServ) on a fixed ratio (FR) schedule for 4 days each week using a choice paradigm in order to identify pellet-preferring (PP) and cocaine-preferring (CP) individuals, which are respectively thought to be resilient and susceptible to drug addiction. Motivation for cocaine and the flavored food pellets was also assessed once each week on a progressive ratio (PR) schedule. Social interactions between self-administering subjects and their familiar sibling were also examined once each week to determine how voluntary drug use affects social motivation and familial relationships. Alloparental behavior was probed early and late

during self-administration in order to examine how drug use altered the propensity to care for an unrelated pup. Finally, we paired self-administering subjects with a naïve member of the opposite sex in order to examine the effects of prior self-administration on mating and partner preference formation. Collectively, these experiments will lay the groundwork for understanding how voluntary drug use affects a variety of social relationships and the way the brain processes and prioritizes social signals, which may lead to the development of novel treatments for the negative social consequences associated with addiction.

Disclosures: **A.N. Perry:** None. **B.S. Cushing:** None.

Poster

830. Cocaine: Behavioral Studies II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 830.16/FFF23

Topic: G.08. Drugs of Abuse and Addiction

Support: CAPES

CNPq

Ligue 132

Ministério da Justiça

AMTEPA

Title: The saccharin presence decrease the value of cocaine on conditioning place preference but not for rats created in an enriched environment

Authors: *L. FREESE[1], F. B. ALMEIDA[3], G. CALETTI[3], N. HEIDRICH[4], L. ZAVARIZE[4], R. GOMEZ[5], **H. M. T. BARROS***[2];
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Abstract: Environmental enrichment (EE) may mimic positive life experiences and prevent the development of drug addiction. Conditioning Place Preference (CPP) indirectly measures the

drug rewarding and reinforcing and enables the exploration of motivation pathways for the preference that occurs after conditioning paired with cocaine or other reward, as saccharin. Our objective was to verify if EE and the possibility of choosing between saccharin vs. cocaine changes the behavior of rats on cocaine CPP. Fifty male Wistar (21 PND) were raised in standard environment (ST) or in EE groups until adulthood (~ 350g). The EE wards hold 7 to10 rats in a large cage (70×60×80cm) divided in 3 floors connected by two ladders, with five/six toys replaced weekly and cardboard tunnels. The ST wards hold 2-3 rats in a standard polycarbonate cage (40×33×18 cm). The CPP boxes (40×60×38cm) had three distinct chambers equipped with photobeams. There were two larger conditioning chambers (40×23×38cm) connected by a central smaller neutral chamber (40×14×38cm) separated by doors containing distinct visual (vertical or horizontal lines/walls) and tactile (bars or leaked aluminum plate/floor) characteristics. The procedure started with CPP 1 (*cocaine vs. saline*): 1)*Pre-conditioning*: rats were placed in the neutral chamber and allowed free access (open doors) to all three chambers (15min). 2)*Conditioning*: over the next 8 days, rats underwent a daily 30 min conditioning session in which they were injected on alternate days with either saline (0,1mL; i.p.) or cocaine (15mg/kg; i.p.) and confined to the respective paired chamber. 3) *Post-conditioning*: identical to the pre-conditioning test allowed the measure the time spent in the cocaine-paired chamber. For the CPP 2 (*saccharin vs. cocaine*) we observed the same stages above, but a saccharin solution [0,2%] was offered in place of saline. Results: The rats living in standard wards presented 2 times longer stay in the cocaine paired chamber than their own preconditioning side. In CPP2 we did not find differences. Thus, the EE decreased the motivation for cocaine rewarding in our animals and the presence of sweet reward on cocaine CPP test in place of saline changed the behavior of all groups. We believe that is possible to better respond to the many questions we have regarding drug addiction using an animal models that's consider as well their lifestyle as for his choices. Prospects: Analyze the mRNA of BDNF levels, by Real-Time qPCR, to verify the BDNFs potential expression on prefrontal cortex and the hippocampus regions on the ST and EE groups.

Disclosures: **L. Freese:** None. **F.B. Almeida:** None. **G. Caletti:** None. **N. Heidrich:** None. **L. Zavarize:** None. **R. Gomez:** None. **H.M.T. Barros*:** None.

Poster

830. Cocaine: Behavioral Studies II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 830.17/FFF24

Topic: G.08. Drugs of Abuse and Addiction

Support: NIDA Grant DA021278 (WLS)

NIDA Grant DA023215 (JDS)

Title: Gender differences in motivational effects of natural rewards and cocaine

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Abstract: The development of drug addiction involves a transition from casual to compulsive drug use, with the individual progressively losing his ability to regulate drug seeking and drug taking. Sex differences in motivational response to cocaine have been reported in clinical and preclinical studies. Because the measurement of motivation for cocaine typically occurs after a period of cocaine SA training, it is unclear whether such differences are resulted from the differential changes induced by cocaine or the preexisting difference in the general motivational responses to rewards. This study aimed to determine how motivational responses to natural and cocaine rewards may differ between sexes and whether motivational responses to natural rewards (sucrose) can predict the differential motivational responses to cocaine in either sex. Male and female Wistar rats were first trained to press a lever to self-administer sucrose under a chained schedule. The progressive ratio schedule (PR) was used to determine the maximum effort that rats are willing to make to earn rewards. To determine the basal sensitivity of the motivational system and whether there are sex-dependent differences, motivation for sucrose was measured in both male and female rats with two different reward values (1 and 3 pellets per reinforcement) and in two different phases of estrous cycle (estrus and diestrus). After jugular catheterization, rats were first trained to self-administer different doses of cocaine: 0.125 and 0.25 mg/infusion in a daily 2-hour sessions. Once they reached the training criteria for each dose, the breaking points under the PR schedule were measured. Our data showed that males had significantly higher motivation for both sucrose and cocaine. Moreover, motivation for cocaine but not sucrose was modulated by the phases of the estrous cycle. In particular, females showed significantly higher motivation for cocaine in estrus than diestrus. The sensitivity to the different doses of cocaine, however, did not differ between the two phases. The levels of motivation for sucrose did not predict the motivation for cocaine in either sex. In addition, the motivational sensitivity to the quantitative change of rewards did not differ for either sucrose or cocaine between sexes but, was significantly higher in males in response to the qualitative change of the rewards from sucrose to cocaine.

Disclosures: **M. Martini:** None. **U. Datta:** None. **W. Sun:** None.

Poster

830. Cocaine: Behavioral Studies II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 830.18/FFF25

Topic: G.08. Drugs of Abuse and Addiction

Support: DA006886

Title: Individual differences and predisposition to drug abuse

Authors: *N. J. BEACHER, J. KULIK, J. STAMOS, K. COFFEY, A. PAWLAK, D. ESTRIN, M. DAMCEVSKA, M. WEST;
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Abstract: The ability to identify individual predispositions to drug abuse is important for long term prevention of drug addiction. A brain region of interest, the Nucleus Accumbens (NAcc), has been studied in the context of addiction and motivation. Changes in firing rates of NAcc neuron as a function of drug self-administration is vital to our understanding of drug abuse. In this study, we studied whether individual differences within a sign and goal tracking paradigm would predict variances in abuse and relapse in subsequent cocaine self-administration (SA). Male and female Long Evans rats were trained on a sign and goal tracking paradigm for 1hr sessions over 7 days. Following the STGT procedure, rats were then divided into sign trackers (ST) and goal trackers (GT) and surgically implanted with a 16 channel microwire arrays into the right NAcc, as well as a jugular catheter. Following a 7 day recovery, subjects were then trained for 14 days in a 6-hour daily cocaine self-administration task with a tone-cue discriminative stimulus. After a 4 day abstinence period, subjects received a final 1 day relapse test with both tone-cue and drug available. Measurements of behavior during the SA phase of the experiment included the latency to react to the tone-cue, variations in drug consumed, and rate of ultrasonic vocalizations (USVs). USVs were recorded during different phases of the self-administration task and overnight during the withdrawal phase to address each subject's affective state. Neural data were recorded every other day of the SA phase of the experiment and comparisons of each neuron's firing rate was made pre and post tone-cue. Analysis of NAcc firing rates and these behavioral measures can determine if individual differences among STGT performers correlate with predisposition to drug abuse, in particular, to cocaine cue reactivity.

Disclosures: N.J. Beacher: None. **J. Kulik:** None. **J. Stamos:** None. **K. Coffey:** None. **A. Pawlak:** None. **D. Estrin:** None. **M. Damcevska:** None. **M. West:** None.

Poster

830. Cocaine: Behavioral Studies II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 830.19/FFF26

Topic: G.08. Drugs of Abuse and Addiction

Support: FRQS

Title: The speed of intravenous cocaine delivery in the past predicts the risk of relapse to drug use in the future

Authors: *A. B. GUEYE, F. ALLAIN, A.-N. SAMAHA;
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Abstract: The vulnerability to relapse is what makes drug addiction a chronic disorder. Studies in both humans and rodents show that craving for drugs like cocaine intensifies or "incubates" during abstinence. This means that the risk of relapse increases with time since the last drug exposure. Recent work in rats shows that, within a bout of cocaine consumption, both how fast drug levels rise in the brain and how often they rise and fall are critical in predicting the emergence of addiction-like behaviours. This growing literature suggests that a rapid drug onset and spikes and troughs in brain levels of drug (as achieved by an intermittent pattern of drug intake) might both push the addiction process forward most effectively. Our objective here was to determine how variation in the speed of drug onset influences relapse behaviour after short and long abstinence periods. To this end, rats were first allowed to press a test lever to self-administer intravenous injections of cocaine (0.25 mg/k/injection) during 10 intermittent-access sessions (6h/session, 1 session/every other day). During each session, cocaine was available in 6-min bins, separated by 26-min time-out periods, as adapted from Zimmer et al. (2011). This achieves spikes and troughs in brain cocaine levels during the session. We manipulated the speed of drug onset by delivering each cocaine injection over 5 seconds in one group of rats, and over 90 seconds in another. A light-tone signal accompanied each earned injection, thus becoming a cocaine-predictive cue. One and 45 days later, we gave all rats a single extinction session (6 h) during which they could lever-press but the cocaine reward was no longer given. Lever-pressing behaviour significantly decreased over the 6-h session in both groups. Immediately following this extinction session, we assessed cocaine cue-induced reinstatement of lever-pressing behaviour. Although cocaine intake is similar between the two groups during the consumption phase, on both days 1 and 45 of withdrawal, the cocaine cue reinstated lever-pressing behaviour only in the 5s-Rats. Thus, exposure to rapidly rising spikes in brain cocaine levels increases the risk of relapse during abstinence, while exposure to more sustained drug injections decreases this risk. This suggests that a rapid drug onset might facilitate addiction by evoking changes in the brain that lead to increased drug craving and relapse in the presence of drug cues. Work is

underway to determine whether relapse behaviour changes from day 1 to 45, and whether there are group differences in cocaine-primed relapse behaviour.

Disclosures: **A.B. Gueye:** None. **F. Allain:** None. **A. Samaha:** None.

Poster

830. Cocaine: Behavioral Studies II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 830.20/GGG1

Topic: G.08. Drugs of Abuse and Addiction

Support: NIDA R15 DA035432

Title: A history of chronic restraint stress increases vulnerability to drug-priming-, but not cue-induced reinstatement of cocaine seeking in rats

Authors: *K. T. BALL, E. STONE, O. BEST, H. EDSON, S. NARDINI, P. NEUCILER, M. SMOLINSKY;
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Abstract: Drug addiction is a chronic disorder characterized by high rates of relapse, even after long periods of abstinence from drug use. Evidence from the clinical literature suggests that relapse is often triggered by exposure to stress. Using an animal relapse model, it has been shown that acute exposure to various stressors induces relapse to both drug and palatable food seeking in rats. However, few systematic studies on the effects of *chronic* stress on relapse have been conducted. We reported recently that chronic exposure to the pharmacological stressor yohimbine following extinction of both 3,4-methylenedioxymethamphetamine seeking and palatable food seeking potentiated later reinstatement (relapse) induced by acute yohimbine. To extend these findings in the present study, we tested the effect of chronic restraint stress on cocaine seeking in rats using both abstinence- and extinction-based relapse models. First, all rats (male, Sprague-Dawley) were trained to press a lever for i.v. cocaine infusions (0.50 mg/kg/infusion) paired with a discrete tone + light cue in daily 3-hr sessions. Subsequently, in Exp. 1, cocaine seeking (i.e., responding for conditioned cues under extinction conditions) was assessed during forced abstinence both before and 7 days after a chronic restraint stress procedure (3 h/day x 7 days) or control procedure (unstressed). In Exp. 2, a separate group of rats was exposed to the same chronic stress procedure during the first 7 days of a 13-day extinction period during which lever presses had no programmed consequences. Following the last day of extinction training, cue- and drug-priming-induced reinstatement tests were conducted. Results showed that prior chronic restraint stress had no significant effect on responding for cocaine cues

during forced abstinence (Exp. 1) relative to unstressed rats; specifically, both groups of rats displayed a similar time-dependent increase in cocaine seeking (i.e., incubation of craving). In Exp. 2 (extinction-reinstatement), prior chronic restraint stress was associated with increased drug-priming-, but not cue-, induced reinstatement of cocaine seeking. These results suggest that exposure to chronic stress during early withdrawal causes lasting changes in motive circuit neurons such that cocaine's ability to increase the incentive motivational properties of cocaine-associated cues is strengthened. From a clinical perspective, these results suggest that chronic stress may leave cocaine addicts more vulnerable for future relapse that is precipitated by re-exposure to the drug.

Disclosures: K.T. Ball: None. **E. Stone:** None. **O. Best:** None. **H. Edson:** None. **S. Nardini:** None. **P. Neuciler:** None. **M. Smolinsky:** None.

Poster

830. Cocaine: Behavioral Studies II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 830.21/GGG2

Topic: G.08. Drugs of Abuse and Addiction

Title: The association between operant novelty seeking and cocaine withdrawal on cue-induced reinstatement in rats.

Authors: *D. P. HAGARTY, A. K. SUTER, I. GONZALEZ, F. PINEDA, C. HARRIS, A. M. GANCARZ;
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Abstract: An important facet of cocaine addiction is a high propensity to relapse following drug cessation and there is ample evidence that relapse to cocaine is highest following extended periods of withdrawal. In humans, many individuals experiment with drugs, but relatively few become addicted. Because of such strong individual differences, there has been increasing interest in identifying factors that predispose individuals toward uncontrolled drug use and relapse. A personality trait that has been linked with drug addiction is Sensation Seeking which is generally described as preference for novel sensations and experiences with high Sensation Seeking implicated in greater drug use. In rodents, operant novelty seeking (ONS), an animal model of Sensation Seeking, has been shown to be predictive of acquisition of drug self-administration (Gancarz et al., 2013). The primary goal of this research is to evaluate the hypothesis that sensitivity to the reinforcing effects of novel visual/auditory stimuli predicts more intensive aspects of drug-taking behaviors such as relapse. Here, we evaluated the relationship between ONS and cue-induced reinstatement following various periods of

withdrawal.
To test this, rats were first habituated to a dark experimental chamber in which responses were recorded but resulted in no programmed consequences. Rats were then tested for ONS, during which chambers were dark and active responses were reinforced according to a VI 1 min schedule of reinforcement. Reinforced responses resulted in a complex visual/auditory stimulus, which consisted of illumination of a stimulus lights of various colors (duration varied between 2 to 8 s) and presentation of an auditory stimulus (1 to 3 s). Following ONS, rats were assigned to self-administer (SA) either water or cocaine reinforcers. In SA sessions, active responses were reinforced according to a FR3 and resulted in presentation of 10 ul of water or 1.0 mg/kg/inf cocaine which was accompanied by the onset of a cue light and a 30 s timeout period. Following SA, animals were exposed to 1 or 14 days of withdrawal during which they were left undisturbed in their homecages. Subsequently, all rats were exposed to within-session extinction, during which responses were recorded but did not result in any programmed consequences (Gancarz et al., 2016). Finally, rats were tested in a single session for cue-induced reinstatement. Active responses resulted in illumination of the cue light previously paired with water/cocaine delivery. This project is currently ongoing and final results will be presented at the meeting. We hypothesize that ONS will be predictive of reinstatement to cocaine but not water reinforcers.

Disclosures: D.P. Hagarty: None. **A.K. Suter:** None. **I. Gonzalez:** None. **F. Pineda:** None. **C. Harris:** None. **A.M. Gancarz:** None.

Poster

830. Cocaine: Behavioral Studies II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 830.22/GGG3

Topic: G.08. Drugs of Abuse and Addiction

Support: NIDA/NIH Grant DA034776

Title: Sex dependent differences in cocaine seeking by rats under punishment

Authors: *U. DATTA, M. MARTINI, W. SUN;
Pharmacol., Univ. of Tennessee, Memphis, TN

Abstract: Transition from recreational drug use to addiction is marked by the inability to regulate drug intake despite negative consequences. While gender differences have been demonstrated for all major phases of drug abuse; the role of gender in compulsive drug seeking has remained relatively unexplored. Here we investigated sex differences in compulsive cocaine use by measuring punishment sensitivity in rats that received foot shocks contingent to their

responses for cocaine. Male and female rats were trained to self-administer cocaine intravenously on a fixed-ratio 1 chain schedule. Over the course of study, rats self-administered cocaine at three different doses starting from 0.125 mg/infusion, followed by 0.25 and 0.5 mg/infusion. Each dose was self-administered for at least 10 sessions (2h/session; 1 session/day) before sensitivity to punishment was assayed. Drug seeking by male and female rats under punishment were compared at all three doses. During punishment, responding for cocaine was assessed at 4 different shock intensities (0.2, 0.3, 0.4 and 0.5 mA) against stable levels of responding observed during training sessions. To determine whether compulsive cocaine seeking is a property dependent on cocaine taking history or a pre-existing condition, we also tested each subject under the same punishment paradigm with sucrose as reinforcer. Correlations between sucrose and cocaine self-administration in presence and absence of punishment were examined. The results from this study provide insight into the behavioral sex differences in terms of compulsive drug seeking.

Disclosures: **U. Datta:** None. **M. Martini:** None. **W. Sun:** None.

Poster

831. Cocaine: Brain Circuitry II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 831.01/GGG4

Topic: G.08. Drugs of Abuse and Addiction

Support: JSPS KAKENHI Grant Num. 16K10197

Title: Sphingosine-1-phosphate and fingolimod regulate PKA/DARPP-32 signaling in striatal medium spiny neurons via neuronal S1P receptor mechanisms.

Authors: *K. UEMATSU[1,2,3], T. SHUTO[3], Y. SYOJI[1], N. UCHIMURA[2], A. NISHI[3];
[1]Cognitive and Mol. Res. Inst. of Brain Dis., [2]Dept. Neuropsychi., [3]Dept. Pharmacol., Kurume Univ. Sch. of Med., Kurume, Fukuoka, Japan

Abstract: Sphingosine-1-phosphate (S1P) is a bioactive sphingolipid metabolite that regulates critical cellular processes such as proliferation, survival and migration as well as immune responses. S1P exerts its function by activating S1P receptors (S1PRs). There are five S1PR subtypes: $S1P_1R$, $S1P_2R$, $S1P_3R$, $S1P_4R$ and $S1P_5R$. It has been reported that S1PRs are expressed in many cell types including neurons and glias in the brain. There are few reports about a possible role of S1P and fingolimod in neurons. Fingolimod (FTY720) is an agonist of S1PRs and a new oral drug for multiple sclerosis. Fingolimod binds to all S1PR subtypes except $S1P_2R$. In this study, we investigated the effect of S1P and fingolimod on cAMP/PKA signaling

in mouse striatal slices by monitoring the phosphorylation states of an intracellular phosphoprotein, dopamine- and cAMP-regulated phosphoprotein of M_r 32 kDa (DARPP-32) at Thr34 (PKA-site). In striatal slices prepared from D_1-DARPP-32-Flag/D_2-DARPP-32-Myc transgenic mice, fingolimod (100 nM) increased DARPP-32 Thr34 phosphorylation in D_2-type/striatopallidal neurons at 30 sec by 2-fold, but decreased it in D_1-type/striatonigral neurons at 30 min to 60% of control. The rapid increase in DARPP-32 Thr34 phosphorylation in striatopallidal neurons was mimicked by treatment with S1P (10 μM) (3-fold increase at 1 min of incubation) and with a selective $S1P_1R$ agonist SEW2871 (10 μM) (2.2-fold increase at 1min of incubation). To examine the role of the slow fingolimod effects in striatonigral neurons, the effects of cocaine and a D_1 receptor agonist were examined after 30 min of preincubation with fingolimod. The cocaine (100 μM)- and a dopamine D_1 agonist (±)-SKF-81297 (1.0 μM)-induced increases in DARPP-32 Thr34 phosphorylation were abolished by pre-treatment of slices with fingolimod (100 nM) for 30 min. In behavioral studies, pretreatment with fingolimod (1.0 mg/kg, i.p.) attenuated cocaine (20 mg/kg, i.p.)- and R(+)-SKF-81297 (0.7 mg/kg, i.p.)- induced locomoter activities. Thus, fingolimod and S1P activates cAMP/PKA signaling via activation of S1PRs in striatopallidal neurons at an early time point, whereas fingolimod inhibits cAMP/PKA signaling in striatonigral neurons at a late time point, resulting in the suppression of psychostimulant-induced activation of dopamine signaling and behavior.

Disclosures: **K. Uematsu:** None. **T. Shuto:** None. **Y. Syoji:** None. **N. Uchimura:** None. **A. Nishi:** None.

Poster

831. Cocaine: Brain Circuitry II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 831.02/GGG5

Topic: G.08. Drugs of Abuse and Addiction

Support: NIH R01DA035008

NIH T32DA007234

Title: Overexpression of caveolin-1 in the nucleus accumbens enhances cocaine-induced locomotor activity

Authors: ***K. GROSS**[1], K. TONN[1], L. MARTINEZ[1], B. HEAD[2], P. MERMELSTEIN[1]; [1]Dept. of Neurosci., Univ. of Minnesota, Minneapolis, MN; [2]Dept. of Anesthesiol., Univ. of California San Diego, San Diego, CA

Abstract: Caveolin-1 (Cav1) is an integral membrane protein that contributes to the organization and signal transduction of neuronal receptors. Although Cav1 is expressed throughout the brain, little is known regarding its function within the nervous system. Recent work has suggested that in regions where Cav1 has been overexpressed it enhances structural and functional plasticity. Within the nucleus accumbens (NAc), plasticity in response to drugs of abuse is a hallmark of addiction, hence we tested the hypothesis that overexpression of Cav1 would lead to enhanced responses to cocaine. Sprague-Dawley rats were injected with a neuron-targeted virus for the overexpression of Cav1 or a control protein (RFP) into the NAc, and the effects on psychostimulant-induced locomotor sensitization were assessed. Control animals did not demonstrate sensitized locomotor activity in response to a subthreshold sensitization protocol. In contrast, sensitization was observed in animals with elevated Cav1 in the NAc, as evidenced by a significant increase in locomotor activity from the first to the final day of cocaine treatment. Cav1 overexpression did not affect baseline ambulatory behavior. Considered together, this suggests that Cav1 does influence cellular organization and signaling in the NAc tied to the functional output of this region. Future work will explore the molecular mechanisms of this effect and the effects of Cav1 overexpression on NAc structural plasticity.

Disclosures: K. Gross: None. **K. Tonn:** None. **L. Martinez:** None. **B. Head:** None. **P. Mermelstein:** None.

Poster

831. Cocaine: Brain Circuitry II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 831.03/GGG6

Topic: G.08. Drugs of Abuse and Addiction

Support: NIDA

Title: Multi-scale regulation of nucleus accumbens somatostatin interneurons controls sensitivity to cocaine

Authors: *E. A. RIBEIRO, E. J. NESTLER;
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Abstract: Somatostatin (Sst) expressing interneuron loss has been observed in individuals who suffer from diseases including depression, schizophrenia, bipolar disorder, and Parkinson's disease across multiple cortical and hippocampal brain regions. While Sst signaling has previously been shown to modulate behavioral responses to psychostimulants, a circuit based molecular understanding of this mechanism is still unknown. To address this, we employed a

cell-type specific, multi-scale approach to characterize Sst interneurons in the nucleus accumbens (NAc), a critical mediator of cocaine reward, in vivo following exposure to cocaine. First, we isolated RNA from NAc Sst interneurons and sequenced their total transcriptome from individual reporter mice after cocaine exposure. We identified cell-type specific transcriptional changes in coding and non-coding transcripts across the genome specific to Sst interneurons that were distinct from transcriptional changes identified in whole NAc issue. To characterize the global circuitry underlying the cell-type specific transcriptional changes in NAc Sst interneurons, we developed a conditional alphaherpes Bartha virus to label the afferent projections specifically to Nac Sst interneurons. We found that Sst interneurons are only innervated by a subset of global afferents targeting the NAc. By performing circuit tracing in D1-cre and D2-cre mice, we showed that NAc Sst interneurons innervate DRD1 and DRD2 MSNs to the same anatomic degree in the NAc. Next, to determine the causal role of NAc Sst interneuron activity, we used optogenetics to stimulate and silence the cells during cocaine locomotor and CPP testing. We found that Sst interneuron activity bi-directionally controls behavioral sensitivity to cocaine-induced locomotion and reward. Our multi-scale systems approach leverages transcriptome and connectome data to identify a cell-type specific circuit-based mechanism underlying cocaine-induced plasticity, revealing a strategy to identify the molecular etiology of cell-type and circuit-specific pathophysiology of cocaine addiction.

Disclosures: **E.A. Ribeiro:** None. **E.J. Nestler:** None.

Poster

831. Cocaine: Brain Circuitry II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 831.04/GGG7

Topic: G.08. Drugs of Abuse and Addiction

Support: NIDA grant # DA03174

Title: Social stress increases cocaine seeking via CRF-DA interaction in VTA

Authors: ***X. HAN**, D. R. ROSE, C. S. KO, J. F. DEBOLD, K. A. MICZEK;
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Abstract: Exposure to stress during abstinence can increase the rate of drug relapse in former addicts. The neural mechanisms via which stress can promote drug intake and relapse are still unclear. One of the hypotheses underlying stress effects on drug use disorders is the interaction between the stress neuropeptide corticotropin releasing factor (CRF), and dopamine (DA) signaling. To assess this hypothesis, we employed social defeat stress in mice, mimicking some

salient features of social stress in humans. Mice were allowed to intravenously self-administer cocaine (1.0 mg/kg/infusion) for ten days in 3-h daily sessions, and then animals were subjected to ten days of drug abstinence. During the abstinence phase, mice from the stress group experienced social defeat stress once per day for five days, while controls were left in their home cages without any disruptions. One day after the last episode of social defeat, the mice were tested for cocaine seeking behavior. We found that social stress increased cocaine seeking behavior. To further evaluate whether the stress effect was long-lasting, we extended the ten days of the abstinence phase to one month. A robust and significant social stress effect was observed even after one month of abstinence, which confirmed that social stress effects on cocaine seeking was long-lasting. In a separate group of mice, we found that escalated cocaine seeking responding was correlated with higher DA release in the nucleus accumbens shell (NAcSh). This could be the result of stress induced mesolimbic dopamine activity. Recently our lab has found that stress-escalated cocaine seeking involved CRF release in rats. To further study the relationship between CRF and DA, we microinjected a CRF receptor type 1 (R1) antagonist (CP 376,395; 1 μg/ 0.2 μl) into the ventral tegmental area (VTA) and then measured cocaine seeking behavior and dopamine release. We found that intra-VTA CRF R1 antagonist not only significantly reversed the social stress effects on seeking behavior, but also blocked stress modulation of dopamine activity. The present studies confirmed the role of VTA CRF in influencing dopamine release and cocaine seeking in animals with a history of cocaine self-administration. These findings suggest that social stress-induced CRF release can alter VTA dopamine neurons and ultimately results in increased cocaine seeking behavior.

Disclosures: X. Han: None. **D.R. Rose:** None. **C.S. Ko:** None. **J.F. DeBold:** None. **K.A. Miczek:** None.

Poster

831. Cocaine: Brain Circuitry II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 831.05/GGG8

Topic: G.08. Drugs of Abuse and Addiction

Support: Fyssen Foundation

NIH DA 003906

NIH DA12513

Title: Role of intra-accumbens brain-derived neurotrophic factor on cocaine seeking.

Authors: *A.-C. BOBADILLA, C. GARCIA-KELLER, V. CHAREUNSOUK, J. HYDE, J. HEINSBROEK, P. W. KALIVAS;
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Abstract: Brain-derived Neurotrophic Factor (BDNF) has been shown to have a critical role not only on neurite growth during early stages of development, but also on physiological functions in the adult brain, as well as on maladaptive behaviors like addiction. Several studies have explored the role of BDNF in addiction-related brain regions like the nucleus accumbens core (NAcore), a critical region driving cue-induced reinstatement after drug self-administration. Both D1- and D2-receptors expressing medium spiny neurons (MSNs) of the NAcore express the primary receptor for BDNF, TrkB, which activation induces several intracellular signaling cascades such as MAPK, PI3K, phospholipase C-g.
Here we sought to understand the rapid, acute effects of BDNF in the NAcore on drug seeking, using the behavioral model of cocaine self-administration in rats. To study the non-transcriptional effects of BDNF in the NAcore, we microinjected BDNF 15 min before cue-induced reinstatement. BDNF induced a clear decrease of reinstatement that endured for days after administration. Conversely, we used TrkB/Fc, a soluble fusion protein that blocks BDNF binding to TrkB, to test whether blocking endogenous BDNF-induced activation of TrkB could prevent this effect. Blocking TrkB activation 15 min before reinstatement potentiates reinstatement and prevents co-administration of BDNF from antagonizing reinstated cocaine seeking. The potentiation of drug seeking in the first minutes of the session was also observed after microinjecting in the NAcore the selective TrkB antagonist ANA-12, confirming that the effects of endogenous BDNF requires binding with TrkB receptor. The capacity of BDNF to decrease cocaine seeking was specific to this drug, since this effect was not observed in animals that underwent cued-reinstatement after sucrose self-administration. We then examined if BDNF-induced decrease of seeking necessitated the recall of the cue memory by microinjecting BDNF at different time points before the reinstatement. When BDNF was microinjected before an extinction session or without any behavioral session post-injection, BDNF did not induce any changes in cued-reinstatement.
These results suggest that, in addition to the long lasting transcriptional effects of BDNF described in literature, acute activation of the TrkB intracellular pathway by BDNF just before cue- or context-induced reinstatement prevents cocaine seeking, and this effect is maintained several days. BDNF-induced decrease in cocaine seeking is specific for cocaine and not sucrose, and requires the recall of the cue memory.

Disclosures: A. Bobadilla: None. **C. Garcia-Keller:** None. **V. Chareunsouk:** None. **J. Hyde:** None. **J. Heinsbroek:** None. **P.W. Kalivas:** None.

Poster

831. Cocaine: Brain Circuitry II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 831.06/GGG9

Topic: G.08. Drugs of Abuse and Addiction

Support: NIH Grant DA041199-01A1

Title: The role of Hypocretin Receptor 1 in the VTA in modulating motivated behavior and dopamine neurotransmission

Authors: *D. L. BERNSTEIN[1], C. E. BASS[2], R. A. ESPAÑA[3];
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Abstract: The hypocretin / orexin (HCRT) system has been recognized to modulate motivated behavior via actions on the mesolimbic dopamine (DA) system. This neuroexcitatory peptide system sends extensive projections to numerous reward-related regions including the ventral tegmental area (VTA) where both the HCRT receptor 1 (HCRTr1) and HCRT receptor 2 subtypes are found. HCRT peptides have been shown to drive VTA DA cell activity, increase DA responses to cocaine in the nucleus accumbens (NAc), and promote cocaine self-administration, while blockade of HCRTr1 produces the opposite effects. Although the existing literature points to the HCRTr1 as an important regulator of reward and reinforcement processing, the majority of studies have employed acute, pharmacological manipulations of HCRT signaling. Moreover, these studies have traditionally relied on peripheral delivery of the HCRTr1 antagonist, SB-334867. Therefore, currently little is known about the long-term, modulatory role of HCRTr1 in the brain, or the specificity of actions at this receptor within the VTA. To address these issues, we knocked down HCRTr1 in the VTA and assessed effects on behavior, dopamine neurotransmission, and the expression of dopamine-associated proteins. We measured the effects on the acquisition and maintenance of cocaine self-administration behavior, and controlled for effects on arousal using sleep electrophysiology. Next, we use fast scan cyclic voltammetry to measure the effects on baseline and cocaine-induced changes to DA signaling in the NAc. Finally, we utilized western blotting to measure the effects on TH and DAT expression. Our results indicate that that long-term knockdown of VTA-HCRTr1 disrupts DA neurotransmission in the NAc under baseline and cocaine conditions, and reduces cocaine self-administration behavior, without substantial effects on arousal. When considered in the context of the existing literature, our experimental findings provide further support for the involvement of HCRTr1 in the VTA in regulating reward and reinforcement processes, and further suggest that HCRTr1 may be an effective target for future pharmacotherapies to treat substance abuse, particularly the abuse of cocaine.

Disclosures: **D.L. Bernstein:** None. **C.E. Bass:** None. **R.A. España:** None.

Poster

831. Cocaine: Brain Circuitry II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 831.07/GGG10

Topic: G.08. Drugs of Abuse and Addiction

Support: NiH/NIDA Grant DA08467 (FW)

NIH/NIDA Grant DA033344 (RMF)

Title: Administration of orexin-A in the paraventricular nucleus of the thalamus activates hypothalamic orexin neurons in animals with a history of cocaine dependence

Authors: ***A. MATZEU**[1], F. WEISS[2], R. MARTIN-FARDON[3];
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Abstract: Orexin (Orx) projections from the lateral hypothalamus (LH) to the paraventricular nucleus of the thalamus (PVT) are implicated in drug addiction. We previously reported that administration of orexin-A (Orx-A) in the PVT reinstates extinguished cocaine-seeking behavior in animals with cocaine short access (ShA, 2 h/day) or long access (LgA, 6 h/day, a model of cocaine dependence) as well as sweetened condensed milk (SCM) seeking. Intra-PVT administration of Orx-A induced a stronger level of reinstatement in the LgA group *vs.* the ShA and SCM groups. This suggests that a history of cocaine dependence (i.e., LgA) leads to neuroadaptive changes at the level of the PVT, resulting in an increase in the sensitivity to the behavioral effects of Orx-A. Knowing that the PVT sends projections back to the hypothalamus, the present study examined the neural activation pattern of the LH, dorsomedial hypothalamus (DMH), and perifornical area (PFA), following intra-PVT Orx-A administration in LgA, ShA, and SCM animals that may partially explain the higher level of reinstatement in LgA animals. Male Wistar rats were trained to self-administer short-access cocaine (ShA), long-access cocaine (LgA), or SCM for 21 days. After achievement of the training procedure, the animals underwent extinction training for 2 weeks in 2 h daily extinction sessions, during which the reinforcers were withheld. Once the animals' behavior was extinguished, they received intra-PVT microinjections of Orx-A (0.5 μg) or the respective vehicle (saline) and then were placed into operant chambers under extinction conditions for 2 h. At the end of the behavioral assays, the brains were prepared for Fos and Orx immunolabeling. The results showed that Orx-A reinstated reward-seeking behavior in all of the groups (LgA, ShA and SCM) as reported earlier. Interestingly, only in

animals that self-administered cocaine (ShA and LgA), Orx-A produced a strong increase of neuronal activation (i.e., Fos expression) in the LH, DMH, and PFA. However, when analyzing the activation (Fos^+) of Orx neurons (Orx^+), a significant increase in Orx^+/Fos^+ expression was observed in the LH, DMH, and PFA only in LgA animals. These data indicate that the PVT↔LH/DMH/PFA connections are strongly recruited in animals with a history of cocaine dependence and are suggestive of a neuronal circuit mediating cocaine-seeking behavior.

Disclosures: **A. Matzeu:** None. **F. Weiss:** None. **R. Martin-Fardon:** None.

Poster

831. Cocaine: Brain Circuitry II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 831.08/GGG11

Topic: G.08. Drugs of Abuse and Addiction

Support: NIH/NIDA DA033344 (RMF)

NIH/NIDA DA08467 (FW)

NIH/NIAAA AA020608 (OG)

Title: Opposing roles of orexin and dynorphin in the paraventricular nucleus of the thalamus

Authors: *R. MARTIN-FARDON[1], M. KALLUPI[2], F. WEISS[1], O. GEORGE[2], P. SCHWEITZER[2], A. MATZEU[1];
[1]MCND, [2]CNAD, Scripps Res. Inst., La Jolla, CA

Abstract: A recent study showed that orexin (Orx) and dynorphin (Dyn) play opposing roles in reward and motivation in the ventral tegmental area (VTA; Muschamp et al., 2014, *PNAS*, 111: E1648-55). Knowing that Orx neurons contain Dyn and that Orx projections from the lateral hypothalamus (LH) to the paraventricular nucleus of the thalamus (PVT) are implicated in drug addiction, this study investigated whether there is a functional interaction between Orx and Dyn in the PVT. Neurons were recorded from PVT brain slices from naive 12- to 14-week-old male Wistar rats. Exposure of PVT neurons to 1 μM Orx-A increased the frequency of spontaneous excitatory postsynaptic currents (sEPSCs), indicating an increase in glutamate release. The addition of 0.2 μM Dyn-A (1-17) in the continued presence of Orx-A completely reversed the effect of Orx-A. In another group of neurons, superfusion of 0.2 μM Dyn-A alone decreased the sEPSC frequency, and the subsequent addition of 1 μM Orx-A in the continued presence of Dyn-A partially reversed the effect of Dyn-A. The amplitude of sEPSCs was unaffected by Dyn-A or Orx-A, indicating a presynaptic effect of Dyn-A and Orx-A on glutamate release. The data show

that Orx-A and Dyn-A have opposite effects on excitatory transmission in PVT neurons and interact to regulate glutamate release. Dyn-A completely neutralized the effect of Orx-A, but Orx-A only partially reversed the effect of Dyn-A. To investigate whether such a Dyn/Orx interaction can be behaviorally measured in animals with a history of cocaine dependence, male Wistar rats were trained to self-administer long-access cocaine (LgA, 6 h/day) for 21 days. After achievement of the training procedure, the animals underwent extinction training for 2 weeks in 2 h daily extinction sessions, during which cocaine was withheld. Once the animals' behavior was extinguished, they received intra-PVT microinjections of Orx-A (0.5 μg), Dyn-A (4 μg), a combination of Orx-A + Dyn-A, or the respective vehicle (saline) and then were placed into operant chambers under extinction conditions for 2 h. Dyn-A blocked the reinstating effects of Orx-A, whereas Dyn-A alone had no effect. These data suggest that Dyn-A in the PVT prevents cocaine seeking through an inhibition of Orx-A-dependent increase in glutamate release. As observed by others in the VTA, Orx and Dyn play opposite roles in the PVT, identifying a novel therapeutic target to prevent drug relapse.

Disclosures: **R. Martin-Fardon:** None. **M. Kallupi:** None. **F. Weiss:** None. **O. George:** None. **P. Schweitzer:** None. **A. Matzeu:** None.

Poster

831. Cocaine: Brain Circuitry II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 831.09/GGG12

Topic: G.08. Drugs of Abuse and Addiction

Support: F30DA038893

P50DA015369

TL1TR001451

T32GM008716

R01DA003906

R01DA012513

Title: Extinction training is required for transient synaptic potentiation in accumbens core and shell

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[1]Neurosci., Med. Univ. of South Carolina, Charleston, SC; [2]Col. of Charleston, Charleston, SC; [3]Psychology, Arizona State Univ., Tempe, AZ

Abstract: Cocaine addiction is a remitting and relapsing neuropsychiatric disorder. Both remission and relapse can be modeled in animals using the self-administration/extinction/reinstatement paradigm, in which cocaine seeking is suppressed by return to an extinguished context and reinstated by re-exposure to drug-paired cues. Transient synaptic potentiation (tSP), a rapid and temporary increase in synaptic strength, occurs in nucleus accumbens (NA) core during cue-induced reinstatement. NA core is a node in the reinstatement circuit, and we hypothesized that NA shell, a node in the inhibitory circuit in this model, would demonstrate tSP in parallel with suppression of drug seeking behavior. We further hypothesized that tSP associated with reinstatement and suppression of drug seeking requires extinction training. Animals underwent daily 2-hour sessions of cocaine self-administration with conditioned cues (a tone + light compound stimulus) for 10 days. Animals then underwent 2 weeks of withdrawal with either extinction training in the same operant chambers previously associated with cocaine, or were left in their home cages. Finally, both groups of animals underwent a test of suppression or reinstatement of drug seeking either in the presence or absence of drug-paired cues. Animals were sacrificed during this final test for measurement of AMPA:NMDA ratios using whole cell patch clamp electrophysiology. A separate group of animals were sacrificed at "baseline" (24 hours after the last day of extinction training or withdrawal). tSP was defined as increased AMPA:NMDA ratio in the behavioral test group relative to their respective baseline. Drug seeking was suppressed by return to the extinguished context and reinstated by drug-paired cues and/or context. Animals who underwent extinction training prior to testing displayed tSP in NA shell during suppression of drug seeking and tSP in NA core during reinstatement of drug seeking, indicating differential involvement of the subcompartments of the NA in suppression versus activation of drug-motivated behavior. In contrast, animals who underwent home cage withdrawal showed tSP neither in NA core nor shell in any test condition. This study further clarifies the divergent roles of NA core and shell during reinstatement and suppression of drug seeking behavior, and suggests that these circuits are differentially modulated depending on prior extinction training.

Disclosures: D. Roberts-Wolfe: None. **C. Shields:** None. **C. Gipson:** None. **J. Heinsbroek:** None. **A. Bobadilla:** None. **P. Kalivas:** None.

Poster

831. Cocaine: Brain Circuitry II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 831.10/GGG13

Topic: G.08. Drugs of Abuse and Addiction

Support: NIDA Grant DA016511

Title: Antagonism of mGlu2/3 receptors in the nucleus accumbens prevents oxytocin from reducing cued methamphetamine-seeking in male and female rats

Authors: *A. BERNHEIM, S. GHEE, C. M. REICHEL;
Neurosciences, Med. Univ. of South Carolina, Charleston, SC

Abstract: Methamphetamine (meth) addiction is a prevalent health concern for men and women worldwide, yet remains without approved pharmacological treatments. Our lab has shown that oxytocin decreased cued meth seeking in males and females, but the neuronal underpinnings remain unknown. However, it is known that glutamatergic synaptic function in the nucleus accumbens core (NAcc) is deregulated following meth. Here we suggest that oxytocin interacts with presynaptic glutamatergic regulation in the NAcc. To this end, we blocked mGlu2/3 receptors with LY-341495 (antagonist of mGlu2/3) before oxytocin using systemic and site-specific application of the drugs. In both experiments, male and female (Sprague-Dawley) rats self-administered meth on an escalating FR ratio for 13 days, and then underwent at least 8 days of extinction to a criteria of less than 25 lever presses on two consecutive sessions. In the first experiment, rats received LY-341495 (1mg/kg, ip) or vehicle 5 min before oxytocin (1mg/kg, ip) or saline before the cued reinstatement sessions. During this session a response on the drug-associated lever resulted in a presentation of the light+tone stimulus complex originally associated with meth. In the second experiment, rats received a LY-341495 (1.3nmol/0.25µl/side) or saline (0.25µl/side) followed by oxytocin (0.6nmol/0.25µl/side) or saline (0.25µl/side) directly into the NAcc (+1.2 posterior, ±2.4 mediolateral, −7.2 ventral from bregma, with a 6° angle) before the cue test. Rats were tested twice in each experiment. In both experiments, all rats readily acquired meth self-administration, and the majority met extinction criteria during the 8 extinction sessions. Males and females did not differ in lever pressing during acquisition or extinction, but meth intake was higher in females. As expected, both males and females reinstated to meth associated cues, and LY-341495 alone did not impact reinstatement in either study. Oxytocin injected systemically or infused into the NAcc decreased cued reinstatement. LY-341495 injected systemically before oxytocin prevented oxytocin from reducing cued reinstatement. Moreover this finding involves the NAcc, because site-specific application of LY-341495 before oxytocin also prevented a reduction in cued reinstatement. No difference was found between males and females on reinstatement tests. These results

demonstrate an interaction between oxytocin and mGlu2/3 receptors, and indicate that oxytocin may work by restoring tone on presynaptic regulation of glutamate in the NAcc.

Disclosures: **A. Bernheim:** None. **S. Ghee:** None. **C.M. Reichel:** None.

Poster

831. Cocaine: Brain Circuitry II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 831.11/GGG14

Topic: G.08. Drugs of Abuse and Addiction

Support: NIDA Grant DA016511

NIDA Grant T32 DA7288

Title: Oxytocin's impact on cocaine-seeking is mediated by the subthalamic nucleus

Authors: ***K.-C. LEONG**, C. M. REICHEL;
Dept. Of Neurosciences, Med. Univ. of South Carolina, Charleston, SC

Abstract: Cocaine addiction remains a persistent societal problem in our country. Oxytocin has increasingly gained therapeutic value for the treatment of cocaine addiction in both men and women. Consistently, work from our lab shows oxytocin attenuates cocaine-seeking in male and female rats. However, the specific site of action for this effect is still unknown. The subthalamic nucleus (STN) plays a critical role in encoding the value of reward, mediating cocaine taking and seeking and contains oxytocin receptors. Oxytocin directly infused into the STN attenuated formation of conditioned place preference to methamphetamine and reduced meth-seeking. Here, we hypothesized that the STN is involved in oxytocin's ability to decrease cocaine seeking. Rats underwent 12 days of cocaine self-administration followed by 7 days of extinction and were then tested for cue induced reinstatement. Immediately prior to reinstatement tests, rats were administered an intra-STN oxytocin (1.2 or 6 mM) or vehicle infusion. Rats were given two separate cue tests in a counterbalanced fashion with a minimum of 3 extinction days between tests. All rats readily acquired cocaine self-administration and extinguished to criteria. Infusions of vehicle and 1.2 mM oxytocin resulted in robust reinstatement to cocaine conditioned cues. However, 6 mM reduced cocaine-seeking relative to the other groups. This is among the first reports showing a local infusion of oxytocin (6 mM) directly into the subthalamic nucleus (STN) impacts addition related behaviors. Albeit speculative, we propose the underlying mechanisms are through oxytocin receptor interactions with GABA and glutamate systems.

Disclosures: **K. Leong:** None. **C.M. Reichel:** None.

Poster

831. Cocaine: Brain Circuitry II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 831.12/GGG15

Topic: G.08. Drugs of Abuse and Addiction

Support: NIDA Grant DA016511

NIDA Grant T32 DA7288

Title: Antagonism of mGlu2/3 receptors prevents oxytocin from reducing cocaine seeking in male and female rats

Authors: *C. M. REICHEL, K.-C. LEONG, A. BERNHEIM;
Neurosciences, Med. Univ. of South Carolina, Charleston, SC

Abstract: Multiple neuropsychiatric disorders, including addiction, may benefit from oxytocin treatment. Oxytocin effectively reduces reinstated drug seeking however the underlying mechanisms have not been completely identified. The oxytocin system is sexually dimorphic with differences in the number of cell bodies in the paraventricular nucleus and receptors expressed within the addiction circuit. Glutamatergic function is a common system disrupted by drug abuse. In this study, we tested whether oxytocin interacted with metabotropic glutamate (mGlu) receptors to change responding during cocaine-cued reinstatement in both males and females. Before this, we determined the effects of oxytocin on motivated cocaine-taking on a progressive ratio (PR) schedule of reinforcement in both male and female rats. In general, females reached higher break points than males and oxytocin reduced break point only in females on a PR test. Then rats underwent cued reinstatement testing to determine whether oxytocin impacts cocaine-seeking through an mGlu2/3, mGlu1a, and/or mGlu5 receptor mechanisms. In separate experiments, rats went through cocaine self-administration on an escalating FR ratio and extinction, then received the mGlu2/3 receptor antagonist LY379268 (1 mg/kg, ip), the mGlu1a antagonist CPCCOEt (10 mg/kg, ip), or the mGlu5 receptor positive allosteric modulator DPFE (1 mg/kg, ip) or vehicle 35 min before chamber placement, and oxytocin (1 mg/kg) or saline 30 min before chamber placement. In each experiment, females took more cocaine than males, but there were no differences in responding during extinction. Consistent with previous findings, oxytocin attenuated reinstated cocaine seeking to cues. LY379268, alone, did not impact reinstatement, however, concurrent administration of LY379268 and oxytocin prevented oxytocin's reduction of reinstated cocaine seeking in response to cues. CPCCOEt and DPFE did not impact cued reinstatement or oxytocin's effects. In summary, oxytocin decreased reinstated cocaine seeking to cues in males and females and this attenuation was prevented through blockade of mGlu2/3 receptors indicating presynaptic mechanisms.

Disclosures: **C.M. Reichel:** None. **K. Leong:** None. **A. Bernheim:** None.

Poster

831. Cocaine: Brain Circuitry II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 831.13/GGG16

Topic: G.08. Drugs of Abuse and Addiction

Support: NIH DA034192

NIH DA039999

Title: Effect of DREADD-mediated modulation of Gq-coupled signaling in lateral habenula neurons on cue-induced reinstatement of cocaine seeking in rats

Authors: ***S. G. NAIR**, J. BROWNE, M. M. ESTABROOK, J. F. NEUMAIER;
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Abstract: The lateral habenula (LHb), an epithalamic nucleus located in the dorsal diencephalon is an important regulator of midbrain dopaminergic systems that are known to be involved in the reinforcing properties of cocaine. We previously determined that activation of G_q-coupled signaling in LHb neurons decreases both operant cocaine self-administration and cocaine-induced reinstatement of lever responding. Here, we further examined the effect of DREADD (hM_3D_q)-induced transient activation of G_q-coupled signaling in LHb neurons on reinstatement of cocaine seeking induced by contingent tone and light cues. Male, Long-Evans rats were injected with hM_3D_q into the LHb and implanted with jugular venous catheters. Approximately two weeks after viral infusions, rats were trained to self-administer cocaine (0.75 mg/kg/infusion) on a fixed ratio 1 reinforcement schedule and the operant response was subsequently extinguished. Initial results indicate that activation of hM_3D_q in the LHb by the pharmacologically inert synthetic ligand clozapine-N-oxide CNO (3 mg/kg, i.p) has no effect on cue-induced reinstatement of cocaine seeking. Secondly, a distinct cohort of rats was infused with viral vectors as described above and trained for five days (two trials/day) on a rotarod. CNO (1 and 3 mg/kg i.p) - induced activation of hM_3D_q in the LHb had no effect on motor co-ordination in the rotarod test. Taken together, our results suggest that DREADD-mediated transient activation of G_q-coupled signaling in LHb neurons specifically decreases cocaine-induced reinstatement of cocaine seeking and this effect is not due to any deficits in motor co-ordination in rats.

Disclosures: **S.G. Nair:** None. **J. Browne:** None. **M.M. Estabrook:** None. **J.F. Neumaier:** None.

Poster

831. Cocaine: Brain Circuitry II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 831.14/GGG17

Topic: G.08. Drugs of Abuse and Addiction

Title: The nucleus accumbens core is less active during reinstatement to cocaine seeking in animals with a history of alcohol use as compared to cocaine use only

Authors: *B. STENNETT, B. JACKSON, L. KNACKSTEDT;
Univ. of Florida, Gainesville, FL

Abstract: One of the difficulties in successful treatment of cocaine addiction is reducing the high risk of relapse that exists even after long periods of abstinence. Relapse can be modeled in animals using the extinction-reinstatement paradigm. This paradigm involves training animals to lever-press for cocaine reinforcement in an operant chamber. The operant response is then extinguished and reinstated with cues previously paired with the response made to attain cocaine delivery and an IP injection of cocaine. Previous research has established the role of nucleus accumbens (NA) core glutamate transmission in the reinstatement of cocaine-seeking. However, it is estimated that 60% to 90% of cocaine addicts use alcohol with cocaine. The combination of alcohol and cocaine potentially produces unique neuroadaptations that differ from those produced by either drug alone. Therefore, we developed a model of poly-drug addiction in which rats self-administered cocaine for two hours in an operant chamber and subsequently drank alcohol (20% v/v) from bottles in the home cage for 6 hours (CE rats). Another group of rats was provided water immediately following the cocaine self-administration session (Coc). Following two weeks of drug consumption, animals underwent extinction training for a minimum of two weeks. Animals were then tested for cue+cocaine-primed reinstatement, where an IP injection of cocaine was given and the light and tone previously paired with drug delivery were delivered upon lever pressing. Immediately following reinstatement, brains were recovered and sliced for c-fos staining. A control group received saline in the operant chamber and drank water in the home cage. Both CE and Coc rats significantly reinstated cocaine-seeking and there were no group differences in reinstatement. While both CE and Coc rats displayed significantly greater c-fos expression in the NA than control rats, CE rats showed significantly less c-fos expression in the NA core than Coc rats. These results agree with our previous finding that NA core glutamate does not increase during reinstatement in CE rats while it does in Coc rats. Given that both CE

and Coc rats reinstated cocaine-seeking, we conclude that the NA core is less active during relapse in animals with a history of both cocaine and alcohol intake. In conclusion, as CE rats display the same degree of lever pressing during reinstatement as Coc rats, it is likely that other brain regions are recruited to mediate reinstatement to drug seeking following a history of both alcohol and cocaine use.

Disclosures: **B. Stennett:** None. **B. Jackson:** None. **L. Knackstedt:** None.

Poster

831. Cocaine: Brain Circuitry II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 831.15/GGG18

Topic: G.08. Drugs of Abuse and Addiction

Support: R01DA034097

Title: Effects of environmental enrichment and abstinence on cocaine seeking and RNA expression within the nucleus accumbens shell

Authors: ***M. ST. PETER**[1,2], G. L. POWELL[2,3], T. BENSON[2], T. CHAUDHURY[2], D. ALCAZAR[2], R. BASTLE[2], N. PERRONE-BIZZOZERO[4], J. NEISEWANDER[2];
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Abstract: Discovery of novel mechanisms involved in cocaine seeking can be implicated from correlations between RNA and behavior. Our lab found that two variables affecting the degree of cocaine-seeking behavior are length of abstinence and housing conditions during abstinence. Animals express increased cocaine seeking after longer durations away from drug and decreased cocaine seeking when housed in environmental enrichment (EE) rather than in isolation during the abstinence period. We therefore examined the effects of environmental enrichment during abstinence on cocaine-seeking behavior and on RNA levels in the nucleus accumbens shell (NAsh) following cocaine self-administration training. Male Sprague-Dawley rats were trained to self-administer cocaine (0.75 mg/kg/infusion i.v., paired with a light + tone cue) across 21 sessions. Control rats received saline infusions yoked to a cocaine partner. Rats were then placed into abstinence for either 1 or 21 days, in either standard isolation housing or an enriched environment housing condition. The enriched environment held 3-6 rats, a running wheel, tubes, toys, and communal food and water. Upon completion of abstinence, animals were given a 1-h test session during which cocaine-paired cues were presented response-contingently but no cocaine was available. Rats were immediately sacrificed after the session. Brain tissue was

extracted, flash frozen, and tissue punches of the NAsh were collected and processed for RNA analysis using RNA-seq. In isolated animals, abstinence from cocaine exposure for 21 days caused increased lever pressing compared to abstinence for 1 day (i.e., incubation effect). Environmental enrichment blocked this effect, significantly reducing active lever pressing after 21 days of abstinence compared to animals in standard housing conditions. Analysis of alterations in RNA expression with enrichment and abstinence found significant changes in multiple RNAs. Using this data we are able to manipulate expression of specific RNAs to validate any roles in cocaine-seeking behavior and to ascertain pharmacologic targets for future treatments. Additionally, we now have a large database of RNA from the NAsh as a guide for future research, and several other structures available for testing the effects of environmental enrichment on RNA.

Disclosures: **M. St. Peter:** None. **G.L. Powell:** None. **T. Benson:** None. **T. Chaudhury:** None. **D. Alcazar:** None. **R. Bastle:** None. **N. Perrone-Bizzozero:** None. **J. Neisewander:** None.

Poster

831. Cocaine: Brain Circuitry II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 831.16/GGG19

Topic: G.08. Drugs of Abuse and Addiction

Support: R00 DA035251

Title: Using Kappa Opioid Receptor DREADDs to transiently inactivate rat basolateral amygdala during conditioned cocaine seeking and fear learning

Authors: *E. CASTILLO, R. DANG, S. V. MAHLER;
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Abstract: The Basolateral Amygdala (BLA) is crucial for both aversive and appetitive Pavlovian learning and motivation. Here, we use a novel chemogenetic approach to transiently inhibit BLA during conditioned cocaine seeking and fear learning, examining consequences on behavior and neural activity. DREADDs are synthetic G-protein coupled receptors that do not respond to endogenous neurotransmitters, but are instead activated by an exogenous ligand that is otherwise inert. Here, we test a new variant of DREADDs that transiently inhibits neuronal activity via the use of Kappa-Opioid Receptor-based inhibitory DREADDs, or KORDs. KORDS are unresponsive to endogenous opioids, but are activated by the otherwise inert drug salvinorin B (SAL B).To test the efficacy of this new approach in our hands, we examined behavioral effects

of KORD inhibition of BLA during cue-induced reinstatement of cocaine seeking, and acquisition of a Pavlovian fear memory. We also examined Fos expression associated with fear cue exposure in animals previously trained under BLA KORD inhibition. First, KORDs were expressed in BLA glutamate neurons of long-evans rats (n=16) via i.c. injection of an AAV CAMKII-KORD-mCitrine vector. They were trained to self-administer i.v. cocaine+ a tone/light cue with lever presses during 10 daily 2hr sessions, then extinguished of this behavior over 7+d extinction training. They then underwent 2 cue-induced reinstatement sessions, in which lever presses yielded cocaine cues, but no cocaine. 15min before these sessions, they received (in randomized order) vehicle (DMSO) and SalB (s.c. SalB, 15mg/kg). Following reinstatement testing, animals underwent one 10min fear conditioning training session where three pairings of a 30sec auditory cue terminated with a 0.75mV, 500ms foot shock. 15min prior to this training session, they received either vehicle (n=8) or SalB (n=8). 48hours later, they were exposed 6 times to the shock-paired cue without shock, and freezing and other behaviors were examined. 90min after the fear expression test, they were perfused, and brains were processed for c-Fos expression in BLA KORD-expressing neurons, and anatomically connected brain regions.

Disclosures: **E. Castillo:** None. **R. Dang:** None. **S.V. Mahler:** None.

Poster

831. Cocaine: Brain Circuitry II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 831.17/GGG20

Topic: G.08. Drugs of Abuse and Addiction

Support: R00DA035251

Title: Ventral Pallidum in Context: Roles for VP and its inputs in cocaine and natural-reward seeking behavior

Authors: *H. SCHOCH, J. CEVALLOS, S. V. MAHLER;
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Abstract: Ventral pallidum (VP) is a key subcortical structure for reward-seeking, especially when it is elicited by Pavlovian reward cues. VP is deeply embedded within mesolimbic reward circuits, and is densely, reciprocally connected with nucleus accumbens, ventral tegmental area, and other mesocorticolimbic regions. Accordingly, VP is implicated in drug seeking behavior, since inhibition of either VP itself, or VP projections to VTA with designer receptors exclusively activated by designer drugs (DREADDs) blocks relapse to cocaine seeking in a self-administration/extinction/reinstatement model of relapse to drug use in addiction. While the

importance of VP for conditioned cocaine seeking is clear, less is known about its functional connectivity with wider reward circuits. Here, we examine VP's role in addiction-related circuits by quantifying reinstatement-related Fos expression in VP-projecting neurons throughout the brain. We also show that DREADD-inhibition of VP alters operant responding for palatable foods, cocaine conditioned place preference, and cocaine-induced locomotor sensitization. These results support a crucial role for VP as a regulator of motivation for both drug and natural rewards, and characterize addiction-related anatomical inputs to VP, placing this structure in its wider limbic circuit context.

Disclosures: H. Schoch: None. **J. Cevallos:** None. **S.V. Mahler:** None.

Poster

831. Cocaine: Brain Circuitry II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 831.18/GGG21

Topic: G.08. Drugs of Abuse and Addiction

Support: R00 DA035251

Title: A Punishment-Induced Abstinence Model of Cocaine Relapse: Characterization in male and female rats, and effects of chemogenetic ventral pallidum inhibition

Authors: *C. RUIZ, M. HUERTA, H. SCHOCH, S. V. MAHLER;
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Abstract: Drug abuse and relapse models in rodents frequently employ a self-administration/ extinction/ reinstatement paradigm imposing forced abstinence from drug, or operant extinction of drug seeking, prior to reinstatement elicited by drug cues, priming injections, or stress. However, many have noted that aspects of this paradigm fail to model the typical course of drug abuse and relapse in humans. Generally, humans choose to quit using drugs due to negative consequences of excessive drug use. Here, we adapted a punishment-induced abstinence model (Marchant, et al, 2014) for use with cocaine, and characterized the procedure in male and female long evans rats. We trained rats to self-administer i.v. cocaine plus a tone/light cue via lever presses (increasing on a variable interval schedule) in context A for 14 days. In a second phase modeling negative consequences of continued drug use, we placed animals in a distinct context B, where lever presses still always yielded cocaine/cues, but also a mild foot shock on 50% of earned infusions. Rats underwent this procedure for 3+ days, until less than 2 cocaine infusions were earned in 2 consecutive daily 2hr sessions. Next, rats were returned to context A for three relapse sessions (48hrs apart), where lever presses yielded cocaine cues, but no additional

cocaine or shocks. Males and females showed similar cocaine self-administration, punishment-induced suppression, and context/cue-induced relapse in this paradigm. Next, we examined effects of chemogenetic (DREADD) inhibition of ventral pallidum (VP) on cocaine relapse in this clinically-relevant punishment-induced abstinence model—a manipulation that we have previously shown to reduce cue reinstatement in conventional extinction-based cocaine reinstatement model. These results will elaborate upon the role of VP in cocaine seeking, and characterize a new translationally-relevant rat model of relapse in cocaine addiction. Funding provided by PHS grant: R00 DA035251

Disclosures: **C. Ruiz:** None. **M. Huerta:** None. **H. Schoch:** None. **S.V. Mahler:** None.

Poster

831. Cocaine: Brain Circuitry II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 831.19/GGG22

Topic: G.08. Drugs of Abuse and Addiction

Support: NIH Grant DA032701

NIH Grant DA034696

Title: Selective deletion of GIRK 2 channels in dopamine neurons increases cocaine self-administration and produces a bidirectional locomotor response

Authors: *S. DOMINGUEZ-LOPEZ[1], A. L. SHARPE[3], R. SHARMA[2], K. D. WICKMAN[4], M. J. BECKSTEAD[1];
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Abstract: We investigated if the lack of G-protein-gated inwardly rectifying K^+ subtype 2 (GIRK2) channels in dopamine neurons affects cocaine self-administration and cocaine-induced locomotion in mice. A *Girk*2 conditional (*Girk2*$^{flox/flox}$) mouse line was generated and crossed with a mouse line that expresses Cre recombinase under control of the dopamine transporter (DAT) promoter (DAT-Cre mice). This generated a conditional knockout mouse line where GIRK2 channels were selectively deleted in dopamine neurons expressing DAT ($GIRK2_{DA}KO$). In our experiments, male $GIRK2_{DA}KO$ mice and their wildtype littermates ($GIRK2_{DA}WT$) were implanted with indwelling catheters in the right jugular vein. A week after surgery, mice were trained to nose-poke for cocaine in daily 2 h sessions. No differences were found between the

two genotypes in the average training sessions necessary to meet self-administration criteria ($GIRK2_{DA}$WT: 6.4 ± 0.7 days; $GIRK2_{DA}$KO: 7.0 ± 0.7 days). When the animals were exposed to increasing doses of cocaine (0.03, 0.1, 0.3, 1.0 and 3.0 mg/kg/infusion), a significantly higher number of infusions were observed in $GIRK2_{DA}$KO mice on days where lower doses of cocaine (0.03 - 0.3 mg/kg/inf) were available (Genotype x Dose: p=0.026). In further analysis, we found that $GIRK2_{DA}$KO have higher cocaine intake (corrected for body weight) per session compared with their litter mates, independently of the dose being tested (Genotype: p = 0.024). Locomotor activity assessed immediately after self-administration sessions showed a bidirectional response in $GIRK2_{DA}$KO mice. After self-administration sessions with low cocaine intake (0-4 mg/kg), locomotor response was reduced (p = 0.003 vs. $GIRK2_{DA}$WT), whereas a high cocaine intake (5-25 mg/kg) produced increased locomotor response (p =0.033 vs. $GIRK2_{DA}$WT). Drug seeking behavior was then assessed using an extinction protocol. In both genotypes, cocaine seeking behavior extinguished at the same rate and recovered similarly during cue-induced reinstatement. Our results support an inhibitory role of GIRK2 channels on cocaine self-administration, limiting cocaine consumption and modulating locomotor response, without affecting acquisition of self-administration or the reinforcing properties of cocaine.

Disclosures: S. Dominguez-Lopez: None. **A.L. Sharpe:** None. **R. Sharma:** None. **K.D. Wickman:** None. **M.J. Beckstead:** None.

Poster

831. Cocaine: Brain Circuitry II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 831.20/GGG23

Topic: G.08. Drugs of Abuse and Addiction

Support: DA006886

Title: The role of Accumbens in cue induced relapse

Authors: *J. KULIK[1], N. BEACHER[2], J. STAMOS[2], K. COFFEY[2], D. ESTRIN[2], M. WEST[2]; [1]Rutgers The State Univ. of New Jersey, Piscataway, NJ; [2]Rutgers Univ., Piscataway, NJ

Abstract: The Nucleus Accumbens (NAc) is a region of Basal Ganglia involved in motivation and processing of reward information, as well as reward-motivated behavior. Abnormal plasticity in NAc Core and Shell is believed to be a major factor in drug addiction. Thus, it is of particular interest to understand how activity in NAc Core and Shell changes with chronic access to cocaine. In particular, we were interested in how NAc Core and Shell neurons process drug-associated cues that lead to relapse of drug taking. For this purpose, neurons in NAc (Core and

Shell) were recorded while animals (male and female rats) self-administered (SA) cocaine during six hour daily sessions via a nose poke response. Cocaine availability was signaled to the animal by the presence of an auditory tone cue which served as a discriminative stimulus presented at 1-6 min intervals. A nosepoke during the tone terminated the tone, produced an infusion of cocaine (0.35 mg/kg/infusion) and initiated a new interval. The first infusion, i.e., the first response to the tone each day was referred to as "Relapse". Following the two week self-administration period, animals were withdrawn and no tone cues were presented for a period of 72 hours following the final day of SA. After 3 days' abstinence, the tone was presented to initiate a typical SA session, and then this cycle was repeated every 3 days as long as neural recordings remained stable. The current project's goal was to understand how NAc Core and Shell neurons process the tone cue, drug-free, preceding "Relapse" after 18 hour withdrawal and 72 hour abstinence periods. Additionally, previous work has identified female addicts as having shorter spans of abstinence and earlier life onset of drug use. The second goal of the project was to investigate whether these sex differences existed in cued NAc responsiveness, and if this could lead to different patterns of behavior in cue-induced relapse by males vs females.

Disclosures: J. Kulik: None. **N. Beacher:** None. **J. Stamos:** None. **K. Coffey:** None. **D. Estrin:** None. **M. West:** None.

Poster

831. Cocaine: Brain Circuitry II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 831.21/GGG24

Topic: G.08. Drugs of Abuse and Addiction

Support: NIH Grant K01 DA030445

NIH Grant R01 DA037897

Title: Activation of amylin receptors in the ventral tegmental area attenuates cocaine seeking in rats

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Abstract: Cocaine addiction continues to be a significant public health problem for which there are currently no effective FDA-approved pharmacological treatments. Therefore, there is a clear need to identify and develop novel pharmacotherapies for cocaine craving and relapse. The neurobiological mechanisms underlying drug taking overlap, to some degree, with those of food

seeking. Amylin is a metabolic factor secreted by the pancreas that regulates energy balance by activating amylin receptors expressed in the brain. Activation of amylin receptors in the ventral tegmental area (VTA) reduces intake of palatable food. Since the rewarding and reinforcing effects of cocaine are mediated, in part, by VTA dopamine neurons, these results support the hypothesis that activation of VTA amylin receptors may also prevent the reinstatement of cocaine seeking in rats, an animal model of relapse. Initially, rats were allowed to self-administer cocaine (0.25 mg/infusion i.v.) for 21 days on a fixed-ratio 5 (FR5) schedule of reinforcement. Voluntary cocaine taking was then extinguished by replacing cocaine with saline. Once cocaine taking was extinguished, rats received an acute priming injection of cocaine (10 mg/kg, i.p.) to reinstate cocaine-seeking behavior. During subsequent reinstatement test sessions, rats were pretreated with intra-VTA infusions of Amylin (0, 0.04 and 0.4 μg) prior to a priming injection of cocaine. Here, we show that administration of Amylin directly into the VTA dose-dependently attenuated cocaine priming-induced reinstatement of drug-seeking behavior. Parallel studies examining the effects of intra-VTA Amylin infusions on the reinstatement of sucrose seeking are being conducted. Preliminary data suggest that administration of Amylin directly into the VTA dose-dependently attenuates sucrose reinstatement. Overall these results potentially highlight a novel role for central amylin receptors in motivated behaviors, generally, and cocaine seeking, specifically.

Disclosures: C.A. Turner: None. **N.S. Hernandez:** None. **J.M. Maurer:** None. **H.D. Schmidt:** None.

Poster

831. Cocaine: Brain Circuitry II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 831.22/GGG25

Topic: G.08. Drugs of Abuse and Addiction

Support: NIH Grant DA029035

Title: Transfer of cue-triggered cocaine-seeking behavior and its dependence on dopamine signaling

Authors: *S. B. OSTLUND, A. T. LIU, B. HALBOUT;
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Abstract: Cues associated with drug use can become potent triggers of drug seeking, and likely contribute to compulsive drug use and relapse. While drug cues may act, at least in part, by directly eliciting specific drug-seeking habits, this account does not readily explain anecdotal

reports of how these cues elicit intense and persistent drug cravings capable of triggering relapse even when familiar modes of obtaining drugs are not available. This capacity for drug cues to set into motion *any* course of action that might lead to drug use is a fundamental feature of addiction. However, there are very few preclinical studies on this phenomenon, perhaps because a robust animal model of general (response-independent) cue-motivated drug seeking has yet to be established. For this purpose, we trained rats to self-administer intravenous cocaine by performing two distinct lever-press actions (left and right). Rats had continuous access to only one lever in each training session. While they could perform this action at any time, lever pressing only resulted in cocaine administration during cue presentations (house light or white noise, depending on lever). As a result, each cue came to signal the availability of cocaine reinforcement for one of the two actions (S1→R1 and S1→R2), but was never directly associated with the alternate action. After initial training, we conducted a series of tests to characterize the ability of these cues to transfer their response-invigorating influence from one action to another (e.g., S1→R2), which was accomplished by embedding nonreinforced probe trials with each cue type during otherwise normal reinforced sessions, again, with only one lever available in any given session. We found that while these cues were more effective in eliciting the action that they were paired with during training, they were also highly effective in motivating performance of the alternate action. Furthermore, pre-treating rats with the nonspecific dopamine receptor antagonist flupentixol (0-0.3 mg/kg, i.p.) prior to testing resulted in dose-dependent attenuation of cue-triggered cocaine seeking, regardless of trial type, suggesting the involvement of a common dopamine-mediated incentive motivational process.

Disclosures: **S.B. Ostlund:** None. **A.T. Liu:** None. **B. Halbout:** None.

Poster

831. Cocaine: Brain Circuitry II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 831.23/GGG26

Topic: G.08. Drugs of Abuse and Addiction

Title: Corticostriatal c-fos expression in differentially reared rats following reinstatement of cocaine-seeking behaviors

Authors: *Z. S. ORBAN, C. A. JOHN, K. M. EVENSON, O. R. LOPEZ, D. A. JANTZ, K. R. OLESEN, M. J. GILL;
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Abstract: Drug addiction is a multi-factorial disorder, with the environment significantly impacting one's susceptibility to addiction. In particular, rearing rats enriched (EC) or

impoverished (IC) conditions produces neurobiological, neurochemical, and behavioral changes. In EC rats, this produces a protective effect as EC rats self-administer less psychostimulant than IC rats at low doses (Green, Gehrke, & Bardo, 2002). The current study examined these rearing-induced neurobiological changes, by quantifying differences in *c-fos* neuronal activation of EC and IC rats following cocaine self-administration. Previous research investigating *c-fos* expression in differentially reared rats shows rearing-induced differences following acute amphetamine exposure (Gill, Weiss, & Cain, 2014). In particular, EC rats display a reduction in *c-fos* expression compared to IC rats in the nucleus accumbens (NA). Similarly, EC rats show reduced *c-fos* expression in the nucleus accumbens, striatum, prelimbic, and cingulate cortex compared to IC rats, following sucrose or cocaine relapse (Grimm et al., 2015; Thiel et al., 2010). In the current study, male Sprague Dawley rats arrived at 21 days of age and reared in either EC or IC conditions. Rats underwent a cocaine self-administration model (0.2 mg/50 µl infusion; FR1 schedule), and were perfused immediately following cue-induced (tone + cue light) or cocaine-primed (10 mg/kg, IP) reinstatement testing. Immunohistochemistry was utilized to quantify *c-fos* positive cells. During reinstatement testing, behavioral results revealed a main effect of rearing and a main effect for reinstatement test. Multiple comparisons showed that IC rats displayed greater cocaine-seeking behavior than EC rats during cue-induced reinstatement. *C-fos* quantification revealed that EC rats displayed greater *c-fos* expression following cue-induced reinstatement than following cocaine-primed reinstatement in the dorsolateral striatum. EC rats also had greater *c-fos* expression than IC rats in the dorsolateral striatum following cue-induced reinstatement. Therefore, quantification of *c-fos* expression in the corticostriatal regions of interest suggest that cocaine-seeking behavior in differential reared rats inversely impacts *c-fos* expression.

Disclosures: Z.S. Orban: None. **C.A. John:** None. **K.M. Evenson:** None. **O.R. Lopez:** None. **D.A. Jantz:** None. **K.R. Olesen:** None. **M.J. Gill:** None.

Poster

831. Cocaine: Brain Circuitry II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 831.24/HHH1

Topic: G.08. Drugs of Abuse and Addiction

Title: PEPA and glutamate: the role of infralimbic AMPA receptors in diminishing reinstatement of cocaine seeking behavior of differentially reared rats

Authors: A. LUNDQUIST[1], H. FALZARANO[1], E. SMIGLA[1], E. KENDALL[1], R. WROBLESKI[1], M. MILOVANOVIC[2], M. E. WOLF[2], M. T. STEFANIK[2], *M. J. GILL[1];

[1]Psychology Dept., North Central Col., Naperville, IL; [2]Neurosci. Dept., Rosalind Franklin Univ., North Chicago, IL

Abstract: Early environmental experiences have been shown to play a role in susceptibility to drug-seeking behaviors in adolescence, driven by changes in neuroplasticity. In particular, rats reared in enriched (EC) or impoverished (IC) conditions show rearing-induced neurobiological, neurochemical, and behavioral changes (Green, Gehrke, & Bardo, 2002). These alterations impact drug addiction as enrichment rearing produces a protective effect, resulting in attenuated drug-seeking behavior compared to IC rats. The current study focused on the glutamatergic pathway from the infralimbic cortex (IL) to the nucleus accumbens (NA) shell due to its role in suppressing reinstatement of drug-seeking behavior. We hypothesized that activation of the IL immediately prior to reinstatement sessions would attenuate cocaine-seeking behavior, and to a greater extent in EC compared to IC rats. Male Sprague-Dawley rats arrived at 21 days of age and were randomly assigned to either EC or IC conditions for 30 days. Rats underwent standard cocaine self-administration (0.2 mg/50 µl infusion; FR1 schedule) and extinction training. Immediately prior to reinstatement, rats received micro-infusions of PBS or PEPA, an AMPA positive allosteric modulator, directly into the IL (3 ng/0.3 µl/side). Following cue-induced or cocaine primed reinstatement, the brains of rats treated with PBS were extracted, and immunoblotting was used to measure GluA1 protein levels in the NA of EC and IC rats. During cue-induced reinstatement, EC rats displayed attenuated drug-seeking behavior compared to IC rats when treated with PEPA, while no differences were observed following PBS treatment. Studies quantifying GluA1 protein levels suggest attenuated GluA1 levels in EC compared to IC rats following cocaine-primed reinstatement. These results show that glutamate receptor levels are altered in differentially reared rats following cocaine self-administration, though the role of the IL-NA pathway is dependent upon the type of reinstatement.

Disclosures: A. Lundquist: None. **H. Falzarano:** None. **E. Smigla:** None. **E. Kendall:** None. **R. Wrobleski:** None. **M. Milovanovic:** None. **M.E. Wolf:** None. **M.T. Stefanik:** None. **M.J. Gill:** None.

Poster

831. Cocaine: Brain Circuitry II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 831.25/HHH2

Topic: G.08. Drugs of Abuse and Addiction

Title: Role of nucleus accumbens shell AMPA receptors in cocaine-seeking behavior of differentially reared rats

Authors: *M. R. CROMWELL[1], C. A. JOHN[1], E. BARTOLI[1], R. WROBLESKI[1], A. LUNDQUIST[1], M. MILOVANOVIC[2], M. E. WOLF[2], M. T. STEFANIK[2], M. J. GILL[1]; [1]Dept. of Psychology & Neurosci., North Central Col., Naperville, IL; [2]Dept. of Neurosci., Rosalind Franklin Univ. of Med., North Chicago, IL

Abstract: The environment in which one is raised appears to have a large impact on addiction susceptibility during adolescence. By altering the environment in which one is reared, we observe neurobiological and neurochemical changes to the brain which alter drug-seeking behavior. In particular, rats reared in an enriched condition (EC) post-weaning exhibit a protective effect, as EC rats are less reactant to the rewarding properties of psychostimulant drugs at low doses, and self-administer less drug than rats reared in an impoverished condition (IC) (Green, Gehrke, & Bardo, 2002). Differential rearing has been shown to alter glutamatergic pathways, an effect that is exacerbated following drug exposure. For instance, glutamate is increased in both the nucleus accumbens (NA) and prefrontal cortex of EC rats following an acute amphetamine injection compared to IC rats (Darna et al., 2015; Rahman & Bardo, 2008). The glutamatergic pathway from the infralimbic cortex (IL) to the NA shell is of particular interest because the IL is implicated in extinction and the suppression of cocaine seeking behavior (LaLumiere et al., 2012; Peters et al., 2008). The current study investigated the role of the NA shell in reinstatement of cocaine-seeking behavior of differentially reared rats, by activating the NA shell immediately prior to reinstatement. We hypothesized that activation of the NA shell prior to reinstatement would attenuate cocaine seeking-behavior, having a greater effect on EC compared to IC rats. Male Sprague Dawley rats arrived at 21 days and were randomly assigned to EC or IC contexts for 30 days; after this, rats underwent standard cocaine self-administration (0.2 mg/50 µl infusion; FR1 schedule) and extinction training. Rats were micro-infused with PBS or PEPA, a glutamatergic positive allosteric modulator, into the NA shell (3 ng/0.3 µl/side), immediately prior to reinstatement sessions. Results demonstrate that EC rats infused with PBS display attenuated cocaine seeking behaviors compared to IC rats. However, there are no differences between EC and IC rats that received intra-NAc shell PEPA prior to cue-induced reinstatement. Current studies are underway examining GluA1 protein levels in the IL of EC and IC rats. These results suggest that NAshell AMPAR activation can reverse the deficits of rearing-induced differences during cocaine-seeking behavior.

Disclosures: M.R. Cromwell: None. **C.A. John:** None. **E. Bartoli:** None. **R. Wrobleski:** None. **A. Lundquist:** None. **M. Milovanovic:** None. **M.E. Wolf:** None. **M.T. Stefanik:** None. **M.J. Gill:** None.

Poster

831. Cocaine: Brain Circuitry II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 831.26/HHH3

Topic: G.08. Drugs of Abuse and Addiction

Support: NIH Grant R00-DA033386

Title: Phasic dopamine release in the nucleus accumbens during cocaine self-administration under different operant schedules

Authors: *I. OLIVA, M. J. WANAT;
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Abstract: A hallmark of drug addiction is the willingness to exert considerable time and effort to obtain the drug. The mesolimbic dopamine system plays a crucial role in the development of drug addiction. Dopamine levels in the nucleus accumbens are elevated in response to drug-paired cues in rats self-administering cocaine with a low effort operant schedule (Fixed ratio 1). However, it is not known how the mesolimbic dopamine system responds to drug-paired cues with higher effort operant schedules.
To address this question, we utilized fast-scan cyclic voltammetry to monitor phasic dopamine release using chronically-implanted electrodes in the nucleus accumbens in rats self-administering cocaine under fixed ratio 1, 2, 3 and progressive ratio reinforcement schedules. Specifically, we are examining how the dopamine response to cocaine delivery cues is related to effort, the cocaine concentration in the brain, the time elapsed since the previous drug infusion, and training history. Our preliminary data indicate reduced dopamine release to cocaine-paired cues as the effort needed to get the infusion of cocaine increases.

Disclosures: I. Oliva: None. **M.J. Wanat:** None.

Poster

831. Cocaine: Brain Circuitry II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 831.27/HHH4

Topic: G.08. Drugs of Abuse and Addiction

Support: R21-DA029787 (NIDA)

589-KG-0012 (VA)

Title: Selective breeding for intravenous cocaine self-administration modifies basal levels of dopamine and acetylcholine in the nucleus accumbens shell

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Abstract: Although a number of rodent strains have been selected for differential responding to drugs of abuse based on oral intake, the LS and HS rat lines are the only lines selected for Low and High intravenous drug Self-administration. HS rats have greater cocaine-induced activation of c Fos and dopamine D2 receptors in the nucleus accumbens and ventral tegmental area. Differences in drug-reinforced behavior could also be due to genetic influences on cocaine bioavailability or other neurotransmitters that modulate reward behavior, such as acetylcholine. The current study was designed to determine basal and cocaine-induced levels of extracellular dopamine, acetylcholine, and cocaine in the nucleus accumbens shell. METHODS: Microdialysis probes were implanted in the nucleus accumbens shell, with dialysate collected at 20 minute intervals and stabilized in oxalic and acetic acids. LS or HS rats received injections of vehicle, 3.2, or 16 mg/kg-injection of cocaine at times 0, 1.3, and 3.3 hours. Analytes were separated using reversed-phase chromatography and quantified with a triple quadrupole mass spectrometer. RESULTS: Anatomic location of all probes was verified in the nucleus accumbens shell. Prior to either vehicle or cocaine treatment, baseline levels of both neurotransmitters were decreased in HS rats. Group means and standard error for dopamine concentration were 2.13 ± 0.35 and 0.82 ± 0.20 nM (LS and HS respectively), with acetylcholine values of 135.8 ± 34.8 ± 39.9 ± 7.5 nM. Cocaine increased dopamine at 40 minutes after its low-dose injection, and between 20 and 120 minutes following high-dose cocaine. This pattern did not differ between strains. Across all time points, cocaine-induced increases in acetylcholine were greater in HS rats, relative to LS animals. Rapid and dose-related increases in brain levels of cocaine were observed, which did not differ between strains. CONCLUSION: In the nucleus accumbens shell, HS (high reward) rats have lower basal levels of both dopamine and acetylcholine than their LS counterparts. Treatment with cocaine produced greater increases in acetylcholine in HS rats. However, neither brain levels of cocaine nor cocaine-induced increases in dopamine differed across strain. Because cocaine can increase both dopamine and acetylcholine, lower basal levels are consistent with a self-medication hypothesis, in which drug use restores augments relatively low basal levels of neurotransmitter.

Disclosures: **K.W. Grasing:** None. **H. Xu:** None. **F. Yang:** None. **S. Das:** None.

Poster

832. Cognition and Behavior: Dopamine and Dopamine Receptors

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 832.01/HHH5

Topic: H.01. Animal Cognition and Behavior

Support: Grant-in-Aid for Scientific Research (S) 20212805

Title: Visual input pathways for dopamine responses reflecting predicted reward value in blindsight monkeys

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Abstract: When animals receive sensory information, it is important for the brain to calculate its value or biological significance. This essential brain function is thought to involve the phasic responses of midbrain dopamine (DA) neurons in the form of a signal that uses reward expectation to code reward prediction error. The phasic DA response is thought to be a critical reinforcement signal for reward based learning. Initially, DA neurons respond to unpredicted reward, but when an association is established between a sensory conditioned stimulus (CS) and an unconditioned reward, the phasic DA response appears to shift to the reward-predicting CS. Magnitude of the DA response evoked by the CS reflects value of the predicted reward. It remains to be determined how primary sensory information associated with the CS is relayed to DA neurons in the ventral midbrain. A direct retino-tecto-nigral route has been reported in several species including primates (Comoli et al., 2003; May et al., 2009), which has been shown to be responsibale for short-latency (<100 ms). DA responses evoked by visual stimuli. To confirm contribution of the retino-tecto-nigral route to phasic DA signaling, we classically conditioned three macaque monkeys with unilateral V1 cortical lesions (an animal model of 'blindsight' in humans, in which the superior colliculus (SC) is the principal residual structure for visual processing on the lesioned side). Two CSs were discriminated by their locations within the visual field; one predicting an immediate large reward (LR trial), while another predicting a delayed small reward (SR trial) relative to fixation point. The CS stimuli were presented to the lesion affected and intact visual field. After several days of training, classically conditioned responses (anticipatory licking) were induced at different magnitudes and timings between LR and SR trials. Electroohysiological recording of DA neurons revealed that short-latency phasic responses were evoked by CSs prsented to the lesion affected visual field. These responses reflected differential reward values predicted by CSs in LR and SR trials. Furthermore, both behavioral and DA neural responses elicited by CS presentation to the lesion affected field were

suppressed when the SC was inactivated by a local injection of muscimol. These results demonstrate that conditioned visual cues can support Pavlovian conditioning in the absence of V1 cortex. Moreover, that phasic DA responses representing different CS values can be mediated via subcortical pathway throgh the SC.

Disclosures: **N. Takakuwa:** None. **R. Kato:** None. **P. Redgrave:** None. **T. Isa:** None.

Poster

832. Cognition and Behavior: Dopamine and Dopamine Receptors

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 832.02/HHH6

Topic: G.01. Appetitive and Aversive Learning

Support: NIH/NIAAA Division of Intramural Clinical and Biological Research

Title: Dopamine at indifference: Accumbal dopamine transients are valence dependent

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Abstract: It has been established that accumbal dopamine levels change with the execution of actions that elicit a reward as well as those that terminate or prevent the onset of aversive stimuli. However, it is unclear whether the magnitude of dopamine release differs between positively and negatively reinforced actions. Here we trained C57 mice to press a lever to either: 1) elicit pellet delivery; or 2) prevent a foot shock. In a choice task, we varied the intensity of the shock and measured their preference to identify a behavioral “indifference point” where animals choose between both outcomes equally. We then conducted fast scan cyclic voltammetry on trials in which one response was forced (forced trials) as well as trials in which the animal could choose between responses (choice trials) to assess whether positively and negatively reinforced actions are associated with different magnitudes of dopamine transients in the Nucleus accumbens (NAc). We replicated past findings demonstrating that negatively reinforced actions are associated with NAc dopamine transients. During the choice task, dopamine signals at the cue were larger when preceding a food choice, even when animals chose equally between the two outcomes. Similarly, on forced trials, transients to operant responses for food were larger than those for shock avoidance. We then optogenetically stimulated accumbal dopamine terminals during choice trials in an attempt to bias the animal's preference. These findings suggest a valence-specificity of accumbal dopamine signals responsive to motivated behavior.

Disclosures: **G.C. Loewinger:** None. **G. Esber:** None. **D. Caprioli:** None. **Y. Mateo:** None. **D. Lovinger:** None.

Poster

832. Cognition and Behavior: Dopamine and Dopamine Receptors

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 832.03/HHH7

Topic: H.01. Animal Cognition and Behavior

Support: KAKENHI Grant 15H04275

KAKENHI Grant 16K14579

Takeda Science Foundation

Takeda Pharmaceutical Company Limited

Title: Expression changes in prefrontal cortex after neurotransmission blocking of the nucleus accumbent pathways

Authors: *T. HIKIDA[1], S. YAO[2], A. FUKAKUSA[2], M. MORITA[1], H. KIMURA[2], K. HIRAI[2], T. ANDO[2], H. TOYOSHIBA[2], A. SAWA[3];
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Abstract: The nucleus accumbens (NAc) is a key substrate in the control of motivation, cognition, and psychomotor functions. Dysfunction of the NAc is associated with several mental disorders, such as schizophrenia, depression, and drug addiction. The NAc is part of a loop circuit, including the prefrontal cortex (PFC) - NAc - ventral pallidum (VP) - substatia nigra pars reticulate (SNr) - thalamus pathway. The NAc has two projection neuron types, D1- and D2-receptor expressing medium spiny neurons (D1/D2-MSN), which have distinct roles in reward and aversive learning, respectively. However, molecular mechanisms of information processing via D1/D2-MSN pathways in the PFC-NAc-VP circuit are unknown. We evaluated changes of the transcriptome level in the PFC and VP after blocking neurotransmission of NAc D1- or D2-MSN using a pathway-specific reversible neurotransmission blocking method (D1/D2-RNB: Hikida et al., Neuron 2010). RNA-seq data were calculated using two independent methods, edgeR and voom. The PFC includes many cell types, and gene lists enriched in specific cell lines (Gene Sets GSE13379 and GSE35766) have been published (Doyle et al., Cell 2008; Schmidt et al., Cell 2012). We applied Gene Set Enlichment Analysis (GSEA), in which gene lists were sorted in descending order by edgeR/voom statistics (ranked gene lists), and then compared these

gene lists with the published Gene Sets and calculated the Enrichment Scores (ES). GSEA using both edgeR and voom statistics revealed that the ES of two types of corticothalamic neurons, Glt25d2-positive layer 5b and Ntsr1-positive layer 6 neurons, were downregulated by both NAc D1- and D2-RNB. In contrast, the ES of S100a10-positive corticostriatal neurons were upregulated and downregulated by NAc D1- and D2-RNB, respectively. These data show that cortical neurons are asymmetrically regulated by subcortical pathways in the PFC-NAc-VP circuit.

Disclosures: **T. Hikida:** B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution; Takeda Pharmaceutical Company Limited. **S. Yao:** A. Employment/Salary (full or part-time): Takeda Pharmaceutical Company Limited. **A. Fukakusa:** A. Employment/Salary (full or part-time): Takeda Pharmaceutical Company Limited. **M. Morita:** None. **H. Kimura:** A. Employment/Salary (full or part-time): Takeda Pharmaceutical Company Limited. **K. Hirai:** A. Employment/Salary (full or part-time): Takeda Pharmaceutical Company Limited. **T. Ando:** A. Employment/Salary (full or part-time): Takeda Pharmaceutical Company Limited. **H. Toyoshiba:** A. Employment/Salary (full or part-time): Takeda Pharmaceutical Company Limited. **A. Sawa:** None.

Poster

832. Cognition and Behavior: Dopamine and Dopamine Receptors

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 832.04/HHH8

Topic: H.01. Animal Cognition and Behavior

Support: KAKENHI Grant 15H04275

KAKENHI Grant 16K14579

Takeda Science Foundation

Title: Learning deficits involving nucleus accumbens D2-receptor expressing neurons in a DISC1 mouse model

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Abstract: Learning deficit is a key clinical feature of several mental disorders, however, the mechanism is still unclear. We investigated the effect of the risk factors of psychiatric disorders on learning ability on various learning tasks, using a transgenic mouse model with a putative dominant-negative DISC1 under expression control of the prion protein promoter (DISC1-DN-Tg-PrP), which shows behavioral abnormalities including impaired prepulse inhibition and increased immobility in forced swim test under the genetic-environmental interaction (Niwa et al., Science 2013). The DISC1-DN-Tg-PrP mice showed normal learning performance on an operant conditioning task. However, in a visual discrimination task using a touchscreen system, DISC1-DN-Tg-PrP mice showed significantly slower visual discriminative learning than wild-type mice. The mutant mice also impaired aversive learning in an inhibitory avoidance task. These learning deficits were similar with those in D2-RNB mice, in which the neurotransmission of D2 receptor-expressing medium spiny neurons in the nucleus accumbens was selectively blocked by a reversible neurotransmission blocking technique (Hikida et al., Neuron 2010). These findings suggest that the abnormality in neural circuit activity involving nucleus accumbens D2-receptor expressing neurons may underlie the learning deficits observed in the DISC1 mutant mice.

Disclosures: **M. Morita:** None. **T. Macpherson:** None. **A. Sawa:** None. **T. Hikida:** None.

Poster

832. Cognition and Behavior: Dopamine and Dopamine Receptors

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 832.05/HHH9

Topic: H.01. Animal Cognition and Behavior

Support: NIH R01MH086629

NARSAD Independent Investigator Award

Title: Loss of dopamine D2 receptors in glutamatergic or GABAergic neurons produces differential behavioral outputs

Authors: *D. L. GRAHAM[1,2], T. S. TRAMMELL[1], L. R. ANDERSON[1], G. LEE[1], M. RUBINSTEIN[3], G. D. STANWOOD[1,2];
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Abstract: Many neuropsychiatric disorders, including depression, schizophrenia, and attention deficit disorders, have a developmental basis, particularly due to disruptions in dopamine (DA) homeostasis within the forebrain. We and others have previously demonstrated that loss of DA receptors, particularly the D2 receptor, can alter neuronal migration, cerebral cortical interneuron expression, and behavioral outputs. Dopamine D2 receptors are expressed by diverse cell types in multiple brain regions, and it is unknown which neuronal subpopulations mediate key D2 receptor-mediated effects. Using cre-lox recombination, we deleted the D2 receptor ($Drd2^{flox/flox}$ mice) from forebrain glutamatergic neurons ($Emx1^{tm1(cre)Krj}$ mice) or forebrain GABAergic ($Nkx2\text{-}1^{cre2Sand}$ mice) neurons. Both $Drd2^{flox/flox}$; cre- mice as well as $Drd2^{+/+}$; cre+ mice were used as controls. Conditional knockouts from both lines (Emx1Drd2KO and Nkx2.1Drd2KO) exhibited normal growth patterns with no obvious physical abnormalities, nor did either line demonstrate differences in tests of anxiety- and depression-like behavior relative to controls. Furthermore, using novel object recognition and the y-maze as screens for working and spatial memory deficits, we found no disruptions in performance due to the loss of the D2 receptor in forebrain glutamatergic or GABAergic neurons. While both KO lines performed similarly to controls in open field and spontaneous locomotor behavior, the Nkx2.1Drd2KO mice had significantly increased latencies to fall during the rotarod task, indicating altered motor coordination and perhaps motor learning. Additional tests will determine if loss of D2 receptors in these distinct neuronal populations results in deficits in other behavioral or cognitive domains. We have previously demonstrated that altering D2 receptor signaling results in an increase in GABA+, specifically parvalbumin+, neurons in the anterior cingulate cortex. Assays to determine the expression of projection neuron and interneuron markers are currently underway. These data are key in identifying the specific developmental, cellular, and behavioral roles of the D2 receptor within the various cell types of the telencephalon and how their dysfunction contributes to brain disorders.

Disclosures: D.L. Graham: None. **T.S. Trammell:** None. **L.R. Anderson:** None. **G. Lee:** None. **M. Rubinstein:** None. **G.D. Stanwood:** None.

Poster

832. Cognition and Behavior: Dopamine and Dopamine Receptors

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 832.06/HHH10

Topic: H.01. Animal Cognition and Behavior

Title: Dorsal striatum neurons expressing dopamine-1 receptors are recruited during fear extinction and are activated by DREADD-induced dopamine

Authors: *M. MINER, C. A. BOUCHET, B. A. LLOYD, H. L. HAKE, T. M. NICASTRO, N. M. GRAY, E. C. LOETZ, B. N. GREENWOOD;
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Abstract: Previous studies suggest that dopamine (DA) can enhance fear extinction, but neural circuitry underlying this extinction modulation is largely unknown. Phasic activity of DA systems can be augmented during fear extinction using Designer Receptor Exclusively Activated by Designer Drug (DREADD). DREADD-induced DA efflux would be expected to increase low-affinity D1 receptor signaling in target regions, but this has yet to be verified. Using double fluorescent *in situ* hybridization (FISH) for *cfos* and D1 mRNAs, we investigated whether striatal neurons expressing D1 receptors are recruited during fear extinction, and if activity of these neurons can be augmented by DREADD-induced phasic DA. DREADD virus was microinjected bilaterally into the substantia nigra (1 µl / side). After 4 weeks, to allow ample time for viral expression, adult, male wild-type or TH-Cre Long Evans rats underwent auditory fear conditioning. The following day, rats were injected intraperitoneally with the designer drug Clozapine-N-Oxide (CNO) 30 min prior to fear extinction learning or control conditions. Fear extinction learning increased *cfos* mRNA in D1-expressing neurons of the dorsal striatum (DS), suggesting that D1 receptors in the DS are recruited during fear extinction. Moreover, DREADD-induced DA increased activation of DS D1-expressing neurons, indicating that D1 receptors in the DS are a target of DREADD-induced augmentation of the nigrostriatal DA pathway. Activity of D1-expressing neurons in the ventral striatum is currently being analyzed. These results suggest that DS D1 receptors could be involved in fear extinction, and provide important new information regarding functional effects of DREADD-induced DA activity.

Disclosures: M. Miner: None. **C.A. Bouchet:** None. **B.A. Lloyd:** None. **H.L. Hake:** None. **T.M. Nicastro:** None. **N.M. Gray:** None. **E.C. Loetz:** None. **B.N. Greenwood:** None.

Poster

832. Cognition and Behavior: Dopamine and Dopamine Receptors

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 832.07/HHH11

Topic: H.01. Animal Cognition and Behavior

Support: Multidisciplinary Association for Psychedelic Studies

Title: The effect of 3,4-Methylenedioxymethamphetamine (MDMA, ecstasy) on extinction and reconsolidation of fear memory

Authors: *E. C. LOETZ, A. SANCHEZ RODRIGUEZ, M. R. MONDRAGON, B. LLOYD, C. P. SIMPSON, B. N. GREENWOOD;
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Abstract: Traumatic memories contribute to post-traumatic stress disorder (PTSD). Current therapeutic strategies for PTSD thus focus on strengthening extinction memories or reducing fear memories. Currently, these strategies have poor long-term efficacy. New techniques to enhance standard therapies are greatly needed. Psychotherapy paired with moderate-dose methylenedioxymethamphetamine (MDMA, ecstasy) has shown promise in reducing symptoms of PTSD, but the means by which MDMA reduces fear is unknown. MDMA administered during psychotherapy could either enhance fear extinction (the learning that trauma cues no longer predict threat) or impair fear memory reconsolidation (the process of strengthening fear memories after recall). The goal of these experiments was to determine whether MDMA enhances fear extinction or impairs fear memory reconsolidation. Adult, male Long Evans rats were exposed to auditory or contextual Pavlovian fear conditioning, resulting in persistent discrete or contextual fear memories similar to those present in PTSD. To determine the effect of MDMA on fear extinction, rats were given either saline or MDMA (1, 2, or 3 mg/kg; i.p.) 30min prior to auditory fear extinction learning. Memory for auditory fear extinction was then tested 1 and 7 days later. To determine the effect of MDMA on fear memory reconsolidation, a different cohort of rats was briefly re-exposed to the conditioning context in order to reactivate the contextual fear memory. Saline or MDMA (3 or 5 mg/kg) was administered immediately after fear memory recall, during the fear memory reconsolidation phase. Strength of the fear memory was tested 1 and 7 days later. Results indicate that MDMA interferes with both the learning of auditory fear extinction and the reconsolidation of contextual fear memory. 5 mg/kg MDMA administered during fear memory reconsolidation resulted in a particularly long-lasting reduction in fear to the conditioning context. These data suggest that MDMA could improve long-term efficacy of psychotherapy by interfering with reconsolidation of memories of traumatic events recalled during therapy. Future studies will investigate if MDMA impairs learning and memory in general, or whether the effects of MDMA are selective to fear memories.

Disclosures: E.C. Loetz: None. **A. Sanchez Rodriguez:** None. **M.R. Mondragon:** None. **B. Lloyd:** None. **C.P. Simpson:** None. **B.N. Greenwood:** None.

Poster

832. Cognition and Behavior: Dopamine and Dopamine Receptors

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 832.08/HHH12

Topic: H.01. Animal Cognition and Behavior

Support: University of Colorado Denver Startup Funds

Title: Dopamine release in the nucleus accumbens and dorsal striatum during voluntary exercise

Authors: *G. J. GILLAN[1], S. A. SCHELP[1], K. J. PULTORAK[2], N. M. HADDAD[3], E. B. OLESON[1], B. N. GREENWOOD[1];
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Abstract: Despite the clear health benefits of physical activity, the participation in exercise by the general public is in constant decline. Identifying factors contributing to motivation to participate in exercise could have dramatic effects on quality of life. The neurotransmitter dopamine has been shown to play a crucial role in movement, reinforcement, and goal-directed behavior. There are two well-characterized patterns of dopamine release: tonic and phasic. Tonic is characterized by spontaneously occurring baseline release, and phasic by high-frequency, burst-firing which can drastically increase dopamine efflux. Indeed, phasic DA could increase signaling through low-affinity dopamine 1 receptors thought to be particularly important for reinforcement and the promotion of movement. There is a general assumption that physical activity increases dopamine concentrations in target brain areas that promote reinforcement and movement, however the effect of voluntary exercise on phasic dopamine release has not been investigated. We characterized phasic dopamine release events in rats during voluntary wheel running using fast-scan cyclic voltammetry. Phasic dopamine release was measured in the nucleus accumbens core and dorsal striatum before, during, and after an acute voluntary wheel running bout, in rats with a history of between 1 and 3 weeks of prior nightly exercise. Data indicate that dopamine release in the nucleus accumbens predicts a change in exercise behavioral state, while dopamine release in the dorsal striatum increases during exercise. These data represent the first characterization of phasic dopamine release events during spontaneous, voluntary exercise, and could provide novel insight into the role of dopamine in guiding motivated behavior.

Disclosures: G.J. Gillan: None. **S.A. Schelp:** None. **K.J. Pultorak:** None. **N.M. Haddad:** None. **E.B. Oleson:** None. **B.N. Greenwood:** None.

Poster

832. Cognition and Behavior: Dopamine and Dopamine Receptors

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 832.09/HHH13

Topic: H.01. Animal Cognition and Behavior

Title: DREADD-induced activation of the nigrostriatal dopamine pathway modulates fear extinction and reduces fear renewal

Authors: *C. A. BOUCHET, M. A. MINER, A. J. ROSBERG, N. M. GRAY, T. M. NICASTRO, B. A. LLOYD, E. C. LOETZ, B. N. GREENWOOD;
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Abstract: Identification of novel strategies to reduce fear relapse after extinction is of high priority. Dopamine (DA) can enhance fear extinction, but the distinct DA circuits able to facilitate extinction are unknown. Although mesocortical DA can inhibit fear extinction, the effect of mesolimbic and nigrostriatal DA activity on fear extinction is unclear. Phasic DA release in the striatum increases as fear extinction is learned, due to the error in prediction that the unconditioned stimulus follows the conditioned stimulus (CS). Phasic DA increases signaling at low-affinity D1 receptors implicated in promoting movement and reward, and anatomically linked to fear circuitry. Dorsal striatum (DS) D1 receptors, in particular, are sensitive to manipulations that can enhance fear extinction and reduce fear relapse in new contexts (renewal), such as acute exercise. The DS supports learning strategies that do not involve hippocampal or contextual components, further implicating the DS in the learning of fear extinction memories resistant to contextual modulation. We utilized Designer Receptors Exclusively Activated by Designer Drugs (DREADD), receptors activated by CNO, to increase phasic activity of substantia nigra pars compacta (SNc) DA neurons, the origin of the nigrostriatal pathway, in order to test the hypothesis that activation of the nigrostriatal DA circuit enhances fear extinction. Following auditory fear conditioning, adult male wild-type or TH-Cre rats injected with AAV-hSynrM3DQ-mCherry into the SNc, received either vehicle or CNO (1 mg/kg i.p.) 30 min before 2 sequential fear extinction sessions. Twenty-four hours after the second extinction session, rats were placed (drug-free) into either the familiar extinction context or a novel context and exposed to the auditory CS to assess fear renewal. Activation of the nigrostriatal DA pathway during fear extinction enhanced fear extinction and prevented fear renewal. This effect of nigrostriatal DA activation was mimicked by pharmacological activation of DS D1 receptors elicited by intra-DS SKF38393 (5 µg/µl; 2µl/side). Data suggest that phasic activity of the nigrostriatal DA circuit represents a novel target for rendering fear extinction memory resistant to contextual modulation and relapse.

Disclosures: C.A. Bouchet: None. **M.A. Miner:** None. **A.J. Rosberg:** None. **N.M. Gray:** None. **T.M. Nicastro:** None. **B.A. Lloyd:** None. **E.C. Loetz:** None. **B.N. Greenwood:** None.

Poster

832. Cognition and Behavior: Dopamine and Dopamine Receptors

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 832.10/HHH14

Topic: H.01. Animal Cognition and Behavior

Support: CU Denver Startup Funds

Title: Exercise increases mTOR signaling in brain areas involved in cognition and emotion

Authors: *B. LLOYD[1], H. HAKE[2], J. BURNS[2], E. LOETZ[2], M. FLESHNER[3], S. BLAND[2], B. GREENWOOD[2];
[1]Univ. of Colorado Denver, Denver, CO; [2]Psychology, Univ. of Colorado, Denver, CO; [3]Integrative Physiol., Univ. of Colorado, Boulder, CO

Abstract: Exercise can enhance learning and memory and produce resistance against stress-related psychiatric disorders such as depression and anxiety. In rats, these beneficial effects of exercise occur regardless of exercise controllability: both voluntary and forced wheel running produce stress-protective effects. The mechanisms underlying these beneficial effects of exercise remain unknown. The mammalian target of rapamycin (mTOR) is a translation regulator important for cell growth, proliferation, and survival. mTOR has been implicated in enhancing learning and memory as well as antidepressant effects. Moreover, mTOR is sensitive to exercise signals such as monoamines and metabolic signals. The effects of exercise on mTOR signaling, however, remain unknown. The goal of the present study was to test the hypothesis that exercise, regardless of controllability, increases levels of phosphorylated mTOR (p-mTOR) in brain regions important for learning and antidepressant responses. Rats were exposed to 6 weeks of either sedentary (locked wheel), voluntary, or forced wheel running conditions. At 6 weeks, rats were sacrificed during peak running and levels of p-mTOR were measured using immunohistochemistry. Overall, both voluntary exercise and forced exercise increased p-mTOR-positive neurons in the medial prefrontal cortex, dorsal striatum, nucleus accumbens, hippocampus, and amygdala compared to locked wheel controls. Exercise, regardless of controllability, also increased numbers of p-mTOR-positive glia in the dorsal striatum, nucleus accumbens, hippocampus, and amygdala. For both neurons and glia, the largest increase in p-mTOR positive cells was observed after voluntary running, with forced exercise causing a more modest increase. Interestingly, voluntary exercise preferentially increased p-mTOR in astrocytes (GFAP+), while forced running increased p-mTOR in microglia (CD11+). Results suggest that mTOR signaling is sensitive to exercise, but subtle differences exist depending on exercise controllability. Increases in mTOR signaling could contribute to the beneficial effects of exercise on cognitive function and mental health.

Disclosures: **B. Lloyd:** None. **H. Hake:** None. **J. Burns:** None. **E. Loetz:** None. **M. Fleshner:** None. **S. Bland:** None. **B. Greenwood:** None.

Poster

832. Cognition and Behavior: Dopamine and Dopamine Receptors

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 832.11/HHH15

Topic: H.01. Animal Cognition and Behavior

Support: MH018870-28

Title: The role of prefrontal interneuron subtypes in working memory

Authors: ***A. I. ABBAS**, M. J. M. SUNDIANG, J. A. GORDON;
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Abstract: Schizophrenia has previously been hypothesized to result from a failure of functional connectivity in the brain - "a disconnection syndrome." Accumulating evidence supports this view, though the cellular mediators of functional connectivity within the brain are not well understood. Given data showing that two classes of inhibitory neurons, parvalbumin- (PV) and somatostatin-expressing (SOM) interneurons, are abnormal in individuals with schizophrenia, we hypothesized that prefrontal cortical interneurons support working memory by facilitating functional connectivity. To test this hypothesis, we used the light-activated proton pump Arch3.0 to selectively silence prefrontal PV or SOM interneurons in the medial prefrontal cortex of mice performing the delayed non-match to sample T-maze test of spatial working memory. We simultaneously recorded neural activity in the medial prefrontal cortex (mPFC) and other brain areas known to be involved in working memory, including the dorsal and ventral hippocampus (dHPC and vHPC), and mediodorsal thalamus (MD). We used measures of synchrony such as coherence to characterize the functional connectivity between these various structures. Silencing SOM interneurons during the sample or delay phases of the task significantly impaired working memory performance when the delay length was 30 seconds or 60 seconds, but not 10 seconds. SOM silencing during the sample phase of the working memory task was also associated with a decrease in coherence between local field potentials (LFPs) recorded in the vHPC and mPFC, but coherence between dHPC or MD and mPFC was unaffected. SOM silencing during the delay phase was associated with a decrease in coherence between LFPs recorded in the vHPC and mPFC, as well as the MD and mPFC, while coherence between dHPC and mPFC LFPs was unaffected. SOM silencing had no effect on choice phase coherence between any of the aforementioned brain areas. Silencing PV interneurons had no effect on either synchrony or

working memory performance. These findings suggest that interneuron dysfunction may contribute to cognitive deficits in schizophrenia by disrupting long range synchrony.

Disclosures: **A.I. Abbas:** None. **M.J.M. Sundiang:** None. **J.A. Gordon:** None.

Poster

832. Cognition and Behavior: Dopamine and Dopamine Receptors

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 832.12/HHH16

Topic: H.01. Animal Cognition and Behavior

Support: Hope for Depression Research Foundation

NIH Grant T32 MH015144-36

Title: VTA activity mediates stress-induced oscillations in the nucleus accumbens.

Authors: ***A. HARRIS**[1], L. A. CHAMBERLIN[2], L. N. KRETSGE[1], A. DEMSAS[1], J. A. GORDON[1];
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Abstract: Stressful life events can precipitate depressive disorders, although the underlying circuit mechanism remains unknown. In rodent models of depression, recent findings implicate neural activity in the ventral tegmental area (VTA) to nucleus accumbens (NAc) circuit in mediating susceptibility to chronic stress, but it is unclear how affects neural activity within this circuit. To address this question, we recorded VTA and NAc activity in mice undergoing acute restraint stress. We found that restraint stress induces a prominent low frequency oscillation (3-6 Hz) in local field potential activity of the NAc. During restraint stress, the amplitude of the VTA gamma range (70-120 Hz) oscillations peaks at fixed phases of the NAc low frequency oscillation, suggesting that restraint stress increases coordination between the VTA and the nucleus accumbens. Infusing muscimol (0.5 μg/μL), a GABA-A agonist, into the VTA substantially reduces the low frequency stress-induced oscillation in the NAc (85% reduction in power of peak frequency, n=9, sign rank test; $p<0.005$), demonstrating the necessity of neural activity in the VTA for this oscillation. We are currently using optogenetic tools to dissect the specific projections from the VTA to NAc responsible for generating this stress biomarker.

Disclosures: **A. Harris:** None. **L.A. Chamberlin:** None. **L.N. Kretsge:** None. **A. Demsas:** None. **J.A. Gordon:** None.

Poster

832. Cognition and Behavior: Dopamine and Dopamine Receptors

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 832.13/HHH17

Topic: H.01. Animal Cognition and Behavior

Support: NIH R01 MH081968

NIH R01 MH096274

NIH F30 MH107204

NIH F31 MH102041

NIH K01 MH105731

Title: mPFC activation of BLA SOM+ interneurons mediates safety

Authors: *J. M. STUJENSKE[1], S. GOLDBURG[4], L. DIAZ[2], W. D. HARDIN[2], S. S. BOLKAN[1], T. R. REARDON[1], T. SPELLMAN[5], J. A. GORDON[3], E. LIKHTIK[6]; [1]Neurobio. and Behavior, [3]Psychiatry, [2]Columbia Univ., New York, NY; [4]Barnard Col., New York, NY; [5]Feil Family Brain and Mind Res. Inst., Weill Cornell Med. Col., New York, NY; [6]Biol., Hunter Col., New York, NY

Abstract: It has been postulated that inhibitory circuits of the basolateral amygdala (BLA) are required for proper discrimination between aversive and non-aversive stimuli. Likewise, fear generalization is associated with an underactive medial prefrontal cortex (mPFC) and an overactive BLA. A prevailing hypothesis is that the mPFC mediates safety signaling by activation of BLA interneurons. To test this hypothesis, mice were trained on a discriminative fear conditioning paradigm in which one tone was paired with a foot shock (CS+) and the other was unpaired (CS-). Silencing mPFC inputs to the BLA using Archaerhodopsin-3 (Arch) resulted in fear generalization (n=8, $p<.05$, paired t-test); activating these inputs using Channelrhodopin-2 (ChR2) enhanced discrimination (n=8, $p<.05$, t-test). No effects of light were seen in control animals (n=6-8, $p>.05$, t-tests). Using a rabies-tracing approach, we determined that the mPFC makes direct synaptic contacts onto PV+ and SOM+ interneurons (n=3 animals per cell type), as well as pyramidal cells. Optogenetic activation of ChR2-expressing mPFC inputs led to increased c-fos expression in both PV+ and SOM+ neurons (n=3 animals per cell type, $p<.01$, t-test). C-fos expression in SOM+ neurons was decreased following fear but recovered following extinction (n=10-15 animals / group, $p<.05$, t-test), while expression in PV+ neurons did not change ($p>.05$). Optogenetic silencing of Arch-expressing SOM+ (n=8 Arch, n=8 control, two-way ANOVA, light x group, $p<.001$, post-hoc Bonferroni, $p<.05$) but not PV+ interneurons (n=6 Arch, post-hoc Bonferroni, $p>.05$) impaired fear discrimination. Likewise,

SOM+ silencing during fear extinction impaired both same day learning (n=8 Arch, n=7 control, rm-ANOVA, Virus x Time interaction, $p<.05$) and subsequent extinction recall on the next day (effect of Virus, $p<.05$), consistent with a disruption of prefrontal-dependent safety signaling. PV+ silencing, by contrast, enhanced both fear extinction learning (n=6 Arch, n=6 control, Virus x Time interaction, $p<.05$) and recall (effect of virus, $p<.05$). In summary, our data suggest that recruitment of BLA SOM+ interneurons by mPFC inputs is necessary for successful fear discrimination and extinction.

Disclosures: **J.M. Stujenske:** None. **S. Goldburg:** None. **L. Diaz:** None. **W.D. Hardin:** None. **S.S. Bolkan:** None. **T.R. Reardon:** None. **T. Spellman:** None. **J.A. Gordon:** None. **E. Likhtik:** None.

Poster

832. Cognition and Behavior: Dopamine and Dopamine Receptors

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 832.14/HHH18

Topic: H.01. Animal Cognition and Behavior

Support: NIMH R01 MH096274

IMHRO

Irma Hirschl Trust

Kirschstein Predoctoral NRSA

Title: Receiprocal thalamo-prefrontal activity supports spatial working memory

Authors: *S. S. BOLKAN[1], J. M. STUJENSKE[2], T. X. A. P. SPELLMAN[5], J. A. GORDON[3], C. KELLENDONK[4];
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Abstract: Working memory, the temporary encoding, maintenance and manipulation of behaviorally relevant information, is a fundamental component of cognition. While neural activity in the medial prefrontal cortex (PFC) has long been implicated in working memory, we recently demonstrated that inhibition of the mediodorsal thalamus (MD) in mice impairs both working memory performance and MD-PFC neural synchrony. However, given the dense, reciprocal connectivity between the MD and multiple PFC subregions, it remains unclear (1)

whether direct MD-to-PFC activity is necessary for working memory, (2) whether reciprocal PFC-to-MD activity may also have a role, and (3) the precise temporal windows in which MD-PFC activity is necessary. To address these questions we utilized the light-driven proton pump eArch3.0 to achieve projection-specific and temporally precise optogenetic terminal inhibition in mice performing a delayed non-match to sample (DNMS) T-maze test of spatial working memory. We find that MD-to-mPFC and mPFC-to-MD activity is necessary for T-maze performance in a delay-dependent manner. However, while MD-to-mPFC activity was necessary during the maintenance phase of the task, mPFC-to-MD activity was necessary during the retrieval phase of the task. To further understand the physiological mechanisms supporting these processes we recorded mPFC single-units (538 eArch3.0, 447 eYFP) and mPFC/MD local field potentials while mice performed the T-maze and received phase-specific inhibition of MD-to-mPFC activity. Putative mPFC "maintenance" cells with sustained, elevated activity during the delay period were exceedingly rare (<1%). However, we observed a population of cells with brief bouts of elevated activity that tiled the delay duration. Intriguingly, activity in these neurons was elevated only on correct trials, as compared to incorrect trials. Delivery of light to MD terminals abolished this elevated activity only in eArch3.0 animals and not in eYFP-expressing controls. These findings are consistent with a role for mPFC activity in the maintenance of working memory and reveal a critical role for MD-to-mPFC inputs in this process.

Disclosures: **S.S. Bolkan:** None. **J.M. Stujenske:** None. **T.X.A.P. Spellman:** None. **J.A. Gordon:** None. **C. Kellendonk:** None.

Poster

832. Cognition and Behavior: Dopamine and Dopamine Receptors

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 832.15/HHH19

Topic: H.01. Animal Cognition and Behavior

Support: NIH Grant R01MH081968-08

NSF-GRFP

Title: Theta-frequency oscillatory stimulation of vHPC inputs to the mPFC increases anxiety-like behavior

Authors: *N. PADILLA COREANO[1], S. CANETTA[2], W. D. HARDIN[2], R. WARREN[3], D. R. BLACKMAN[4], C. KELLENDONK[2], J. A. GORDON[2];
[1]Neurobio. and Behavior, [2]Psychiatry, [3]Neurosci., Columbia Univ., New York, NY; [4]Neurosci., Barnard Col., New York, NY

Abstract: Anxiety states are distinguished by an increase in theta-frequency (4-12 Hz) synchrony in the amygdala-hippocampal-prefrontal circuit. Recently, we demonstrated that optogenetically inhibiting the ventral hippocampal (vHPC) input to the medial prefrontal cortex (mPFC) decreases anxiety-like behavior and theta synchrony between the mPFC and vHPC, without affecting other frequencies (Padilla-Coreano et al., *Neuron,* 2016). These data suggest the hypothesis that theta-frequency input from the vHPC plays a causal role in anxiety-like behavior. We therefore asked whether stimulating the vHPC-mPFC at a theta frequency was sufficient to increase avoidance behavior in the elevated plus maze, and whether any such effects might be frequency- and/or pattern-specific. CamKIIa-hChR2-eYFP was expressed bilaterally in the vHPC and optical fibers implanted in the mPFC. In a subset of mice, single-unit recording electrodes were also implanted in the mPFC. Stimulating the vHPC-mPFC pathway with a sinusoidal light pattern at 8 Hz significantly increased avoidance behavior, while stimulating with brief pulses of light at 8 Hz or sinusoidal light at 20 Hz had no effect. These experiments demonstrate that the anxiogenic effect of vHPC terminal stimulation is frequency- (8 Hz but not 20 Hz) and pattern- (sinusoids but not pulses) specific. This result was surprising, as pulses of light are the most common light pattern used to stimulate neurons and terminals optogenetically. To understand how pulses and sinusoidal light modulate mPFC neurons differentially, mPFC pyramidal neurons were recorded both *in vitro* and *in vivo* while stimulating vHPC terminals with the same sinusoidal or pulsatile patterns. *In vitro*, sinusoidal stimulation increased the rate of spontaneous EPSCs, while pulses evoked strong, time-locked EPSCs. Additionally, sinusoidal light resulted in an increase in theta-frequency subthreshold fluctuations in membrane potential in mPFC neurons. *In vivo*, sinusoidal stimulation of vHPC terminals increased the phase-locking of mPFC single units to the optical stimulation pattern without changing overall firing rates. These results suggest that sinusoidal stimulation at 8 Hz increases spontaneous activity in a rhythmic, naturalistic manner that enhances theta-frequency activity in mPFC neurons as well as anxiety-related behavior. Moreover, they suggest that theta-frequency components of neural activity play a privileged role in vHPC-mPFC communication and hippocampal-dependent forms of anxiety.

Disclosures: **N. Padilla Coreano:** None. **S. Canetta:** None. **W.D. Hardin:** None. **R. Warren:** None. **D.R. Blackman:** None. **C. Kellendonk:** None. **J.A. Gordon:** None.

Poster

833. Functional Mechanisms of Attention

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 833.01/HHH20

Topic: H.01. Animal Cognition and Behavior

Support: NEI R01EY022062

Title: Cognitive ERPs in behaving monkeys: spatial attention to the heading direction

Authors: *C. LOCKWOOD, W. VAUGHN, C. DUFFY;
Univ. of Rochester, Rochester, NY

Abstract: Spatial attention continually modulates posterior cortical visual processing. These effects are thought to reflect the reciprocal activation of bottom-up and top-down cortical signals that shape visual processing to better accommodate the demands of ongoing behavior. Posterior cortical responses to visual stimuli propagate anteriorly to activate frontal cortical attentional centers. These centers, in turn, generate reciprocal signals that alter the subsequent posterior cortical activity that guides behavior.
We have previously used an exogenously cued attentional re-orientation task while recording human ERPs to examine the attentional modulation of optic flow responses. Those responses show shifts of lateralized cortical activity with attentional re-orientation from a contralateral cued spatial location to the side of the task relevant focus-of-expansion (FOE) in optic flow.
We have now trained two Rhesus monkeys to maintain centered visual fixation during the same exogenously cued attentional re-orientation task. Left or right sided flashed spots preceded left or right optic flow FOEs. Thereafter, the monkey pressed a button corresponding to the side of the optic flow FOE. In 75% of the trials, the flashed cued was on the same side as the subsequent FOE; a validly cued trial. In 25% of the trials the flashed cue was on the opposite side of the subsequent FOE; invalidly cued trials. As in humans, validly cued trials yield faster RTs than invalidly cued trials.
Optic flow evoked sensory and cognitive ERPs potentials were recorded from 32 intracranially implanted electrodes. The exogenous cueing of optic flow evoked a series of ERP components. A posterior-lateral positive response peaking around 200 ms after optic flow onset and corresponding to a human N200. This is followed by a posterior positive component peaking approximately 500 ms after optic flow onset and corresponding to a human P300. These components are separated by an intervening negative response potentially corresponding to a human N2b.
As in humans, we find the lateralization of differences between valid and invalid waveforms in the N2b interval corresponding to what we have called a human N2VI. Lateralization depended on the interval between the flashed cue and optic flow onset with short intervals yielding N2VIs that were absent in long intervals. We conclude that exogenous cueing of monkey optic flow responses yields a pattern of attentional modulation of posterior cortical activity similar to that seen in humans.

Disclosures: **C. Lockwood:** None. **W. Vaughn:** None. **C. Duffy:** None.

Poster

833. Functional Mechanisms of Attention

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 833.02/HHH21

Topic: H.01. Animal Cognition and Behavior

Support: NIH Grant DA09082

NIH Grant F31MH105211

Title: Attenuated μ-opioid receptor function in female rat locus coeruleus

Authors: *H. M. GUAJARDO[1], A. HO[2], R. J. VALENTINO[3,2];
[1]Neurosci. Grad. Group, Univ. of Pennsylvania, Philadelphia, PA; [2]The Univ. of Pennsylvania, Philadelphia, PA; [3]CHILDREN'S HOSPITAL OF PHILADELPHIA, Philadelphia, PA

Abstract: Stress-related neuropsychiatric pathologies are nearly two times higher in females compared to males. An important component of the stress response is corticotropin releasing factor (CRF)-mediated activation of the locus coeruleus (LC)-norepinephrine system. Evidence suggests that endogenous opioid neuropeptides released during stress provide an inhibitory influence on LC activity that restrains CRF activation and facilitates a return to baseline activity when the stressor terminates. Loss of this inhibition could increase stress vulnerability. We previously demonstrated that female rat LC neurons are less sensitive to inhibition by the μ-opioid receptor (MOR) agonist, DAMGO and western blot analysis suggested that this is due to decreased MOR protein in the female rat LC. The present study determined whether these sex differences translated to sex differences in LC-MOR mRNA and in the behavioral consequences of MOR activation in the LC. Quantitative PCR analysis showed decreased levels of LC-MOR transcripts in females compared to males $F(1,26)=4.87$, $p<0.05$ (n=14/group). To compare the behavioral consequences of activating MOR in the LC the effects of vehicle and DAMGO (3 or 10 pg, intra-LC) on performance in an operant strategy set shifting task that measures simple discrimination (SD), reversal learning and strategy shifting (SHIFT) were tested. Two-way rmANOVA revealed a main effect ($F (5, 46) =5.3$, $p<0.0006$), a dose effect ($F (2, 46) =11.4$, $p<0.001$), a stage effect ($F (2, 45) =46.5$, $p<0.0001$), a dose*stage interaction ($F (4, 90) =6.9$, $p<0.001$) and a trend for dose*stage*sex interaction ($F (4, 90) =2.4$, $p=0.055$). For SD there was a trend for a sex*dose interaction where [3 and 10 pg] DAMGO facilitated performance in male rats when compared to ACSF ($p=0.051$). DAMGO (10 pg) impaired SHIFT performance of male rats only (main effect: $F(5,51)=6.03$, $p<0.0002$); $p<0.05$, Tukey HSD). Analysis of error type revealed that DAMGO (10 pg) increased perseverative errors in female rats ($p <0.05$, Tukey HSD), whereas it increased regressive and random errors in male rats ($p<0.05$, Tukey HSD, both error types). Together, the results are consistent with previous evidence for decreased MOR function in the LC of female compared to male rats. They provide additional molecular evidence

for decreased MOR expression in the female LC that translates to attenuated behavioral consequences of MOR activation. The relatively decreased MOR function in female LC could contribute to greater stress-induced activation of this system and increased vulnerability of females to arousal-related symptoms of psychiatric disorders.

Disclosures: H.M. Guajardo: None. **A. Ho:** None. **R.J. Valentino:** None.

Poster

833. Functional Mechanisms of Attention

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 833.03/HHH22

Topic: H.01. Animal Cognition and Behavior

Support: NIH Grant AG050518

William & Mary Charles Center Honors Fellowship

Title: Effects of protein kinase C activation on attention deficits following loss of corticopetal cholinergic neurons

Authors: *C. S. LEONG, E. B. MANESS, D. I. BARAKI, J. A. BURK;
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Abstract: Alzheimer's disease (AD) is a neurodegenerative dementia characterized by memory loss, cognitive impairment, and attention deficits. Damage to corticopetal cholinergic neurons originating in the basal forebrain is thought to contribute to the attention deficits. Recent evidence had identified G-protein decoupling at the M1 muscarinic acetylcholine receptor as well as decreased levels of protein kinase C (PKC) in rat AD models and the human AD brain. PKC is a signaling kinase that can affect neurite outgrowth, synaptic formation, and neurotransmitter release. PKC activation additionally may affect voltage-gated calcium currents. Previous research in this lab has shown that inhibition of PKC by chelerythrine chloride decreased signal detection in a sustained attention task. The present experiment evaluates the effect of PKC activation on sustained attention following loss of cortical cholinergic projections induced by infusions of 192 IgG-saporin into the basal forebrain. Male and female Sprague-Dawley rats were trained to discriminate between signals (illumination of a central panel light) and nonsignals (no panel light illumination) in a two-lever sustained attention task. Each rat received intraventricular infusions of the PKC activator bryostatin-1 (0, 0.5, 2.0, and 4.0pM) prior to testing. In the middle block of trials, a flashing houselight distracter was included to increase attentional demands. Compared to sham-lesioned animals, lesioned animals showed

poorer signal detection in the distracter block of the task, but no differential effects of lesion on nonsignal trials. Distracter scores (initial block of trials with no distracter - distracter block) were calculated for each behavioral measure. For signal detection, there was a dose × group interaction ($F(3,30) = 3.069$, $p = 0.043$). Bryostatin-1 attenuated signal detection deficits in lesioned animals. Sham-treated animals showed decreased performance with increased bryostatin-1 dosage. Following the highest bryostatin-1 dose, there were no difference in signal detection between the sham and lesioned animals. The present results support the hypothesis that Bryostatin-1 can improve performance in a visual attention task following damage to corticopetal cholinergic neurons.

Disclosures: **C.S. Leong:** None. **E.B. Maness:** None. **D.I. Baraki:** None. **J.A. Burk:** None.

Poster

833. Functional Mechanisms of Attention

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 833.04/HHH23

Topic: H.01. Animal Cognition and Behavior

Support: NIDCR DE022746

Title: BOLD signal amplitude, not functional connectivity, differentiates the awake from anesthetized brain.

Authors: *M. E. GHANTOUS[1,2];
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Abstract: Generally, the conscious brain has been characterized as one that has more integrated information, and has been studied on the bases of functional connectivity patterns. However, neural variability has been shown to distinguish conscious from unconscious brain states, suggesting variability also plays an important role in how the conscious brain integrates information. Here we study variability of global functional connectivity and local fMRI signal during both conscious and anesthesia-induced unconscious states in the rat, to determine which features of variability best distinguish conscious states of the brain. Resting state fMRI was recorded in 32 awake rats and 59 rats under isoflurane anesthesia. Rat brains were segmented into 76 ROIs using a standard rodent atlas; the blood-oxygen level dependent (BOLD) time series were subsequently extracted from each of the ROIs. We calculated both static and dynamic sliding window, functional connectivity between these ROIs by generating correlation matrices using Fisher's z Pearson correlation coefficients, and extracted overall global functional

connectivity strength and temporal variability. We also calculated static and dynamic standard deviation of local BOLD signal to assess local variability. We compared these measures in awake and anesthetized rats to determine which features of variability best distinguished conscious states.
Consistently, we saw a decrease in local BOLD signal variability when the rats were unconscious. BOLD signal variability in anesthetized rats = 25.7 +/- 4.9 and in awake rat = 53.8 +/- 8.8. Spatial distribution of local BOLD variability, while evenly dampened during anesthesia, remained highly similar to awake brains, with a correlation of $r \sim 0.6$. Functional connectivity (both static and dynamic), on the other hand, did not consistently distinguish conscious brain states across data sets. Surprisingly, many anesthetized rats displayed higher connectivity strength and variability than their awake counterparts. Overall, our results suggest that 1) anesthesia-induced unconscious brain activity can remain strongly synchronized, and 2) local BOLD variability will be the better indicator of the conscious state. While most previous studies have focused on integration of information in terms of dynamic and static functional connectivity strength, our results point to the importance of more local neural variability in differentiating a conscious brain from one under anesthesia. Funded by NIDCR DE022746

Disclosures: M.E. Ghantous: None.

Poster

833. Functional Mechanisms of Attention

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 833.05/HHH24

Topic: H.01. Animal Cognition and Behavior

Support: EU-FP7 #607616

Title: Investigating the role of the receptor tyrosine kinase ErbB4 in attention and impulsivity in mice.

Authors: *E. MARCHISELLA[1], E. REMMELINK[1], B. KOOPMANS[1], R. VAN DER LOO[1], R. WIJNANDS[1], A. B. SMIT[2], S. SPIJKER[2], M. LOOS[1];
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Abstract: Schizophrenia is a complex neurodevelopmental disease caused by genetic and environmental factors. It is characterized by a constellation of heterogeneous symptoms including deficits in executive functions, such as impaired attention and inhibitory control. Post-mortem studies of schizophrenia patients have pointed out deficits in GABAergic synaptic transmission due to reduced synapse numbers made by parvalbumin (PV) expressing

interneurons in the cerebral cortex. These interneurons particularly express the receptor tyrosine kinase ErbB4 that regulates different aspects of their maturation and function. Genetic studies have linked ErbB4 to schizophrenia, thus it has been hypothesized that abnormal ErbB4 signaling can alter neuronal function and may contribute to the cognitive deficits observed in schizophrenia. Here, we investigated the role of ErbB4 in the medial prefrontal cortex (mPFC) in attention and inhibitory control in the 5-choice serial reaction time task (5CSRTT) and several other behavioral tests relevant to schizophrenia in mice. We used *ErbB4*$^{-/-}$ mice with a constitutive loss of ErbB4 throughout the brain during development and adulthood. Our results showed that constitutive loss of *ErbB4* in mice did not affect attention and inhibitory control, even though *ErbB4*$^{-/-}$ mice did recapitulate other behavioral phenotypes associated with schizophrenia, such as poor sensorimotor gating. Because our previous research using acute manipulation of ErbB receptors has shown to affect attentional performance (Loos et al., 2016), we are currently investigating the role of prefrontal PV^+ interneurons in attention in the automated 5CSRTT using Designer Receptors Exclusively Activated by Designer Drugs (DREADDs) in Parv-Cre mice. Preliminary data suggest that PV^+ interneurons in the mPFC are important to executive function and that acute manipulation of ErbB4 signaling in the mPFC presents an interesting pharmacological target for restoring cognitive function in schizophrenia.

Disclosures: **E. Marchisella:** None. **E. Remmelink:** None. **B. Koopmans:** None. **R. van der loo:** None. **R. Wijnands:** None. **A.B. Smit:** None. **S. Spijker:** None. **M. Loos:** None.

Poster

833. Functional Mechanisms of Attention

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 833.06/HHH25

Topic: H.01. Animal Cognition and Behavior

Support: PO1DA031656

MH086530

Title: Sign-tracking as an index of poor cholinergic-attentional control extends to complex motor performance and is associated with attenuated choline transporter function

Authors: *M. SARTER[1], A. KOSHY CHERIAN[2], V. PARIKH[3], P. VALUSKOVA[2], B. YEGLA[3], A. KUCINSKI[2];
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Abstract: Some rats (sign-trackers; STs) are especially prone to attribute incentive motivational value to reward cues, relative to others (goal-trackers; GTs), and this, along with other factors, may influence the propensity to relapse in addiction (e.g., Robinson et al., 2014). We previously demonstrated that poor attentional control, as indicated by relatively low and highly variable performance of an operant sustained attention task, is a component of the psychological trait indexed by sign-tracking. Furthermore, attention-associated cortical cholinergic activity was severely attenuated in STs (Paolone et al, 2013). Here we asked whether the relatively poor attentional control of STs extends to their ability to deploy attentional resources for supporting complex movements. STs and GTs were tested on the Michigan Complex Motor Control Task (MCMCT) that assesses the attentional control of gait, posture control and complex movement (Kucinski et al, 2013). Compared to GTs, STs committed more slips and fell more frequently while traversing rotating rods, particularly when the rotating direction was changed to a less familiar direction. Furthermore, the presentation of a distractor caused more falls in STs. Secondly, we asked whether the relatively low cholinergic activity in STs is associated with attenuated choline transporter (CHT) function, as CHT capacity limits the upregulation of cholinergic activity. Brains were harvested immediately following the animals' last MCMCT trial. MCMCT performance did not increase frontal cortical CHT-mediated choline uptake in either group but, in STs, choline uptake regressed below levels seen in non-performing STs. Next, we sought to determine if more robust stimulation conditions would reveal further abnormalities in cholinergic function in STs by assessing the effects of basal forebrain electrical stimulation (Parikh et al., 2013). Stimulation failed to increase choline uptake levels above those seen in nonstimulated control STs, whereas in GTs uptake was significantly elevated. Furthermore, total CHT levels were significantly lower in STs and, at baseline, the ratio of synaptosomal to intracellular CHT density in STs was 1, contrasting with the expected ratio of 0.2 to 0.3 observed in GT. Thus, in STs, CHT distribution suggests abnormally upregulated CHT function at baseline that is associated with a limited capacity for further CHT mobilization and increases in cholinergic activity. Together, these results suggest that dysregulation of CHT distribution and mobilization account for the cholinergic-attentional deficits of STs.

Disclosures: **M. Sarter:** None. **A. Koshy Cherian:** None. **V. Parikh:** None. **P. Valuskova:** None. **B. Yegla:** None. **A. Kucinski:** None.

Poster

833. Functional Mechanisms of Attention

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 833.07/HHH26

Topic: H.01. Animal Cognition and Behavior

Support: Australian Research Council DP140103184

Title: Frequency tags in virtual reality: studying the neuronal mechanisms of visual selective attention in *Drosophila melanogaster*

Authors: *M. J. GRABOWSKA, B. VAN SWINDEREN;
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Abstract: Insects such as fruit flies show a remarkable number of behaviours that are comparable in their complexity to behaviours observed in higher mammals, such as experience-dependent decision-making, suggesting that similar brain processes are likely to be involved. The wide range of genetic tools that *Drosophila melanogaster* provides makes the fly an ideal model organism for studying the neuronal underpinnings of these processes, such as selective attention and operant learning. The central complex (CC), a region in the central brain of insects, has been increasingly implicated in the control of higher order behaviours and decision-making. Based on its function and circuitry, the CC has been hypothesized to be a homologue of the mammalian basal ganglia (Strausfeld and Hirth 2013, Science). Furthermore, the proposed function of the CC as an integrative centre for attention-like behaviour is supported by several *Drosophila* studies that investigate visual responsiveness and learning. We studied neuronal correlates of visual selective attention in the CC, in particular neural activity associated with the ellipsoid body (EB), a neuropil in the CC which was recently shown to be associated with orientation and path integration (Seelig and Jayaraman 2015, Nature). In our study, we applied a novel behavioural paradigm that provides insight into fly visual preferences as well as visual learning and selective attention (Van de Poll et al. 2015, Journal of experimental Biology), and we combined it with electrophysiology in the EB. Tethered, walking flies in a closed-loop environment were presented with competing visual stimuli that flickered with different frequencies, in a virtual reality LED arena. In this way the fly was able to control the position of the competing stimuli relative to its frontal visual field. As a neuronal readout for the distinct stimuli we examined the power of competing 'frequency tags' in various structures of the CC, by analysing local field potentials and performing spike-sorting analyses. Depending on the position of the stimulus relative to the frontal visual field of the fly, we observed an increase in power within the narrow frequency domains corresponding to the flicker frequency of selected visual stimuli, as well as cross-modulations of these frequencies in the EB specifically. Our results provide a better understanding of how visual information is integrated in the CC during complex behavioural choice tasks, and supports our view that the EB is involved in visual selective attention in addition to being involved in visual orientation and motor control.

Disclosures: **M.J. Grabowska:** None. **B. van Swinderen:** None.

Poster

833. Functional Mechanisms of Attention

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 833.08/HHH27

Topic: H.01. Animal Cognition and Behavior

Support: Innovative Medicine Initiative Joint Undertaking under grant agreement n°115008 of which resources are composed of EFPIA in-kind contribution and financial contribution from the European Union's Seventh Framework Programme (FP7/2007-2013)

Biotechnology and Biological Sciences Research Council Doctoral Training Partnerships

Title: Pharmacological manipulation of the cholinergic system for cognitive enhancement in young healthy rats

Authors: *B. FISHER[1,2], A. C. MAR[3], L. M. SAKSIDA[2], T. J. BUSSEY[2], T. W. ROBBINS[2]; [1]Dept. of Psychology, Univ. of Cambridge, Cambridge, United Kingdom; [2]Wellcome Trust and MRC Behavioural and Clin. Neurosci. Inst., Cambridge, United Kingdom; [3]New York Univ. Med. Ctr., New York, NY

Abstract: Rationale: Targeting of the cholinergic system for cognitive enhancement in young healthy subjects is of interest for the development of pro-cognitive enhancer drugs. Further research is required to establish the neuropharmacological and behavioural mechanisms underlying the putative cognitive enhancing effects of the acetylcholinesterase inhibitor donepezil in this population.
Method: The current experiments investigated the effects of donepezil (0-1 mg/kg, i.p.) in young healthy rats on the 5-Choice Serial Reaction Time Task (5-CSRTT) which measures spatial divided attention for visual detection, and on the novel touchscreen based rodent Continuous Performance Task (rCPT) which measures sustained focused attention for both visual detection and identification. The ability of the non-selective nicotinic receptor antagonist, mecamylamine (1mg/kg, i.p.), pretreatment to modulate the effects of donepezil (1mg/kg, i.p.) was also investigated. Drug manipulations were tested under conditions of decreasing stimulus durations to tax attention.
Results: Donepezil-induced enhancements in cognitive performance (% accuracy) on the 5-CSRTT were observed reliably only in the context of mecamylamine impairment. By contrast, on the rCPT, donepezil alone showed a linear trend for enhanced performance (increased hit rate and d'prime) in a dose-dependent related manner during the longest stimulus duration. Enhancements in rCPT task performance (decreased false alarm rate) following donepezil administration were also observed in the context of mecamylamine pretreatment, which itself had no effect on rCPT performance *per se*.

Discussion: These findings suggest that donepezil may enhance aspects of attention in young healthy subjects as measured on the rCPT, whilst enhancing impaired subjects in the case of the 5-CSRTT. These findings highlight the potential of the novel touchscreen-based rCPT task as a promising sensitive and translational behavioural tool for assessing enhancements of cognition in young healthy subjects.

Disclosures: B. Fisher: None. **A.C. Mar:** None. **L.M. Saksida:** F. Consulting Fees (e.g., advisory boards); Campden Instruments. **T.J. Bussey:** F. Consulting Fees (e.g., advisory boards); Campden Instruments. **T.W. Robbins:** B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution; Lilly, Lundbeck, GSK. F. Consulting Fees (e.g., advisory boards); Cambridge Cognition, Lilly, Lundbeck, Teva, Shire Pharmaceuticals and Merck, Sharp and Dohme.

Poster

833. Functional Mechanisms of Attention

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 833.09/HHH28

Topic: H.01. Animal Cognition and Behavior

Title: Pattern of anatomical connectivity between the midbrain lateral tegmental nucleus and the superior colliculus in the mouse.

Authors: *W.-K. YOU[1], S. P. MYSORE[2];
[1]Neurosci., The Johns Hopkins Univ., Baltimore, MD; [2]Psychological and Brain Sci., Johns Hopkins Univ., Baltimore, MD

Abstract: The periparabigeminal lateral tegmental nucleus, called pLTN, is a collection of GABAergic neurons in the mammalian midbrain tegmentum. Conserved across vertebrate species, this nucleus is called the isthmi pars magnocellularis (Imc) in birds and reptiles. Recent work in birds has highlighted a critical role for the Imc in the competitive selection of the most important stimulus across space. Notably, this function is subserved by its specialized pattern of anatomical connectivity with the midbrain sensorimotor hub, the optic tectum (OT, avian analog of the mammalian superior colluiculus, SC). Imc neurons receive focal input from the OT, but send long-range inhibition back broadly across the OT space map. Here, with dye and viral injection methods combined with anatomical tracing, we examine the pattern of connectivity between the pLTN and key midbrain areas in the mouse. Understanding the structure of the pLTN circuit in this genetically tractable model is an important starting point for examining its functional contribution to competitive stimulus selection in mammals.

Disclosures: **W. You:** None. **S.P. Mysore:** None.

Poster

833. Functional Mechanisms of Attention

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 833.10/HHH29

Topic: H.01. Animal Cognition and Behavior

Title: Combinatorial inhibition for efficient location-invariant stimulus selection.

Authors: ***N. R. MAHAJAN**, S. P. MYSORE;
Johns Hopkins Univ., Baltimore, MD

Abstract: Stimulus selection, the selection of the most important stimulus in the environment, must operate independently of the relative as well as absolute locations of the competing stimuli. In other words, stimulus selection must be location-invariant. In this study, we examine the neural underpinnings of location-invariant selection. The superior colliculus (SC), a midbrain sensorimotor hub, is known to play a crucial role in competitive stimulus selection for spatial attention. In turn, a GABAergic nucleus in the midbrain tegmentum, called the isthmi pars magnocellularis (Imc) in birds, has been shown to be necessary for generating the long-range competitive inhibition that underlies stimulus selection in the optic tectum (OT; avian analog of the SC). Here, using extracellular recordings in the barn owl midbrain, we show that the Imc uses a special combinatorial inhibition strategy to implement location invariant stimulus selection in the OT space map. Additionally, with computational modeling, we show that this strategy constitutes an optimal neural implementation. These findings reveal new insights into how fundamental neural computations for stimulus selection are achieved by neural circuits.

Disclosures: **N.R. Mahajan:** None. **S.P. Mysore:** None.

Poster

833. Functional Mechanisms of Attention

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 833.11/HHH30

Topic: H.01. Animal Cognition and Behavior

Support: NIDA Grant PO1 DA031656

Title: Cholinergic-dependent shifts to cue-directed behavior

Authors: *K. B. PHILLIPS, M. SARTER;
Psychology, Univ. of Michigan, Ann Arbor, MI

Abstract: Successful cue detection requires cortical cholinergic signaling. Recent evidence has elucidated the role of phasic, short-timescale, regionally-specific cholinergic signals, termed "cholinergic transients", in cue detection. Cholinergic transients in the right prefrontal cortex were exclusively observed in trials in which cues were detected ***and*** when such trials followed non-cued trials yielding correct rejections or falsely perceived non-cued trials (cues that were missed). Thus, these cholinergic transients were interpreted as mediating shifts from performance guided by internally-guided attention to cued-directed behavior (Howe et al., 2013). In contrast to cholinergic transients mediating shift-hits, such transients were not observed during consecutive hits. Transients may be actively suppressed during consecutive hits in order to constrain a potential detection bias and maintain behavioral flexibility (Sarter et al., 2015). Here we removed cholinergic innervation to the right prefrontal cortex in rats to test the hypothesis that the right hemispheric cortical cholinergic projection system is necessary for shift-hits. Rats were trained on a sustained attention task (SAT) consisting of a random sequence of signal trials and non-signal trials, both requiring a distinct lever response from the subject. Following stable task performance, half of the subjects received right unilateral cholino-selective lesions of the basal forebrain by infusions of the immunotoxin 192 IgG-saporin, while the remaining subjects received sham surgeries. Rats were then familiarized with performing a modified version of SAT which consisted of engineered trial sequences to provide an "aggressive" test of the hypothesis based on the performance of pre-defined trials. In particular, the modified SAT included long strings of non-cued trials that were followed by a cued trial, with lesioned animals expected to miss specifically that latter trial. Conversely, neither hits during long strings of cued trials, nor correct rejections during non-cued trials that followed long strings of consecutive hits were expected to be affected by the lesion. Results indicate that right cholinergic losses selectively impair shift-hits. These findings are consistent with recent results from our optogenetic studies showing that cortical cholinergic transients are necessary and sufficient for the detection of cues (Gritton et al., 2016) and they extend these findings by specifying that in the absence of cortical cholinergic activity, subjects remain arrested in a state of perceptual or intrinsic attention.

Disclosures: K.B. Phillips: None. **M. Sarter:** None.

Poster

833. Functional Mechanisms of Attention

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 833.12/HHH31

Topic: H.01. Animal Cognition and Behavior

Title: Context-specific activity in Caudate Nucleus during a covert attention task

Authors: *F. ARCIZET[1], R. J. KRAUZLIS[2];
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Abstract: The mechanisms for spatial attention are not restricted to cortical areas, but also extend to subcortical circuits, including the superior colliculus, thalamus and the basal ganglia. Last year, we showed that neurons in the caudate nucleus, a major input structure of the basal ganglia, show cue-related modulation during a covert attention task and response-related activity that depends on the sensory context. Here we present additional results supporting the interpretation that caudate neurons are part of a mapping function between sensory signals and action selection. Two rhesus macaques started the motion-change detection task by fixating a central spot and pressing down a joystick. After 250 ms of fixation, a spatial cue was flashed for 200 ms at a peripheral location (~12 deg eccentric), indicating the spatial location he should monitor. Next, two motion patches were presented. In some trials, the cued motion patch changed direction slightly, and the animal had to release the joystick within 1000 ms to get rewarded. In other trials, the motion change occurred at the non-cued location, and the animal was rewarded for not releasing the joystick. We focused our analysis on 77 phasically active neurons (PANs) recorded in the head and body of the caudate nucleus that showed a phasic response after the motion change. The phasic activity was strongly dependent on the context in which the joystick was released. For most neurons, response-related activity was significantly elevated from baseline when the joystick was correctly released on “hits” (76/77 neurons) or mistakenly released on “false alarms” (35/68 neurons). However, many fewer neurons showed significant response-related activity when the joystick was released at the end of “correct rejects” to initiate the next trial (47/72 neurons), and most showed significantly lower activity for “correct rejects” than “hits” (63/72 neurons). In contrast, the phasic activity was not strongly dependent on which hand was used to control the joystick. For a subset of caudate neurons (n=20), we directly compared phasic activity between blocks of trials using the right and left hands; for most neurons (12/20), the phasic activity did not depend on which hand controlled the action. Together, these results clarify how caudate PANs contribute to the performance of covert attention tasks. The context-specific activity is consistent with the idea that the caudate is not only important for action selection, but also for identifying the sensory and behavioral context associated with the action.

Disclosures: **F. Arcizet:** None. **R.J. Krauzlis:** None.

Poster

833. Functional Mechanisms of Attention

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 833.13/HHH32

Topic: H.01. Animal Cognition and Behavior

Support: PHS Grant MH104800

Title: Immediate early gene response in the medial prefrontal cortex does not vary under conditions of context and object novelty

Authors: ***Q. CHANG**, M. STEINFELD, A. W. KUSNECOV;
Psychology, Rutgers Univ., Piscataway, NJ

Abstract: The study of neural mechanisms underlying novelty detection is relevant to studies on attention and memory. Here, we investigated the behavior of male C57BL/6J mice under different conditions of object and context novelty. Further, after exposure to novelty, the number of c-Fos-positive cells in the prelimbic (Prl) and infralimbic (IL) regions of the medial PFC were determined, since they have been associated with responses to novel contexts. In particular, we compare exposure to specific objects, with spatial attributes of context minimized through habituation. As such, this study controls for the more prominent procedure of placing home cage (HC) animals into a novel context for the first time, which is ultimately a strong stressor. Mice were divided into five groups designated Fam/Fam, Fam/Nov, App/Nov, HC/App, and HC/HC. There were N=6/gp, except F/F and F/N (N=12). On Days 1-9 animals received either nothing (HC/HC) or 10 mins object and/or context habituation, which involved exposure to an open field that was either empty (App/Nov group) or contained an object in the center (F/F and F/N groups). The object was either a golf ball or similar size metal tube, and this was counterbalanced. On Day 10, the HC/App group was placed in the open field (with an object) for the first time, and the other groups were returned to the open field and given the same object (F/F gp), a different object (F/N gp), or an object (golf ball or metal) for the first time (App/N gp). The HC/HC group remained in the home cage as previously. Behavior on all days was measured using Any-Maze tracking software and revealed obvious detection of object novelty. That is, the F/N group had significantly ($p < 0.05$) higher novel object approach and contact than the F/F group exposed to the same object as on Days 1-9. Surprisingly, the App/N group showed lowest object contact, and spent significantly less time near the object than the HC/App group. A general linear regression model suggested that this was due to a higher anxiety-like level. Immunohistochemical staining (IHC) for c-Fos in the Prl and IL PFC showed that relative to the

HC/HC animals, all other groups had significantly greater numbers of c-Fos positive cells. Surprisingly, there were no differences in Fos numbers between any of the behaviorally tested groups (i.e. F/F = F/N = App/N = HC/App). Although the behavioral data suggests different cognitive strategies in each group on the test day, this appears to be dissociated from the Prl and IL c-Fos data. Additional c-Fos counts are being conducted on hippocampal, hypothalamic, striatal and amygdaloid regions to determine differences in regions that provide input to the medial PFC.

Disclosures: **Q. Chang:** None. **M. Steinfeld:** None. **A.W. Kusnecov:** None.

Poster

833. Functional Mechanisms of Attention

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 833.14/HHH33

Topic: H.01. Animal Cognition and Behavior

Support: National Research, Development and Innovation Office, K 109790

ERC-2011-ADG-294313-SERRACO

National Brain Program of Hungary

Title: Dynamics of theta oscillation during multiple components of exploration

Authors: ***A. M. BARTH**, A. DOMONKOS, T. F. FREUND, V. VIKTOR;
Inst. of Exptl. Medicine, HAS, Budapest, Hungary

Abstract: Exploration of novel environments is a complex behavior vital for survival. It is composed of a multitude of elementary actions each tuned for information seeking. The encoding of newly acquired spatial information is centered in the hippocampal formation that is dominated by the highly regular theta rhythm during the reckoning of unexplored places. Theta may provide the temporal metric for the coding mechanism. Many reports uncovered positive correlation between running, one component of exploration, and the frequency and power of theta. However, activity pattern in the coding circuitry during other major components of exploratory behavior i.e. rearing and poking is totally unknown despite their indispensable role in mapping new environments. Rearing is found in many mammals and notably, it is widely used as an indicator of exploratory behavior in pharmacological studies.In this study we aimed to uncover hippocampal activity during rearing behavior. We deployed a fast (120 FPS) multi-camera motion capture system for tracking animals' head positions at high spatio-temporal resolution. Hippocampal activity was sampled by high channel count silicone probes. In our experimental

arrangement the mice were allowed to freely explore an open field arena and rearing events were detected offline.Based on the 3 dimensional head positional data we decomposed exploration into multiple components including running and rearing. Unexpectedly, we detected the highest theta frequency and power during rearing events with peak values even surpassing high speed running. Moreover, the onset of the gradual frequency elevation preceded the onset of head lifting and started to decrease by the time the head reached its highest position. The end of a rearing episode was marked by a significant drop of theta power.To examine whether frequency increment is specific to the head elevation we also investigated the electrophysiological signature when the animal pokes into a hole drilled into the floor of the arena. We found similar pattern and dynamics of theta frequency and power. Our data uncovers that the multiple components of exploration can be separated not only behaviorally but also electrophysiologically and may be generated by distinct mechanisms.

Disclosures: **A.M. Barth:** None. **A. Domonkos:** None. **T.F. Freund:** None. **V. Viktor:** None.

Poster

833. Functional Mechanisms of Attention

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 833.15/HHH34

Topic: H.01. Animal Cognition and Behavior

Support: NIH Grant 050518

Title: Effects of N-desmethylclozapine on attentional performance following loss of basal forebrain corticopetal cholinergic inputs

Authors: *E. B.-L. MANESS, C. S. LEONG, J. A. BURK;
Psychology, Col. of William and Mary, Williamsburg, VA

Abstract: Corticopetal cholinergic neurons play a vital role in attentional processing, and dysregulation of this system contributes to central nervous system disorders whose main attributes include an inability to engage in sustained attention, such as Alzheimer's disease. The cholinergic muscarinic-1 (M1) receptor is known to be necessary for normal attentional processing. In general, there has been a trend towards supporting drugs that provide allosteric agonism of cholinergic receptors as an approach that may yield greater benefits than drugs that act at orthosteric receptor sites. There exists contention in the literature regarding the action of N-desmethylclozapine (NDMC), a partial M1-preferring agonist, that is thought to act at an allosteric site on the M1 receptor. The goal of the present experiment is to further evaluate NDMC's activity at these sites in a lesion model of cholinergic dysfunction using an operant task

assessing attentional capacity. After training in an attention-demanding task requiring differentiation between signal trials (500, 100, and 25ms illumination of a central panel light) and non-signal trials (no light illumination), Sprague Dawley rats received intrabasalis infusions of either saline or the cholinergic neurotoxin 192 IgG-saporin, and attentional performance was later measured following intracerebroventricular infusions of NDMC. In general, NDMC impaired attentional performance, particularly for lesioned animals. These findings suggest that NDMC may functionally decrease acetylcholine stimulation of M1 receptors or that the actions of NDMC at other receptor sites disrupt any beneficial effects of NDMC at the M1 receptor.

Disclosures: E.B. Maness: None. **C.S. Leong:** None. **J.A. Burk:** None.

Poster

833. Functional Mechanisms of Attention

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 833.16/HHH35

Topic: H.01. Animal Cognition and Behavior

Support: NIH Grant MH086530

Title: Choline transport in peripheral lymphocytes as a proxy for brain cholinergic capacity

Authors: *A. KOSHY CHERIAN[1], V. PARIKH[2], Q. WU[3], Y. MAO-DRAAYER[3], R. BLAKELY[4], M. SARTER[1];
[1]Dept. of Psychology, Univ. of Michigan, Ann Arbor, MI; [2]Psychology and Neurosci., Temple Univ., Philadelphia, PA; [3]Neurol., Univ. of Michigan Med. Sch., Ann Arbor, MI; [4]Biomed. Sci., Florida Atlantic Univ., Jupiter, FL

Abstract: The synaptic uptake of choline via the high-affinity, hemicholinium-3-dependent (HC-3) choline transporter (CHT) strongly influences the capacity of cholinergic neurons to sustain elevated levels of acetylcholine synthesis and release. Generally, sub- and overcapacity variations of CHT capacity, imposed by genetic manipulation of the CHT or present in populations, are hypothesized to bias subjects toward bottom-up (low CHT capacity) versus top-down (high CHT capacity) attentional control. For example, we have previously demonstrated relatively low cholinergic-attentional capacities in heterozygous CHT mice (Parikh et al., 2013, Paolone et al., 2013). We also reported that humans expressing a sub-capacity variant of the CHT (I89V SNP) are highly distractible and do not show the right frontal activation seen in wild type humans performing a demanding attention task (Berry et al., 2014, 2015). Recently, we observed variations in CHT capacity in rats screened for a psychological trait ("sign-tracking") that involves low attentional control and that may be also present in humans (Sarter et al., this

meeting). To advance research on the impact of CHT capacity in humans, we searched for a measure of CHT function in humans. Based on previous evidence indicating the presence of several cholinergic markers in T-cells, here we first demonstrated the presence of the neuronal CHT in human lymphocytes. Next, we developed an assay to measure CHT-mediated choline transport in human T-cells and found that compared with choline uptake by synaptosomes, a significantly higher proportion of human T-cell choline uptake is blocked by HC-3 (95% in T cells versus 68% in mouse cortical synaptosomes). To further demonstrate the validity of using choline uptake in T-cells as a proxy for brain CHT capacity, we isolated T-cells from the spleen and synaptosomes from the cortex of CHT-overexpressing mice (CHT-OXP; Holmstrand et al., 2014) that are capable of sustaining relatively high levels of cholinergic activity and are resistant to attentional distractors. Comparable with the elevated CHT capacity in cortical synaptosomes from CHT-OXP mice, choline uptake capacity in their T-cells was two-fold higher than in wild type mice. Thus, this lymphocyte-based measure of CHT capacity serves as a proxy for synaptosomal CHT function and brain cholinergic capacity. We will employ this measure to index cholinergic capacity in human populations with and without defined genetic CHT variants and to test the hypothesis that cholinergic capacity is associated with a bias toward bottom-up versus top-down attention.

Disclosures: **A. Koshy Cherian:** None. **V. Parikh:** None. **Q. Wu:** None. **Y. Mao-Draayer:** None. **R. Blakely:** None. **M. Sarter:** None.

Poster

833. Functional Mechanisms of Attention

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 833.17/HHH36

Topic: H.01. Animal Cognition and Behavior

Title: Pharmacosynthetic inhibition of the rat subthalamic nucleus impairs attentional set-formation

Authors: ***S. S. DHAWAN**, D. S. TAIT, V. J. BROWN;
Univ. of St Andrews, St Andrews, United Kingdom

Abstract: Dysregulation of the subthalamic nucleus (STN) as a result of Parkinson's disease yields characteristic motor symptoms – treatment of which by deep-brain stimulation ameliorates gross motor impairments, yet may impair cognition. We have previously reported that rats with cell body lesions of the STN do not form attentional set in the intradimensional/extradimensional (ID/ED) attentional set-shifting task (ASST).
The rodent ID/ED ASST presents a series of two-choice discriminations, using stimuli differing

between two perceptual dimensions – odor and/or digging medium – only one of which is relevant for each discrimination. Two stages with novel stimuli (ID and ED) provide an index of set-shifting ability. To explore how STN inactivation (STN_{in}) might block set-formation we modified the ASST by adding an additional four ID stages, delayed reversals, a 'probe' stage, and a bi-conditional (bi-con) stage. If, instead of reducing their attention to the irrelevant dimension, STN_{in} rats learn configurally, then a probe stage, where only the irrelevant dimension stimuli change, should disrupt performance relative to control rats. If STN_{in} rats fail to form set because novel stimuli cause current information to be discarded, then an intermediate stage between novel learning and a reversal should lead to the reversal being treated as novel. Finally, the bi-con stage, where reward is contingent on one stimulus from each dimension (i.e. if odor A, then medium B), should favor configural learning over having an attentional set.
18 male Lister hooded rats received 0.5µl AAV5-CaMKIIa-hM4D(Gi)-mCherry viral vector, bilaterally into the STN. Inhibitory designer receptors selectively silenced transfected cells only after administration of the designer drug, clozapine *N*-oxide (CNO). Prior to behavioral testing, rats were either treated with CNO (10mg/kg, ip; n= 9) or saline (n=9).
When CNO-treated, rats required more trials than when saline-treated to complete the probe stage; failed to demonstrate a cost of shifting set at the ED stage; and required fewer trials at the bi-con stage. Analysis of response errors at the delayed reversal stages indicated that the rats do remember prior learning. These data confirm that rats with STN_{in} do not form an attentional set, and instead solve the discriminations using configural learning. We therefore conclude that an active STN is crucial to the formation of attentional-set, allowing the extrapolation of dimensional information from configural stimuli.

Disclosures: **S.S. Dhawan:** None. **D.S. Tait:** None. **V.J. Brown:** None.

Poster

833. Functional Mechanisms of Attention

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 833.18/HHH37

Topic: H.01. Animal Cognition and Behavior

Title: Inhibition of prelimbic cortex glutamatergic signalling induces deficits in attentional set-shifting

Authors: *A. J. WHYTE, D. S. TAIT, E. M. BOWMAN, V. J. BROWN;
Univ. of St Andrews, St Andrews, United Kingdom

Abstract: The intradimensional/extradimensional (ID/ED) attentional set-shifting task (ASST) measures behavioral flexibility, and as it is translatable between humans and rats, it is used in

rodent models to gain insight into the mechanisms underlying executive dysfunction in human disorders such as schizophrenia. The ID/ED ASST measures executive function through a series of two-choice discriminations. Key measures in the task includes performance at the reversal stages and the ED stage, in which the subject shifts responding to a previously irrelevant dimension. We have previously reported that ibotenic acid lesions of rat prelimbic cortex (PL) induce deficits at the ED shift stage. Here, we further those findings by showing that temporary inhibition of the PL induces the same deficit and provide evidence for the underlying mechanisms.

Adult male Lister Hooded rats (Charles River; n = 12) received AAV5-CamKII-hM4Di microinjections into the PL. After recovery, the rats were tested twice on the ID/ED ASST either 30 minutes following injection of clozapine *N*-oxide (CNO; 10 mg/kg, ip) to inhibit PL glutamatergic neurons, or a saline injection. Half the rats received CNO in the first test, and the other half received CNO in the second test. PL-inhibited (PL_{in}) rats exhibited a robust increase in the number of trials to criterion (TTC) solely at the ED stage, consistent with previous findings after PL lesions.

We then tested the rats in a variant of the ID/ED ASST. The 4-stage task consisted of a simple discrimination, a compound discrimination, a reversal stage, and an ED. During the reversal stage each stimulus within the relevant dimension was paired with only one stimulus from the irrelevant dimension (i.e. only two compound stimuli were used). At the ED stage the now-correct stimulus was the stimulus from the previously irrelevant dimension that had been paired with the previously-correct stimulus in the reversal stage. PL_{in}-rats acquired this ED in fewer TTC than controls.

We interpret these findings as arising from a weakening of down-regulation of attention to redundant cues in PL_{in}-rats. This manifests as a set-shifting impairment in the standard ID/ED ASST, because PL_{in}-rats are unable to down-regulate attention to a previously attended dimension. However, it improves ED shift performance when the previously-irrelevant dimension, hence unattended by control rats but salient to the PL_{in}-rats, in fact provides information about the correct ED stimulus.

Disclosures: **A.J. Whyte:** None. **D.S. Tait:** None. **E.M. Bowman:** None. **V.J. Brown:** None.

Poster

833. Functional Mechanisms of Attention

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 833.19/HHH38

Topic: H.01. Animal Cognition and Behavior

Support: NARSAD Young Investigator Grant from the Brain & Behavior Research Foundation (JC)

Connecticut State University Research Grant (JC)

Title: Sleep loss impairs attention and memory performance in the object recognition task

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Abstract: The object recognition task is widely used to test cognition in rodent models of CNS disorders. The task procedure consists of an acquisition phase (familiarization), a delay, and a test phase (novel object recognition). First, a mouse is simultaneously presented with two identical objects to allow for familiarization by object investigation. Subsequently, when both a familiar and a novel object are presented, time spent investigating the novel object typically increases. Sleep deprivation (SD) *after* familiarization has been shown to impair novel object recognition, an effect thought to reflect interference with memory consolidation. Importantly, attention in humans and rodents is also impaired by sleep deprivation. We therefore applied SD *before* the object recognition task, to investigate the impact on both attention and memory. Mice were sleep deprived for 12h during the inactive period immediately preceding testing. SD was induced using a slow but continuously rotating bar which mice stepped over to ensure >95% wakefulness, as assessed using electroencephalography. SD prior to the object recognition task significantly reduced the amount of time spent per object investigation and the time to reach criterion level of investigation, during object familiarization. We interpret these data to indicate that sleep deprived mice had an impaired ability to attend to objects. Subsequent preference to spend time investigating novel objects, an index for object recognition memory, was significantly impaired. Thus, attention deficits introduced by sleep loss may have also contributed to memory impairment. To begin to investigate mechanisms of attention impairment, we used optogenetics to selectively stimulate basal forebrain GABA neurons thought to mediate cortical rhythms associated with cognition. ArchT-mediated inhibition of GABA neurons during familiarization impaired object recognition, similar to mice experiencing SD. These neurons may be necessary to the attention and memory processes impaired by sleep loss, which we show is a good model for investigating the cognitive dysfunction observed in mental illness.

Disclosures: H. Rosenblatt: None. **J. Kry:** None. **K. McNally:** None. **J. Cordeira:** None.

Poster

833. Functional Mechanisms of Attention

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 833.20/HHH39

Topic: H.01. Animal Cognition and Behavior

Support: NIMH Silvio Conte Center 1P50MH094271

Japan Society for the Promotion of Science

The Uehara Memorial Foundation

Title: Lynx1 dampens arousal and attention in adult mice

Authors: *Y. MAKINO[1], R. REH[1], A. COVELLO[1], W. STAGNARO[1], T. K. HENSCH[1,2]; [1]Dept. of Mol. and Cell. Biol., Harvard Univ., Cambridge, MA; [2]Dept. of Neurol., Boston Children's Hosp., Boston, MA

Abstract: Cholinergic transmission underlies a variety of essential brain functions, such as arousal, attention, learning and memory. However, endogenous molecules which fine-tune the activity of acetylcholine receptors in a cell-type-specific manner to control these functions remain largely unknown. The prototoxin Lynx1 binds to nicotinic acetylcholine receptors (nAChRs) and dampens their activity (Miwa et al, 1999). It is reportedly enriched in certain inhibitory neurons (Morishita et al., 2010; Demars & Morishita, 2014), suggesting a circuit basis for cholinergic modulation of cortical activity. Here, we directly examined arousal and attention in Lynx1 knockout (KO) mice. First, we performed EEG recordings and found that KO mice display a fragmented sleep pattern, while total sleep amount remained unchanged. Moreover, these mice displayed reduced sleep rebound after a short (4hr) sleep deprivation, indicating a reduced sleep need as in the *Drosophila* homolog SLEEPLESS. Consistent with this, Lynx1KO mice demonstrated enhanced attentional behavior on a touchscreen-based two-choice visual attention task, while task learning and motivation were normal. Attentional enhancement in Lynx1KO mice was abolished by systemic blockade of α7-nAChRs but not of α4/β2-nAChRs, highlighting a specific role for Lynx1 inhibition of α7-nAChRs in attention regulation. In parallel, Lynx1KO mice showed enhanced cognitive flexibility in a shape discrimination/reversal task, possibly reflecting higher attentiveness to the stimulus-response associations. These results suggest that Lynx1 might serve as an endogenous regulator of nAChR activity in inhibitory neurons to attain optimal levels of arousal and attention, subserving adult brain function and cognitive behavior.

Disclosures: **Y. Makino:** None. **R. Reh:** None. **A. Covello:** None. **W. Stagnaro:** None. **T.K. Hensch:** None.

Poster

833. Functional Mechanisms of Attention

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 833.21/HHH40

Topic: H.01. Animal Cognition and Behavior

Support: National Science Centre Grant 2011/01/D/NZ4/04958

Title: dopamine transporter in reversal learning & attention.

Authors: *A. CYBULSKA[1], J. DABROWSKA[1,3], S. NIEDZIELEC[3,2], R. ZAKRZEWSKA[2]; [1]Nencki Inst., Warszawa, Poland; [2]Nencki Inst., Warsaw, Poland; [3]Cardinal Stefan Wyszynski Univ. in Warsaw, Warsaw, Poland

Abstract: Executive function of attention is regulated by dopaminergic (DA) system. Dopamine transporter (DAT), regulating DA neurotransmission, likely plays a role in controlling the influence of DA in cognitive processes. We examined the role of DAT in attention. Mice with DAT gene genetically deleted (DAT+/- heterozygotes) were compared with the wild type (WT) mice in Attentionl Set-Shifting Task (ASST), where attentional set-shifting, associative and reversal learning were tested. DAT level in the striatum of mice was compared using DAT immunohistochemistry. Neuronal activity during ASST was visualized with the egr-1 and egr-2 immunohistochemistry and with 2-deoxyglucoes (2DG) autoradiography in orbitofrontal (OFC) cortex and dorsomedial striatum (DSM). Heterozygotes did not differ behaviorally from WT mice in ASST sub-tests that measure associative learning. However, they were significantly impaired in reversal learning and attentional set-shifting, i.e. processes requiring executive control. Significant differences in expression of egr-1 and egr-2 immunoreactivity between WT and DAT+/- mice were observed in OFC and DMS in several ASST subtests. 2DG labeling intensity was significantly lower in DAT mutant mice during the reversal learning in the ASST. Results of egr-1 and egr-2 immunohistochemistry and 2DG autoradiography suggests deficient neuronal activation of areas associated with attentional functions and reversal learning, during performance of attentional tasks, in mice with reduced DAT protein level.

Disclosures: **A. Cybulska:** None. **J. Dabrowska:** None. **S. Niedzielec:** None. **R. Zakrzewska:** None.

Poster

833. Functional Mechanisms of Attention

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 833.22/III1

Topic: H.01. Animal Cognition and Behavior

Title: Dissociable effects of D1 partial agonists and positive allosteric modulators on prefrontal excitability, neurotransmitter release, and cognitive performance

Authors: *D. YOUNG, A. ROSSI, S. GEE, P. TIERNEY, G. BEKHEET, L. ZHANG, W. HOWE, R. KOZAK;
Pfizer Inc, Cambridge, MA

Abstract: Dopaminergic D1-type receptors play a crucial role in modulating executive functions through their actions in the prefrontal cortex (PFC), and have long been a target for putative cognition enhancers. In addition to canonical agonists and partial agonists (PA) for this receptor subtype, recent years have seen an increased interest in the potential of positive allosteric modulators (PAM) of D1 receptors as a means of modulating neural circuitry relative to cognitive function while preserving the temporal fidelity of endogenous neurotransmitter release. In the present set of experiments, we set out to directly compare and contrast the effects of a D1 PA (SKF 38393) with a D1 PAM on neural excitability and neurotransmitter release in the prefrontal cortex, as well as performance in an operant test of attention (sustained attention task; SAT). At the level of neural excitability, in vitro application of the D1 PA agonist SKF 38393 increased PFC layer 5 pyramidal cell spiking in response to an injection of a depolarizing current (n=5). The D1 PAM was found to similarly potentiate pyramidal cell excitability when administered in conjunction with a sub-threshold amount of dopamine (200 nM, n=2). Using choline- and glutamate-sensitive biosensors, we next assayed the capacity of systemically administered SKF 38393 (0.56 mg/kg) and the D1 PAM (17.8 mg/kg) to modulate acetylcholine and glutamate release in vivo in anesthetized rats. Specifically, we looked at the capacity of the two compounds to modulate a glutamate-acetylcholine (ACh) interaction mediated by nicotinic receptors that is central to attentional function. We found that neither compound significantly altered the amplitude of glutamate and ACh release evoked by local nicotinic receptor stimulation (n=4 for both ACh and glutamate). However, the two compounds had dissociable effects on the decay rate of evoked ACh release, with the D1 PAM being associated with faster clearance. In line with previous studies showing that compounds that preserve fast ACh release events benefit attentional performance (Howe et al., 2010), the D1 PAM also appeared to modestly improve the recovery of performance in the SAT following distraction in a dose-dependent manner (n=15; 0, 3.2, 10, 17.8 mg/kg). Follow-up studies will directly assess the effect of SKF 38393 on performance in the SAT. Our combined results demonstrate that the capacity of putative cognition enhancers to modulate neurotransmitter release evoked by specific

circuit interactions can predict performance efficacy, and suggest that D1 PAMs may offer an attractive alternative to canonical D1 PAs for the modulation of attention.

Disclosures: **D. Young:** A. Employment/Salary (full or part-time): Pfizer Inc. **A. Rossi:** A. Employment/Salary (full or part-time): Pfizer Inc. **S. Gee:** A. Employment/Salary (full or part-time): Pfizer Inc. **P. Tierney:** A. Employment/Salary (full or part-time): Pfizer Inc. **G. Bekheet:** A. Employment/Salary (full or part-time): Pfizer Inc. **L. Zhang:** A. Employment/Salary (full or part-time): Pfizer Inc. **W. Howe:** A. Employment/Salary (full or part-time): Pfizer Inc. **R. Kozak:** A. Employment/Salary (full or part-time): Pfizer Inc.

Poster

833. Functional Mechanisms of Attention

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 833.23/III2

Topic: H.01. Animal Cognition and Behavior

Support: NIH DA R01 027222

Title: Comparison of acute and chronic effects of methylphenidate on the locus coeruleus and ventral tegmental area

Authors: T. KARIM, C. REYES-VASQUEZ, *N. DAFNY;
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Abstract: Methylphenidate (MPD), also known as Ritalin, is a psychostimulant used to treat attention hyperactivity disorder. However, it is increasingly being misused by normal adolescents and young adults for recreation and academic advantage. The neurophysiological mechanism of action and behavioral effects of MPD treatment are not fully understood. It is important to elucidate the activity of MPD in normal subjects in order to optimize disorder treatment and prevent adverse long-term effects in patients. MPD inhibits the reuptake of norepinephrine (NE) and dopamine (DA) into presynaptic terminals in the central nervous system (CNS). The locus coeruleus (LC) and the ventral tegmental area (VTA) are the main sources of NE and DA within the CNS, respectively. The LC and VTA normally mediate attention, response habits, and drug reward and pleasure behaviors. Selective neuronal connections between the LC and VTA have been identified implicating interdependence between the structures. The objective of this study was to compare the dynamics of neuronal activity within the LC and VTA of adolescent rats using an acute and chronic MPD dose response protocol. Freely behaving animals were implanted with permanent electrodes in the LC and VTA. Each subject was administered either saline, 0.6, 2.5, or 10.0 MPD mg/kg on experimental

days 1-6. This period was followed by 3 days of washout and MPD re-challenge on experimental day 10. Changes in locomotor activity after chronic MPD exposure were used to separate the animals into groups exhibiting either behavioral tolerance or behavioral sensitization. The neuronal activity recorded from each group was evaluated separately. 94, 98, and 94% of LC units responded significantly to chronic doses of 0.6, 2.5, or 10.0 mg/kg MPD, respectively. Similarly, 91, 98, and 100% of VTA units exhibited significant changes in neuronal activity to the same chronic doses of MPD, respectively. Acute MPD elicited excitation in most LC and VTA units. The majority of LC units recorded from subjects exhibiting behavioral sensitization displayed further increased neuronal response after MPD re-challenge demonstrating neurophysiological sensitization. The majority of LC units recorded from subjects exhibiting behavioral tolerance displayed attenuation of neuronal response after MPD re-challenge indicating neurophysiological tolerance. The responses from VTA units expressed a different pattern. The activity of the LC and VTA units indicates that the mechanism of action of MPD is more dynamic than previously thought, a characteristic that physicians must consider during treatment.

Disclosures: **T. Karim:** None. **C. Reyes-Vasquez:** None. **N. Dafny:** B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution; NIH DA R01 027222.

Poster

834. Cognition: Corticostriatal Circuits

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 834.01/III3

Topic: H.01. Animal Cognition and Behavior

Support: FCT-MCTES doctoral grants SFRH/BD/52445/2013

Sainsbury Wellcome Centre

Champalimaud Foundation

Title: The role of cortex in dynamic interactive environments, a “Videogame” for rats

Authors: *L. CALCATERRA[1,3], G. LOPES[3], J. NOGUEIRA[3], J. FRAZÃO[3], A. KAMPFF[2,3]; [1]Kampff Lab., [2]Sainsbury Wellcome Ctr., London, United Kingdom; [3]Champalimaud Neurosci. Programme, Champalimaud Ctr. for the Unknown, Lisbon, Portugal

Abstract: An organism's behaviour is a continuous stream of actions and reactions to the changing demands of its complex and unpredictable environment. We are able to approximate a naturalistic level of complexity with a closed-loop back projection setup that engages rats in complex visual motor tasks, i.e. "videogames". Using a dynamic data stream processing tool developed in our laboratory we can precisely control a large variety of parameters in the environment relative to the animal's behaviour, generating a rich dataset for quantitative analysis. We were then interested in exploring and characterizing the role of cortex in "playing" the different "videogames". Thus far we have focused our attention on the dorsal portion of the cerebral cortex spanning frontal, motor, somatosensory, parietal and visual cortex (FMSPV cortex). We trained Long Evans rats on a foraging ("Pac-Man") task in which spots of lights, at unpredictable positions, must be collected to earn rewards. Rats quickly learned the rules of this game, reaching asymptotic performance within one week. We then performed bilateral FMSPV thermocoagulatory lesions. Lesioned rats, compared to shams, did not show any major impairments in "Pac Man" as they could learn and perform the task both having experienced it before lesion or when naïve. We are now designing new levels of complexity to further challenge rats (and cortex) in a variety of tasks and dynamic environments containing both physical and augmented reality elements. We will then implant transcortical (multi-shank) silicon probes for distributed recording across FMSPV and simultaneously monitor every layer of many different cortical areas during the behaviour. Finally, we will also perform full decortications to better assess the fundamental role of cortex in "videogames" of increasing difficulty.

Disclosures: L. Calcaterra: None. **G. Lopes:** None. **J. Nogueira:** None. **J. Frazão:** None. **A. Kampff:** None.

Poster

834. Cognition: Corticostriatal Circuits

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 834.02/III4

Topic: H.01. Animal Cognition and Behavior

Support: Veteran Affairs

CRC-15-04-KIST

NIMH R01 MH039683

NHLBI HL095491

NINDS R21 NS093000

Korea NRF 2015R1D1A1A01059119

TM received partial salary compensation and funding from Merck MISP, but has no conflict of interest with this work

Title: Cortically projecting basal forebrain parvalbumin positive neurons regulate top-down processing in mice

Authors: *J. CHOI[1], H. EUNJIN[1], B. KIM[1], H. HAN[1], R. BROWN[2], R. MCCARLEY[2], J. T. MCKENNA[2], T. KIM[3];
[1]Korea Inst. of Sci. and Tech. (KIST), Seoul, Korea, Republic of; [2]Harvard Med. Sch., Brockton, MA; [3]Kyunghee Med. Hosp., Seoul, Korea, Republic of

Abstract: Particular behaviors are associated with different spatio-temporal patterns of cortical EEG oscillations. A recent study (Kim et al., 2015 PNAS) suggests that cortically-projecting parvalbumin-positive (PV+) inhibitory neurons in the basal forebrain (BF) play an important role in 40 Hz gamma oscillations in cortex. However, the cortical regions impacted by BF PV+ neurons and their functional consequences are not clearly understood. In this study, we investigated the topographic and dynamic characteristics of cortical oscillations induced by optogenetic stimulation of BF PV+ neuron with or without auditory stimulation at 40 Hz. The responses across the cortex were recorded by extracranial high density EEG (Choi et al., 2010 J Neurophysiol). Optogenetic stimulation of BF PV+ neurons via expression of ChR2 in BF PV neurons in PV-Cre mice, led to a significant increase of 40 Hz oscillations preferentially in prefrontal cortex and the connectivity within prefrontal/frontal cortex increased statistically significantly. Next, the auditory steady state responses (ASSR) were analyzed at various time delays between optogenetic and sound stimulation. The preferential increase of prefrontal/frontal gamma oscillations evoked by BF PV+ neuronal stimulation was maintained under simultaneous sound stimulation at 40 Hz, however the dynamic pattern was different for different time delays between light and sound stimulation. For example, compared to sound-only stimulation, the gamma oscillation in the prefrontal cortex had a maximal and sharp response when the BF PV+ neurons were excited 6.25 ms ($\pi/2$) earlier than the sound, whereas the anti-phasic stimulation (12.5 ms, π) blunted the auditory-steady state responses (ASSR) in the prefrontal cortex. The influence of BF PV+ neurons on ASSR was confirmed by inhibiting BF PV+ neurons by expressing the inhibitory light-sensitive proton pump, ArchT, in BF PV neurons in PV-cre mice: A continuous inhibition of BF PV+ neurons during sound stimulation decreased ASSR statistically significantly, and interestingly the decrease of ASSR was described as a function of time delay between inhibition of BF PV+ neuron and sound. These results imply that BF PV+ neurons participate in regulating top-down influence that the frontal cortex exerts on primary sensory cortices, and supports the idea that the modulating activity of BF PV+ neurons might be a potential target for restoring top-down cognitive functions as well as abnormal frontal gamma oscillations associated psychiatric disorders.

Disclosures: **J. Choi:** None. **H. Eunjin:** None. **B. Kim:** None. **H. Han:** None. **R. Brown:** None. **R. McCarley:** None. **J.T. McKenna:** A. Employment/Salary (full or part-time): Merck MISP. B. Contracted Research/Research Grant (principal investigator for a drug study,

collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution; Merck MISP. C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Merck MISP. **T. Kim:** None.

Poster

834. Cognition: Corticostriatal Circuits

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 834.03/III5

Topic: H.01. Animal Cognition and Behavior

Support: Division of Life Science Recruitment and Retention Fund

NIH Grant NS050465

NIH Grant DA024635

Title: Fructose effects on body weight, food consumption, and striatal dopamine DRD2 and BDNF gene expression

Authors: *A. IZQUIERDO[1], Y. ZOKEN[1], M. GARCIA[1], T. TRUONG[1], E. E. HART[1], A. STOLYAROVA[1], A. B. THOMPSON[1], Z. YING[2], F. GÓMEZ-PINILLA[2,3];
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Abstract: Fructose is a dietary compound that may play an active role in the development of cardiovascular disease, obesity, and metabolic irregularities. Sweeter than both glucose and sucrose, it is used as an added sweetener and is consumed in large quantities in the U.S. By one estimation fructose accounts for approximately 10% of Americans' daily calories, with consumption highest in adolescents (Vos et al. 2008). In experimental animals, there is an emerging connection between fructose and cognition. For example, there is now evidence of decreased hippocampal plasticity and reduced hippocampal neurogenesis after long-term consumption. These neural adaptations co-occur with deficits in spatial learning and episodic memory (Cisternas et al., 2015). Since fructose is hedonically rewarding, it engages mesolimbic dopamine signaling and may promote adaptations in key reward areas upon heavy consumption. Consumption of the compound may impact plasticity in the striatum. Of particular interest may be its effect on striatal dopamine D2 receptors and brain-derived neurotrophic factor (BDNF). These molecular endpoints converge on their putative involvement in addiction, metabolic energy, and synaptic plasticity. In the present investigation, the effects of 3-week fructose

consumption on body weight, food consumption, and *Drd2* and *Bdnf* gene expression were assessed in male Long-Evans rats (n=16). Rats were randomly assigned to receive either 15% fructose in their water (as the only source of liquid) or plain water in their homecage. During this 3-week period, animals were monitored daily for liquid and chow consumption, and body weight. The two groups did not differ significantly in body weight. Fructose rats, however, exhibited consistently lower levels of food consumption than their water-drinking counterparts but consumed more liquid overall, resulting in equivalent caloric intake. Following the 3-week consumption period, rats were euthanized 24 h following removal of fructose and their brains examined for striatal *Drd2* and *Bdnf* gene expression. We found that fructose animals expressed significantly greater *Drd2* compared to water-drinking animals (+70%), but control-level *Bdnf* expression. These findings suggest that learning and behavior dependent on the striatum and modulated by dopamine D2 may be impacted after prolonged fructose, including but not limited to, control over consumption.

Disclosures: **A. Izquierdo:** None. **Y. Zoken:** None. **M. Garcia:** None. **T. Truong:** None. **E.E. Hart:** None. **A. Stolyarova:** None. **A.B. Thompson:** None. **Z. Ying:** None. **F. Gómez-Pinilla:** None.

Poster

834. Cognition: Corticostriatal Circuits

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 834.04/III6

Topic: H.01. Animal Cognition and Behavior

Support: NIH Grant MH081843

NIH Grant MH102211

NIH Grant MH107140

NIH Grant GM001507

Title: Cognitive actions of corticotropin-releasing factor (CRF) across distinct prefrontal cortex (PFC)-dependent cognitive processes

Authors: *S. HUPALO[1], C. W. BERRIDGE[2];
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Abstract: The prefrontal cortex (PFC) regulates cognitive processes critical for flexible, goal-directed behavior. Dysfunction of PFC-dependent cognition is associated with a variety of

psychopathologies, including ADHD. Although it has long been known that corticotropin-releasing factor (CRF) and CRF receptors are present in the PFC, the cognitive actions of CRF signaling in the PFC remain largely unknown.
To test the hypothesis that CRF modulates PFC-dependent cognition, we first examined the effects of intracerebroventricular (ICV; 0.1, 0.2, 1 μg) CRF on performance of rats in two tasks highly dependent on the PFC: 1) a spatial delayed-response test of working memory (t-maze) and 2) an operant-based signal detection test of sustained attention. In both tasks, ICV infusions of CRF elicited robust and dose-dependent impairments in performance.
We then examined whether CRF acts within the PFC to modulate these PFC-dependent cognitive processes. As seen with ICV administration, intra-PFC infusions of CRF (25, 50, 100, 250 ng/hemisphere) impaired working memory performance. This action was topographically organized, such that working memory impairment was only observed with CRF infusion into the caudal aspect of the dorsomedial PFC (dmPFC). However, in contrast to that seen with working memory, CRF infusions (25, 50, 250 ng/hemisphere) into either the caudal or rostral dmPFC had no effect on sustained attention.
Subsequent studies investigated the degree to which *endogenous* CRF signaling modulates PFC-dependent cognition using the CRF antagonist, D-Phe-CRF. Both ICV (2, 4, 10 μg) and intra-dmPFC (50, 200 ng/hemisphere) infusions of this antagonist dose-dependently improved working memory performance. ICV infusion of this antagonist similarly elicited dose-dependent improvement in sustained attention.
Collectively, these observations indicate that CRF modulation of multiple PFC-dependent cognitive processes involves differing neurocircuitry, with working memory involving CRF receptor signaling within the PFC. This research provides novel insight into the neurobiology of PFC-dependent cognition and may have relevance for treating psychopathologies associated with PFC dysfunction. For example, FDA approved treatments for ADHD improve performance in tasks of working memory and sustained attention in rodents and humans. Given a CRF antagonist also improves PFC-dependent cognition, this may represent a novel pharmacological approach for the treatment of ADHD and other disorders associated with PFC-dependent cognitive dysfunction.

Disclosures: **S. Hupalo:** None. **C.W. Berridge:** None.

Poster

834. Cognition: Corticostriatal Circuits

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 834.05/III7

Topic: H.01. Animal Cognition and Behavior

Support: NIH Grant DA037421

Title: Differential modulation of glutamate dynamics in the dorsal striatum and nucleus accumbens during nicotine withdrawal

Authors: *M. ZIMMERMAN, R. D. COLE, V. PARIKH;
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Abstract: Disruption in cognitive processes are hypothesized to contribute to compulsive nicotine use and to increased relapse rates among smokers. We previously found that mecamylamine-precipitated nicotine withdrawal impaired strategy shifting in mice. The frontostriatal circuits subserve executive functions including cognitive control and decision-making processes. Because glutamatergic efferents from the prefrontal cortex (PFC) targeting discrete striatal regions such as the dorsal striatum (DS) and nucleus accumbens (NAc) are important components of these circuits, nicotine withdrawal-related cognitive deficits may be linked to perturbations in glutamate signaling. In the present study, we assessed the effects of nicotine withdrawal on striatal glutamate dynamics using in vivo amperometric recordings. Male C57BL/6J mice received either chronic nicotine (18mg/kg/d) or saline via mini-osmotic pumps for 14 days. Spontaneous nicotine withdrawal was induced by pump removal and glutamate recordings were conducted from the DS and NAc using enzyme-based biosensors from anesthetized mice 24-72 hours later. Changes in extracellular glutamate levels were monitored following the local application of potassium, nicotine and brain-derived neurotrophic factor (BDNF), a modulator of synaptic plasticity. We uncovered that glutamate responses to potassium depolarization dramatically increased in both DS and NAc in nicotine withdrawal mice as compared to the control mice. However, nicotine-evoked glutamate signal amplitudes were found to be higher only in DS but not NAc of withdrawal mice. Interestingly, glutamate declined significantly in the DS of withdrawal animals following BDNF application as compared to the saline group ($p<0.01$). On the contrary, BDNF-induced glutamate release significantly increased in the NAc during nicotine withdrawal. Although the capacity of striatal synapses to release glutamate in response to a depolarization stimulus increased in both DS and NAc during nicotine withdrawal, changes in nicotine-evoked glutamate release patterns may indicate alterations in the functional status of different nicotinic receptors between the two regions. As BDNF modulates cognitive and affective processes, it is possible that differential alterations in glutamate responsiveness to BDNF in the DS and NAc may produce neuroadaptive changes in discrete frontostriatal circuits leading to withdrawal-related deficits in cognitive control processes and induction of anxiety-/depression-like states. How PFC regulation of striatal glutamate signaling contributes to behavioral changes during nicotine withdrawal remains to be explored.

Disclosures: **M. Zimmerman:** None. **R.D. Cole:** None. **V. Parikh:** None.

Poster

834. Cognition: Corticostriatal Circuits

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 834.06/III8

Topic: H.01. Animal Cognition and Behavior

Support: National Sciences and Engineering Research Council (Canada)

Title: Behavioral characterization of female zinc-transporter 3 (ZnT3) knockout mice

Authors: *S. THACKRAY, B. B. MCALLISTER, R. H. DYCK;
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Abstract: The divalent metal zinc is required for proper function of all cells in the body. A proportion of zinc in the brain can be loaded into synaptic vesicles by zinc-transporter 3 (ZnT3) and released into the synapse where it can act on various receptors or enter the postsynaptic cells. High amounts of synaptic zinc are found in the hippocampus, cerebral cortex, and striatum. There are many human diseases/disorders that have zinc dyshomeostasis associated with them; several of which are more prevalent in females than in males including depression and Alzheimer's disease. In addition, the human gene coding for ZnT3 has been associated with high occurrence of schizophrenia in females but not males. Also, estrogen is a negative modulator of ZnT3 and may provide a mechanism for sex-specific effects. ZnT3 knockout (KO) mice that lack synaptic zinc were first created in 1999. Most of the research on these mice to date has focused on male mice or has grouped both sexes together without undertaking sex-specific analyses. The objective of our research was to examine the behavior of female ZnT3 KO mice and compare it with previous findings in male ZnT3 KO mice. Two-three month old female ZnT3 KO and wildtype (WT) mice were examined on three behavioural test batteries. The first consisted of 7 motor tasks to assess the role of synaptic zinc in the motor system. A second battery had 6 tests examining social behavior, anxiety, sensory function, and learning and memory. The third test battery included the Morris water task (MWT) and fear conditioning. Female KO mice were significantly faster to descend a vertical pole. Previous testing of combined male and female KO mice found no significant difference in time to descend. Female KO mice also had a slower locomotor speed in the open field test. While open field behaviour has been examined in male KO mice, locomotor speed was not reported; no differences were found in distance traveled for either sex. Male KO mice have been found deficient on reversal learning in the MWT and on a weak fear conditioning protocol. Our testing found no deficiencies on these tasks in female KO mice compared to WT mice. Consistent with previous findings in males or combined sexes, KO mice performed similarly to WT on prepulse inhibition and forced swim tests. In summary, while male and female ZnT3 KO mice exhibit some similarities on certain behavioral tests, each sex

has a unique behavioural phenotype. This highlights the importance of examining both sexes during behavioral testing.

Disclosures: **S. Thackray:** None. **B.B. McAllister:** None. **R.H. Dyck:** None.

Poster

834. Cognition: Corticostriatal Circuits

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 834.07/III9

Topic: H.01. Animal Cognition and Behavior

Support: NIDA R01 DA013951

NIDA T32 DA007288

Title: "Binge-like" exposure to toluene during adolescence produces alterations in the excitability of mPFC neurons that are sub-region and projection specific.

Authors: ***W. N. WAYMAN**, J. J. WOODWARD;
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Abstract: Inhalants are often one of the first drugs of abuse tried by adolescents. Similar to other drugs of abuse, inhalants, including toluene, are capable of modifying brain reward circuitry such as the medial prefrontal cortex (mPFC) and nucleus accumbens (NAc). Studies conducted in rodents have shown that exposure to toluene vapor *in vivo* increases extracellular DA in the PFC and NAc and even a single exposure to toluene causes alterations in synaptic plasticity that can persist for weeks after exposure. The mPFC is involved in the execution and inhibition of goal-directed/reward-motivated behaviors with the dorsal/prelimbic (PRL) sub-division thought to primarily control the execution of reward-motivated behaviors and the ventral/infralimbic (IL) region having a role in inhibiting these behaviors although these subdivisions are not absolute. This dichotomy has been studied in the context of cocaine, methamphetamine, and ecstasy, and these drug effects are differentially modulated by PRL and IL projections to the NAc based on projection-specific connections. In this study, we hypothesized that "binge-like" toluene exposure would alter the activity of mPFC neurons in a projection specific manner. To address this question, we used whole-cell electrophysiology to assess the intrinsic excitability of PRL and IL pyramidal neurons in adolescent rats previously exposed to air or toluene vapor (5700 PPM). Prior to exposure, fluorescent retrobeads were injected into the NAc core (NAcc) or shell (NAcs) sub-regions in order to identify projection specific mPFC neurons. In toluene treated adolescent rats, NAcc projecting PRL layer 5 (PRL5) neurons exhibited suppressed firing rates

that were associated with an increased rheobase, increased ½ spike duration, increased inward rectification, reduced membrane resistance, and a reduced I_h amplitude. These alterations were not observed in PRL layer 2/3 (PRL2/3) neurons. In contrast NAcc projecting IL layer 5 (IL5) and layer 2/3 (IL2/3) neurons showed enhanced firing in toluene-exposed animals and in IL5 neurons, this effect was associated with a reduction in rheobase. For NAcs projecting neurons, firing rates of IL5 neurons were significantly decreased following toluene exposure and were associated with an increased rheobase and reduced I_h amplitude. Intrinsic excitability of NAcs projecting PRL5, PRL2/3, and IL2/3 neurons were not affected by a single exposure to toluene. These findings demonstrate that specific projections of the reward circuitry are uniquely susceptible to the effects of toluene during adolescence supporting the idea that adolescence is a critical period in the development of drug abuse.

Disclosures: W.N. Wayman: None. **J.J. Woodward:** None.

Poster

834. Cognition: Corticostriatal Circuits

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 834.08/III10

Topic: H.01. Animal Cognition and Behavior

Support: NIDA R01 DA013951

CRAN supplement to NIAAA T32 AA007474

Title: Persistent cognitive and neuroplastic alterations following repeated exposure of adolescent rats to the psychoactive inhalant toluene

Authors: *K. M. BRAUNSCHEIDEL, J. T. GASS, P. J. MULHOLLAND, J. J. WOODWARD;
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Abstract: When intentionally inhaled, the volatile solvent toluene causes neurological and behavioral effects that are similar to those produced by classic drugs of abuse. Although inhalant use is especially high among adolescents, the consequences of solvent exposure during this critical developmental time period are not well known. Identifying behavioral and anatomical abnormalities induced by adolescent toluene exposure in rodent models is necessary in order to guide addiction relapse prevention in humans. To mimic human “binge-like" consumption, we treated male, adolescent (PN 39 at time of first exposure) Sprague-Dawley rats to 15min (twice daily) exposures to toluene vapor (~5700PPM) for five consecutive days. After reaching

adulthood (PN 60), rats were trained in operant boxes to respond for a positive reinforcer to test different types of cognition. Adolescent exposure to toluene enhanced performance in an attentional set-shifting task using a between-session (i.e. shift occurred between days), but not a within-session (shift occurred during a session) test design. To explore possible reasons for differences between these two studies, we determined if adolescent toluene exposure 1) reduces latent inhibition, a known hindrance to cue-reward pairing and 2) enhances extinction behavior given a history of both cue-reward and cue-no-reward contingencies. Latent inhibition was determined using an automated procedure in operant chambers (Nonkes et al 2012) followed by extinction training. Our results show that while a history of toluene exposure blunts cue-reward pairing, it does not alter latent inhibition. Interestingly, toluene exposed rats with both cue experiences extinguish quicker within the first day of extinction, a result that could explain toluene-induced enhancement of between-session set-shifting. Lesion and pharmacological studies indicate that set-shifting requires a functioning medial prefrontal cortex (mPFC) that sends projections to areas involved in goal-directed behavior such as the nucleus accumbens core (NAc). To address whether toluene exposure alters the structural plasticity of these areas, we quantified basal dendritic spine density in DiI-labeled layer 5 mPFC pyramidal neurons and medium spiny neurons in the NAc. While there were no changes in mPFC dendritic spine density, chronic exposure to toluene during adolescence significantly increased spine density in the NAc, an effect driven by changes in long-thin spine subtype. These morphological data will help guide future studies focused on determining the mechanisms that drive persistent neuroanatomical changes induced by adolescent toluene exposure.

Disclosures: K.M. Braunscheidel: None. **J.T. Gass:** None. **P.J. Mulholland:** None. **J.J. Woodward:** None.

Poster

834. Cognition: Corticostriatal Circuits

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 834.09/III11

Topic: H.01. Animal Cognition and Behavior

Support: Human Frontier Science Program Organization

Title: Initial training with a specific sensing modality determines rat ability to integrate unisensory perceptual strategies in a multisensory pattern discrimination task.

Authors: *A. DI FILIPPO, L. GODENZINI, M. ORRÙ, M. DIAMOND, D. ZOCCOLAN; Intl. Sch. For Advanced Studies (SISSA), Trieste, Italy

Abstract: Multimodal perception is a well-known sensory process, whose neuronal basis and principles have been extensively investigated. In terms of behavior, however, such a phenomenon is yet to be properly characterized in rodents, especially for what concerns sensory integration in pattern recognition. A key question is whether and how unisensory perceptual strategies are integrated to form a multimodal representation.
To address this issue, we trained and tested rat ability to discriminate two orthogonally-oriented solid gratings under three different sensing modalities: visual, tactile and visuotactile. Critically, the animals were presented not only with the intact patterns, but also with incomplete versions of the gratings. We then processed rat responses to such altered stimuli using a classification image method that revealed the perceptual strategies of the animals under each modality. Between- and within-group analyses allowed assessing the influence of training with a specific sensing modality on the ability of the animals to learn the discrimination under a different modality, and integrate the individual unisensory strategies into a multisensory one.
Not surprisingly, we observed a general increase in discrimination performance under the visuotactile modality, as compared to the visual and tactile alone. Moreover, rats that had been originally trained in the visuotactile modality showed equal to or better performance than other rats that received unisensory training, during corresponding unisensory trials. In addition, training history had a strong influence on the ability of the rats to transfer the discrimination across modalities: the animals that had been originally trained in the visual task failed to learn the discrimination in the tactile modality, while the rats initially trained in the tactile condition successfully acquired the visual task.
Finally, the classification image analysis showed that rats extracted the discriminatory information about the orientation of the gratings by relying on different parts of the stimuli, depending on the sensing modality. In visual trials they exploited the central stripe of the grating pattern, while, in tactile trials, they preferentially used the bottom region of the grating. Interestingly, we found that perceptual strategy underlying the discrimination of the visuotactile stimuli could be modeled as a weighted sum of the unimodal strategies, but only for the rats originally trained in the visuotactile and tactile conditions. Overall, these results reveal the impact of initial exposure with a specific sensing modality on rat ability to learn and integrate unisensory information.

Disclosures: **A. Di Filippo:** None. **L. Godenzini:** None. **M. Orrù:** None. **M. Diamond:** None. **D. Zoccolan:** None.

Poster

834. Cognition: Corticostriatal Circuits

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 834.10/III12

Topic: H.01. Animal Cognition and Behavior

Support: Max Planck Society

Title: Simultaneous resting-state and visually-driven functional networks in the macaque brain

Authors: *F. A. DE AZEVEDO[1], M. ORTIZ-RIOS[1], L. C. AZEVEDO[1], D. Z. BALLA[1], G. LOHMANN[2], N. K. LOGOTHETIS[1,3], G. K. KELIRIS[4,1];
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Abstract: The primate brain is a complex dynamical system displaying long-range temporally-correlated functional networks. In the absence of external stimulation, several so called resting state functional networks of spontaneous activity have been identified. Their origin and function are not well understood, but such intrinsic architecture could reflect neural fluctuations within anatomically connected areas or active mechanisms related to perception and awareness. On the other hand, when the brain is being stimulated, a different pattern of stimulus-evoked activity emerges. How the brain orchestrates those interwoven patterns of activity is still unclear. We sought to assess the relationship between resting-state and stimulus-driven functional networks by investigating their topographical correspondence by using functional magnetic resonance imaging (fMRI) under specific stimulus paradigms. To this end, we scanned two monkeys (*Macaca mulatta*), while anesthetized or awake, stimulated with three main paradigms: a) no visual stimulation, b) visual stimulation using a one-minute block-design displaying natural movie clips alternated with gray background, and c) continuous visual stimulation using uninterrupted natural movies. Using independent component analysis (ICA), we were able to recover topographically similar patterns of resting state networks contained in stimulus-driven datasets. This suggests that, under certain circumstances, the primate brain is able to cope with both types of functional networks independently. Moreover, our results provide implications for bidirectional causal influences between stimulus-driven and spontaneous activity. This work provides insights of how the brain organizes its functional architecture and we expect it can stimulate further analysis and reinterpretation of a wide range of existing neuroimaging and physiological data.

Disclosures: **F.A. de Azevedo:** None. **M. Ortiz-Rios:** None. **L.C. Azevedo:** None. **D.Z. Balla:** None. **G. Lohmann:** None. **N.K. Logothetis:** None. **G.K. Keliris:** None.

Poster

834. Cognition: Corticostriatal Circuits

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 834.11/III13

Topic: H.01. Animal Cognition and Behavior

Support: K22 AA021414

Title: Functional connectivity of the claustrum in humans and rats at 7T MRI

Authors: D. A. SEMINOWICZ[1], S. KRIMMEL[1], A. RAMSEY[1], J. TEIXEIRA DA SILVA[1], N. HASSELGRAVE[2], M. G. WHITE[3], M. PANICKER[3], D. H. RESER[4], *B. N. MATHUR[3]; [1]Neural and Pain Sci., Univ. of Maryland Sch. of Dent., Baltimore, MD; [2]Physiol., [3]Pharmacol., Univ. of Maryland Sch. of Med., Baltimore, MD; [4]Physiol., Monash Univ., Melbourne, Australia

Abstract: The claustrum has reciprocal connectivity with multiple cortical networks and potentially has an important role in orchestrating activity across these functional networks. However, the claustrum's sheet-like shape and close apposition to medially lying putamen and laterally lying insular cortex have hindered such assessments with functional MRI. To surpass the confounds associated with imaging of claustrum, in both rats and humans we used 7-Tesla fMRI datasets in to examine the whole-brain resting state connectivity of the claustrum compared to its neighboring regions, the insula and striatum. Adult female Sprague-Dawley rats (200-250 g) were scanned on a Bruker BioSpec 70/30USR Avance III 7-Tesla scanner including a high resolution T1-weighted scan (RARE, TR = 2000 ms, TE = 14 ms, 256 x 256, in plane resolution = 100 μm, 24 axial slices, 1 mm slice thickness) and resting state scans (TR = 1500 ms, TE = 35.0966 ms, 75 x 75, in plane resolution = 0.4 x 0.4 x 1 mm, 24 axial slices). We also analyzed a dataset of 17 human subjects scanned on a 7T MR scanner that included a structural 3D MP2RAGE with resolution of 0.7mm isotropic voxels and a resting state functional EPI scan with resolution of 1.5mm isotropic voxels. Preprocessing of both datasets included slice timing correction, realignment, normalization, smoothing, physiological and scanner noise reduction, and band-pass filtering. We performed seed-based connectivity analyses by delineating the putamen/striatum, insula, and claustrum for each subject individually. A cluster-forming threshold of $p<0.001$ was used for all analyses and significant clusters based on FWE correction are reported. In both rat and human, our preliminary findings suggest that the claustrum is functionally connected to widespread cortical and subcortical brain areas. In rats, the connectivity of the claustrum with multiple cortical regions was significantly greater than insula or striatum. Furthermore, there were no regions in the brain that had greater connectivity to the insula or striatum than to the claustrum. In humans, insula connectivity to widespread cortical areas was greater than claustrum, while claustrum had greater connectivity than striatum to sensorimotor and visual cortices. Our results suggest that while it is possible to examine

claustrum connectivity in rodents and humans at high-field MRI, determining specific connectivity of the human claustrum is highly confounded by its three dimensional structure. Our ongoing studies in rats use optogenetic drive of known corticoclaustral pathways to disambiguate claustrum-specific activation signals from neighboring structures.

Disclosures: D.A. Seminowicz: None. **S. Krimmel:** None. **A. Ramsey:** None. **J. Teixeira da Silva:** None. **N. Hasselgrave:** None. **M.G. White:** None. **M. Panicker:** None. **D.H. Reser:** None. **B.N. Mathur:** None.

Poster

834. Cognition: Corticostriatal Circuits

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 834.12/III14

Topic: H.01. Animal Cognition and Behavior

Support: NIH grant MH100029

NIH grant MH078105-01S1

NIH grant MH078105-04S1

NIH grant MH096773

NIH grant MH091645

NIH grant MH086633

NIH grant U54 HD079124

Title: Maturation of prefrontal cortex circuits in primates: a longitudinal neuroimaging study during infancy

Authors: *Z. A. KOVACS-BALINT[1], E. FECZKO[4], E. EARL[4], L. LI[2], J. STEELE[1], M. STYNER[5], J. BACHEVALIER[1], D. FAIR[4], M. SANCHEZ[1,3,6];
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Abstract: The ”social brain hypothesis” proposes that the evolution of the primate brain was driven by the demands of living in a complex social environment, which provides shared resources and protection, increasing the individual’s Darwinian fitness. However, we know little

about the ontogenetic changes in the brain to support the development of social behavior. The goal of this present study was to characterize the development of brain networks underlying social interactions, focusing on socioemotional regulation and reward processes. For this we studied the structural and functional maturation of the prefrontal cortex (PFC) and its connections with the amygdala (AMY) and nucleus accumbens (NAcc) in non-human primate infants.
Structural, resting-state functional MRI (rsfMRI) and diffusion-tensor imaging (DTI) scans were acquired longitudinally (at 2, 4, 8, 12, 16, 20 and 24 weeks) in ten male infant macaques living with their mothers in complex social groups. Structural T1 MPRAGE sequences (TR/TE = 2600/3.46msec, voxel size: 0.5x0.5x0.5mm), BOLD contrast sensitive echo-planar imaging (EPI) sequences (TR/TE=2060/25msec, voxel size: 1.5x1.5x1.5mm) and single-shot dual spin-echo EPI sequences (TR/TE=7043/91msec, voxel size: 1x1x1mm) were acquired using a 3T MRI scanner. Developmental changes in PFC gray (GM) and white matter (WM) volumes, as well as PFC structural and functional connectivity (FC) with AMY and NAcc were analyzed across age using repeated measures ANOVA (level of sig.: $p<.05$).
Our results indicate that PFC WM volume undergoes dynamic changes, with a significant reduction around 8 weeks of age, likely driven by axonal pruning (AGE: $F(6,48)=14.19$). This structural change occurs in parallel to an overall increase in FC between dorsolateral PFC-AMY (AGE: $F(6,48)=5.29$), orbitofrontal cortex-AMY (AGE: $F(6,48)=3.27$), and the orbitofrontal cortex-NAcc (AGE: $F(6,48)=2,25$) as the infants get older. During the first 6 months of life, FC between medial PFC and AMY was weak but may strengthen in later ages. We are currently analyzing the DTI structural connectivity data.
Our findings suggest that PFC-AMY circuits critical for emotion regulation and PFC-NAcc circuits that control reward processes become more strongly connected with age. Drastic and dynamic maturational changes in the first 6 months of life include rapid changes in both PFC structural and functional connectivity with limbic regions, which probably tune the development of cortical brain regions and drive the transition to independence from the mother during the weaning period and the establishments of social experiences with other members of the group.

Disclosures: **Z.A. Kovacs-Balint:** None. **E. Feczko:** None. **E. Earl:** None. **L. Li:** None. **J. Steele:** None. **M. Styner:** None. **J. Bachevalier:** None. **D. Fair:** None. **M. Sanchez:** None.

Poster

834. Cognition: Corticostriatal Circuits

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 834.13/III15

Topic: H.01. Animal Cognition and Behavior

Support: NSF IOS 1457291

Title: Neuroanatomical variation in domestic dog breeds

Authors: *E. E. HECHT[1], D. A. GUTMAN[2], W. DUNN, Jr[2], O. P. KEIFER, Jr[3], S. SAKAI[4], M. KENT[5], T. M. PREUSS[6];
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Abstract: A major goal of modern neuroscience is to understand how variation in behavior, cognition, and emotion relates to underlying neural mechanisms. Domestic dog breeds offer an unparalleled "natural experiment" in this arena. Humans have selectively bred dogs for different abilities and temperaments - herding or protecting livestock, hunting by sight or smell, guarding property or providing companionship. This panoply of specializations must rely on underlying neural specializations. However, the mechanisms governing these behavioral differences are largely unknown. The current study analyzed 3T structural MRI scans from 83 dogs of varying breeds. Differences in brain size, shape, and morphology were plainly visible. In order to quantify this variation, we measured body weight; gray matter, white matter, and ventricular volumes; and lengths across the maximum rostral-caudal, left-right, and dorsal-ventral brain axes. Brain volume varied significantly across breeds, but larger breeds did not have proportionally larger brains. Variation in head shape (cephalic index) was generally reflected in brain shape; i.e., dogs with foreshortened crania show foreshortened brains. In order to examine local variation in gray matter morphology, the software package ANTS was used to create an unbiased group-average template. We measured morphological deviation from this group average in each individual dog and within breeds and breed groups. Variation was statistically significant after multiple comparisons correction in widespread cortical and subcortical regions. Differences between breed groups appear to parallel behavioral specializations. For example, sight hounds show expansion of visual cortex compared to scent hounds, which show expansion of hypothalamus, amygdala, and hippocampus. High variability was also observed in several non-primary cortical regions which may represent higher-order association areas. The brain-wide connectomes of these highly variable regions was explored using 9.4-T diffusion tensor imaging with 300-micron isotropic resolution. 3D reconstructions of the brains of various breeds, heat maps of group-wide and breed-specific anatomical variation, and brain-wide connectivity of highly variable regions are presented. Together, these results establish that brain anatomy varies significantly among different breeds of domestic dogs, a finding that is relevant to both the practical employ of dogs in human endeavors and to the broader study of brain-behavior evolution.

Disclosures: E.E. Hecht: None. **D.A. Gutman:** None. **W. Dunn:** None. **O.P. Keifer:** None. **S. Sakai:** None. **M. Kent:** None. **T.M. Preuss:** None.

Poster

834. Cognition: Corticostriatal Circuits

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 834.14/III16

Topic: H.01. Animal Cognition and Behavior

Support: ANR PallEnody

CNRS

Université Paris-Saclay

Title: Functional and developmental characterization of the visual afferent to the pallium in zebrafish

Authors: *K. YAMAMOTO[1], S. BLOCH[1], C. FROC[2];
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Abstract: Some species of birds and teleost fishes possess higher order cognitive capacities, even though the morphology of the pallium (dorsal telencephalon) is different from the mammalian cerebral cortex. Notably teleosts are phylogenetically far from mammals and birds, and morphogenesis of the pallium is also very different. Thus the teleost is a very interesting model to study convergent evolution of cognition and the structures involved.
As in mammals and birds, the teleost pallium receives prominent sensory inputs of different modalities, and ascending sensory inputs to the pallium is reported to be similar to the "thalamo-cortical pathways". The difference between tetrapods and teleosts is that the major sensory relay nuclei are not located in the dorsal thalamus, but in a ventral structure called the preglomerular nucleus (PG).
Thanks to the availability of enhancer trap transgenic lines in zebrafish, we found a Gal4-GFP transgenic line recapitulating the PG-pallium projections. These fish express GFP in cell bodies of the PG which project in a discrete fashion to a putative visual area in the dorso-lateral pallium. Using DiI tracing methods, we identified that the PG cells receive inputs from the optic tectum, as demonstrated in other teleost species such as goldfish and carp.
For functional validation of this area, we established a color discrimination task using operant conditioning in adult zebrafish. Zebrafish quickly learns to choose the color associated with food reward. After the color discrimination was established, we performed a pallial lesion then the task performance was tested, in order to confirm whether the GFP-positive pallial area is functionally equivalent to the primary visual area in amniotes.
Finally, preliminary data from cell lineage study suggests that the PG is of mesencephalic origin, instead of diencephalic origin as previously believed. This means that the visual afferent in

teleosts (mesencephalon-PG-telencephalon) is relayed via two mesencephalic nuclei, unlike in tetrapods (mesencephalon-diencephalon-telencephalon). Thus the sensory pathways in teleosts and tetrapods are most likely not homologous, and the similarities have evolved independently in these animal groups.

Disclosures: K. Yamamoto: None. **S. Bloch:** None. **C. Froc:** None.

Poster

834. Cognition: Corticostriatal Circuits

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 834.15/III17

Topic: H.01. Animal Cognition and Behavior

Support: NIH grants R01 NS029563

Title: Allyl isothiocyanate differentially modulates the C-start escape response in Danio rerio

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Abstract: The larval form of the zebrafish (*Danio rerio*) holds significant promise as a model vertebrate system for understanding the neural mechanisms of behavior. This promise arises from two particularly attractive properties of zebrafish larva: their translucence, which permits robust optogenetic manipulations, and their possession of a relatively simple neural circuitry, which facilitates cellular analysis of behavior. In particular, activation of the identified Mauthner-cell (M-cell) array, a set of reticulospinal neurons, directs virtually the entirety of the larva's reflexive escape response (the C-start). In the present study, we examined modulation of the C-start in response to acoustic stimuli in larval zebrafish by application of a known zebrafish irritant, allyl isothiocyanate (mustard oil). We found that mustard oil (MO) inhibited the C-start to an acoustic tone of gradually increasing strength. Interestingly, following habituation of the C-start to auditory stimuli of fixed strength, MO produced dishabituation of the C-start. Our results suggest that a noxious stimulus, MO, has a differential effect on the C-start depending upon the behavioral state of the organism.

Disclosures: **J. Alzagatiti:** None. **A. Roberts:** None. **R. Choe:** None. **J. Chornak:** None. **R. Buck:** None. **S. Nemanpour:** None. **D. Wong:** None. **F. Osadi:** None. **M. Hoang:** None. **J. Alipio:** None. **E. Laurent:** None. **D.L. Glanzman:** None.

Poster

834. Cognition: Corticostriatal Circuits

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 834.16/III18

Topic: H.01. Animal Cognition and Behavior

Support: ARO Grant W911NF-12-R-0012-02

NSF Grant DMS-1042134

Title: Alpha oscillatory inputs and short-term depression underlie action inhibitory control in a model of the striatum

Authors: ***S. ARDID**[1], J. SHERFEY[1], M. M. MCCARTHY[1], J. HASS[1,2], N. KOPELL[1]; [1]Dept. of Mathematics & Statistics, Boston Univ., Boston, MA; [2]Dept. of Theoretical Neuroscience, Bernstein-Center for Computat. Neurosci., Central Inst. of Mental Hlth. at Heidelberg Univ., Mannheim, Germany

Abstract: Performance on rule-based tasks depends on context biases acting upon competing sensory-motor alternatives. Buschman et al. (2012) have shown context modulation of rhythmic activity in prefrontal cortex: On stimulus onset, high β rhythms emerge in orientation and color-selective ensembles. This suggests a role for β rhythms biasing downstream action selection. However, a significant difference in strength at the β peak exists only in orientation trials (dominant dimension). In color trials (subordinate dimension), an α rhythm is present in orientation-selective ensembles before stimulation. This suggests a role for α rhythms suppressing the subsequent processing of the dominant dimension.
Using a modeling approach, we here predict: the striatal mechanisms that read out β (or α) inputs to trigger (or halt) actions; the ability of α inputs to gate inhibitory control; and the substrate for processing suppression of information that is dominant but irrelevant.
Our striatal model is composed of D1 and D2 medium spiny neurons (MSNs), input stage of the direct (GO) and indirect (NO-GO) pathways of the basal ganglia. Experimental data constrain this model. D1 and D2 MSNs have dissimilar connectivity profiles (Taverna et al., 2008) and distinct properties of synaptic depression (Tecuapetla et al., 2007). MSNs' spontaneous firing is sparse and noisy. Cortical inputs significantly boost MSNs' activity but do not impose a top-down bias between D1 and D2 MSNs (Ballion et al., 2008).

In the model, the strength and the frequency at which D1 and D2 MSNs resonate depend on MSNs' intrinsic properties, MSNs' excitability, and the spectral components of the input. D1 MSNs have a higher excitability than D2 MSNs in the model because we assume higher dopamine concentration in health conditions compared to in vitro and Parkinson's disease. In these conditions, D2 MSNs resonate at low β and D1 MSNs resonate at high β frequencies. Rhythmic inputs at either α or high β bands preferentially entrain low vs high β rhythms in the local circuit, hence engaging either the indirect or the direct pathway of the basal ganglia. In orientation trials, orientation-associated actions are mediated because the β oscillatory component of the prefrontal input to orientation-D1 MSNs is higher than that to color-D1 MSNs (even though both inputs are equal in average). In color trials, the β oscillatory component of the input is the same for both D1 MSN ensembles. However, the synapses of orientation-selective MSNs are depressed due to the previous α oscillatory input. Thus, α-mediated short-term depression before stimulation opens a window of opportunity during stimulation for acting on color-associated actions.

Disclosures: **S. Ardid:** None. **J. Sherfey:** None. **M.M. McCarthy:** None. **J. Hass:** None. **N. Kopell:** None.

Poster

834. Cognition: Corticostriatal Circuits

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 834.17/III19

Topic: H.01. Animal Cognition and Behavior

Support: ARO Grant W911NF-12-R-0012-02

NSF Grant DMS-1042134

Title: Oscillations guide rule-based action in a laminar model of prefrontal cortex

Authors: *J. SHERFEY[1,2], S. ARDID[2], M. MCCARTHY[2], J. HASS[2], N. KOPELL[2];
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[2]Mathematics and Statistics, Boston Univ., Boston, MA

Abstract: Cell assemblies in prefrontal cortex (PFC) are broadly implicated in working memory and goal-directed behavior. They can undergo transformations integrating context and stimuli to produce top-down biases in service of prospective action. Selection of the appropriate action is guided by PFC assemblies that encode context-specific "rules" with low-rate irregular spiking and oscillations in population activity. How these population dynamics affect cortical

communication and rule-based action is unknown. Using computational modeling and simulation, we investigated this question by studying the impact of population rhythmicity on feedforward communication and context-dependent routing in a laminar model of PFC. First, we studied the effects of Poisson versus rhythmically-modulated population spiking on an action-coding cell assembly in the deep layer network. We found that the assembly responded maximally (resonated) to a preferred input frequency that depended on the time constant of synaptic inhibition as well as the excitability of cells in the network. When spike rates were low, feedforward communication was achieved by only the most resonant inputs. This implies that superficial activity can be made to drive a target assembly or not by simply changing its population rhythmicity (i.e., without changing the amount of spiking). Next, we studied how context-related spectral differences in the superficial layer affected the responses of two action-coding assemblies. Resonance alone produced differences in their activity levels when they were driven by inputs with different population frequencies; these differences were sigmoidally related to the proximity of the input frequency to the target resonant frequency. We found that lateral inhibition between competing assemblies amplified these differences and gave rise to a winning assembly when the connections from pyramidal cells to interneurons were sufficiently strong. That is, network resonance and lateral inhibition were sufficient for a single action-coding assembly to be selected based on context-dependent rhythmicity even when the number of input spikes were equal. Finally, we demonstrated that context-dependent rhythmicity can be controlled by differentially driving two interneuron populations in the superficial layer. Such a mechanism could enable working memory transformations to occur within PFC without being routed downstream to subcortical circuits (e.g., basal ganglia) until an interneuron type-specific "GO" signal is received. Together, these results emphasize the important role that rhythms might play in cortical communication, routing, and rule-based action.

Disclosures: **J. Sherfey:** None. **S. Ardid:** None. **M. McCarthy:** None. **J. Hass:** None. **N. Kopell:** None.

Poster

835. Cognition: Striatal Regions

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 835.01/III20

Topic: H.01. Animal Cognition and Behavior

Support: NSF GRFP

Title: Inactivation of the dorsomedial striatum leads to impairment in spatial working memory

Authors: *H. AKHLAGHPOUR, J. P. TALIAFERRO, J. CHOI, J. AU, I. B. WITTEN; Princeton Univ., Princeton, NJ

Abstract: Working memory is the ability to maintain and manipulate information over short periods of time, and it is a fundamental component of cognition. Although most studies have focused on the role of cortical regions in supporting working memory, subcortical regions are also likely to play an important role. For instance, the dorsomedial striatum, which receives projections from the prefrontal cortex, has been shown to have elevated activity during tasks that involve working memory. To determine if activity in the dorsomedial striatum (DMS) is required for spatial working memory in rats, we trained rats to perform a delayed non-match to position task that involved 1s, 5s, and 10s delay periods. Inactivation of the DMS through the infusion of muscimol led to a decrease in choice accuracy (n=7 rats; $p < 10^{-15}$ for effect of muscimol; mixed effect logistic regression to predict accuracy based on muscimol, delay, and muscimol×delay). Additionally, inactivation of the DMS led to an increase in trial abortions, which may reflect an inability to remember planned actions or the current state of the self-initiated trial ($p < 10^{-15}$ for muscimol; mixed logistic regression to predict abortion based on muscimol, delay, and muscimol×delay). Our results demonstrate that activity in the dorsomedial striatum of rats is necessary for performance of a spatial working memory task.

Disclosures: H. Akhlaghpour: None. **J.P. Taliaferro:** None. **J. Choi:** None. **J. Au:** None. **I.B. Witten:** None.

Poster

835. Cognition: Striatal Regions

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 835.02/III21

Topic: H.01. Animal Cognition and Behavior

Support: the Zhejiang Provincial Natural Science Foundation (No. LQ15H090007)

the Wenzhou Natural Science Foundation (No.Y20150003)

the Start-up Fund from Wenzhou Medical University (No. 89211010 JFC; No. 89212012, JFC and KYQD121004, ZHL)

the Eye Hospital of Wenzhou Medical University Foundation(No.YNCX201509)

NIH grant NS041083-11

NIH grant NS073947

Title: Selective control of the maintenance and retrieval of spatial working memory by the cortico-striatal adenosine A_{2A} receptor under specific cognitive load

Authors: *L. ZHIHUI[1], C. HANGJUN[1], L. FEI[1], C. LONG[1], G. WEI[1], R. XIANGPENG[1], Z. LIPING[1], C. JIANGFAN[1,2];
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Abstract: Spatial working memory (SWM) is fundamental to cognition by caching behaviorally relevant cues on a timescale of seconds. It comprises multiple cognitive subcomponents, which tap into several executive processes including encoding, maintenance, updating and manipulation of information. The striatum is proposed to play a critical role in gating WM representations. The adenosine A_{2A} receptor ($A_{2A}R$) is highly enriched in the striatum where it integrates dopamine and glutamate signaling to modulate cognition, including working memory. Although the pro-cognitive effect of striatal $A_{2A}R$ inactivation is well documented, the specific temporal phases of SWM and the specific contribution of the distinct element of the cortico-stiratal $A_{2A}Rs$ to control SWM is unknown mainly due to the lack of the methods to control $A_{2A}R$ signaling with SWM required spatiotemporal resolution. Using our newly developed optogenetic control of $A_{2A}R$ signaling method ("opto$A_{2A}R$") coupled with a rodent delayed non-match-to-place (DNMTP) task, we demonstrated that optogenetic activation of dorsomedial striatum (DMS) $A_{2A}R$ signaling selectively at the *delay* and *choice* phases (but not the *sample* phase) disrupted SWM performance. Thus, the striatopallidal $A_{2A}R$ signaling selectively control the maintenance and retrieval (but not encoding) of SWM. Furthermore, optogenetic activation of $A_{2A}R$ signaling in the mPFC selectively during the delay (but not the sample and choice) phase improved SWM performance, suggesting that the $A_{2A}R$ signaling in the mPFC and striatopallidal neurons exerts opposite controls of SWM performance. Moreover, the control of SWM performance by both DMS and mPFC $A_{2A}R$ signaling was detected only during the learning phase but not after the mice were well trained and only under specified cognitive loads. These findings suggest a plausible mechanism for the mPFC and DMS to oppositely control SWM maintenance and updating via the $A_{2A}R$ signaling.

Disclosures: L. Zhihui: None. **C. Hangjun:** None. **L. Fei:** None. **C. Long:** None. **G. Wei:** None. **R. Xiangpeng:** None. **Z. Liping:** None. **C. Jiangfan:** None.

Poster

835. Cognition: Striatal Regions

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 835.03/III22

Topic: H.01. Animal Cognition and Behavior

Support: Wellcome Trust Senior Investigator Award [104631 /Z/14/Z] to TWR

SAWJ was supported by a BCNI-MRC studentship

Title: The differential contribution of primate striatal regions to serial reversal learning

Authors: *S. A. JACKSON[1,2], N. K. HORST[1,2], N. HORIGUCHI[1,2], T. W. ROBBINS[1,2], A. C. ROBERTS[3,2];
[1]Dept. of Psychology, [2]Behavioural and Clin. Neurosci. Inst., [3]Physiology, Develop. and Neurosci., Univ. of Cambridge, Cambridge, United Kingdom

Abstract: The neural basis of reversal learning, the adaptation of behaviour in response to changes in stimulus-reward contingencies, has been extensively studied in the context of understanding cognitive inflexibility in neuropsychiatric disorders. Fronto-striatal circuitry, notably including the orbitofrontal cortex, has been repeatedly identified as mediating successful reversal learning. However, the precise part of the striatum that contributes to reversal learning is still unclear; different studies have given evidence for the role of the ventromedial caudate (vm caudate) (Clarke et al., 2011 J Neurosci.) or for the putamen (Groman et al., 2013 Biol. Psychiatry). Thus we chose to investigate the differential contribution of the two areas using localised reversible inactivations in marmosets undergoing a touchscreen-based serial reversal paradigm.

Marmosets were trained to respond on a touchscreen to two stimuli, the pressing of one of which led to delivery of banana milkshake reward whilst pressing the other caused punishment of five seconds of darkness and a brief, mildly aversive loud noise. Once they had learnt the discrimination the response-outcome contingencies were reversed, such that pressing the previously correct stimulus now led to punishment and the previously incorrect stimulus led to reward. Training on such reversal of the response-outcome contingencies continued until a marmoset could reliably reverse their responding within a session. By the end of training, each daily session comprised a retention phase where response-outcome contingencies were the same as those of the previous day, and a reversal phase, where they were inverted. Marmosets were implanted with indwelling cerebral cannulae targeting the vm caudate and putamen using stereotaxic surgery. The $GABA_A$ agonist muscimol was infused into the vm caudate or putamen to reversibly inactivate the respective areas. Putamen inactivation induced a specific deficit in the reversal phase of the task whilst caudate inactivation induced a generalised deficit on both phases of the task.

Reversal learning has been so extensively studied because it is thought to be a prototypical exemplar of cognitive flexibility, defined as “the ability to shift avenues of thought and action in order to perceive, process and respond to situations in different ways”. The wider significance of these data, both in terms of the clarification of the basic science literature on the neural basis of reversal learning, and their implications in terms of cognitive flexibility and the neuropsychiatric disorders theorised to involve deficits in cognitive flexibility, such as OCD, will be discussed.

Disclosures: **S.A. Jackson:** None. **N.K. Horst:** None. **N. Horiguchi:** A. Employment/Salary (full or part-time): NH worked as a visiting scholar from Shionogi & Co., Ltd. **T.W. Robbins:**

B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution; TWR has received research grants from Lilly, Lundbeck and GSK.. F. Consulting Fees (e.g., advisory boards); TWR consults for Cambridge Cognition, Lilly, Lundbeck, Teva, Shire Pharmaceuticals and Merck, Sharp and Dohme. **A.C. Roberts:** None.

Poster

835. Cognition: Striatal Regions

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 835.04/III23

Topic: H.01. Animal Cognition and Behavior

Title: Involvement of thalamic inputs to dorsomedial striatum in inhibitory control in the 5-choice serial reaction time task in rats

Authors: J. SAUND[1], D. DAUTAN[2], C. ROSTRON[3], G. URCELAY[1], *T. GERDJIKOV[4]; [1]Neurosci. Psychology and Behaviour, Univ. of Leicester, Leicester, United Kingdom; [2]Ctr. for Mol. and Behavioral Neurosci., Rutgers Univ., Newark, NJ; [3]Dept Life, Hlth. and Chem. Sci., Open Univ., Milton Keynes, United Kingdom; [4]Sch. of Psychology, Leicester, United Kingdom

Abstract: Corticostriatal inputs are widely implicated in attentional control, however recent neurophysiological evidence suggests a role for thalamic inputs to striatum in responses to salient, reward-paired cues. We investigated the role of parafascicular (Pf) thalamic inputs to the dorsomedial striatum (DMS) in attentional control using the 5-choice serial reaction time task (5CSRTT) in rats. The 5CSRTT requires sustained attention in order to detect spatially and temporally distributed visual cues. Overtrained Long Evans male rats (n=10) underwent chemogenetic inhibition of the Pf-DMS pathway using bilateral AAV2-CaMKIIa-HA-hM4D(Gi)-IRES-mCitrine injections into Pf. Injections of the DREADD agonist, clozapine N-oxide (CNO; 1µl bilateral; 3mM) or vehicle were administered into DMS 1hr before behavioural testing. Viral expression into the target regions was confirmed immunohistochemically after completion of the experiment. After chemogenetic inhibition (or vehicle) task parameters were manipulated to challenge attention and response inhibition. We found that inhibition of the Pf-DMS projection significantly increased perseverative responses (failure of response inhibition) compared to vehicle but had no effect on response accuracy or attentional challenge. These results complement previous lesion work in which the DMS and orbitofrontal cortex were similarly implicated in perseverative responses among other performance measures. This

suggests that the behavioural role of DMS must be considered in the context of both corticostriatal and thalamostriatal inputs.

Disclosures: J. Saund: None. **D. Dautan:** None. **C. Rostron:** None. **G. Urcelay:** None. **T. Gerdjikov:** None.

Poster

835. Cognition: Striatal Regions

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 835.05/III24

Topic: H.01. Animal Cognition and Behavior

Support: Kansas State University startup funds

Title: Anesthetic doses of ketamine improve reversal learning in a go/no-go task in rats

Authors: *A. PAJSER[1], M. K. CRABTREE[2], C. L. PICKENS[2];
[1]Psychological Sci., [2]Kansas State Univ., Manhattan, KS

Abstract: Previous research has shown that repeated subanesthetic doses of ketamine do not alter reversal learning in rats. However, it is unclear whether higher anesthetic doses might have effects that are not seen after exposure to lower doses. We performed an experiment to determine whether repeated higher doses of ketamine might impair reversal learning in a go/no-go task in which the rats were reinforced for withholding responses on no-go trials. We gave male Long Evans rats 0, 50 or 100 mg/kg (i.p.) injections of ketamine for 3 consecutive days, and then tested the rats in reversal learning 3 weeks later. In the reversal learning task, rats were reinforced for pressing one lever (the "go" lever) and for withholding responding from a second lever (the "no-go" lever). Rats were required to perform the correct response or withholding of responding for 26 consecutive trials for three consecutive days. The contingencies then reversed, with the previous go lever becoming the new no-go lever and vice versa. The rats were then required to meet the same criterion as in the original discrimination training. We found that prior ketamine exposure did not alter the initial discrimination learning. Rats that received the higher 100 mg/kg ketamine injections committed significantly fewer commission errors (incorrect responses on no-go trials) than the saline group, and similar numbers of omission errors. Closer inspection of the data revealed that the effect of ketamine on commission errors was limited to the sessions that occurred after the rat's first session to reach the daily performance criterion, but before they had passed for several consecutive days. This suggests that ketamine does not impair perseveration or new learning of the altered response contingencies, but instead leads to regressive errors in which rats revert to the previous contingencies after the new contingencies

are already learned. Other data from our lab (see the Ray, Crabtree, & Pickens poster) suggest that this pattern of data is not consistent with effects of ketamine on orbitofrontal cortex. Future research will examine the neural substrate of ketamine's effect on reversal learning.

Disclosures: A. Pajser: None. **M.K. Crabtree:** None. **C.L. Pickens:** None.

Poster

835. Cognition: Striatal Regions

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 835.06/III25

Topic: H.01. Animal Cognition and Behavior

Support: Progetto di Ricerca di Interesse Nazionale 2011 (prot. 2010AHHP5H) (to PC)

Fondazione con il Sud 2011- PDR-13 (to EDL and PC)

Title: Incremental motor learning induces a DAT-mediated shift in synaptic plasticity in striatal neurons: relevance for prodromal Parkinson' disease

Authors: *E. DE LEONIBUS[1], N. GIORDANO[1], A. IEMOLO[1,2], M. MANCINI[2], F. CACACE[2], M. DE RISI[1], E. LATAGLIATA[2], V. GHIGLIERI[2], G. BELLENCHI[1], S. PUGLISI-ALLEGRA[2], P. CALABRESI[3], B. PICCONI[2];
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Abstract: The striatum is the major recipient of dopamine (DA) projections from the midbrain that regulates the acquisition of skill learning, which is impaired in many neurological and psychiatric disorders, such drug abuse, obsessive compulsive disorder and Parkinson' disease (PD).
The synaptic and molecular mechanisms involved in striatal-dependent learning are poorly understood.
In this study to identify the cellular substrate of skill learning, we used a learning-induced metaplasticity experimental approach, in which a long-term-depression (LTD) protocol was applied to medium spiny neurons in the dorsolateral striatum (DLS) on animals previously subjected to the incremental motor learning training. LTD protocol application led to long-term potentiation (LTP) in mice that underwent an initial motor learning training. Overtraining the animals toward plateau performance rescued the LTD. *In vivo* pre-treatment of the animals with selective DAT inhibitors prevented motor learning-induced LTP, as well as the development of plateau performance. Previous data in the literature demonstrated that practice-mediated

transition toward behavioral automatism is regulated by a neuronal transition from the dorsomedial toward the dorsolateral striatum. The findings we report here unravel a completely novel synaptic mechanism within the DLS, through which behavioral automatism is achieved. We proved the translational relevance of the novel identified form of cellular memory in an animal model of PD generated by overexpressing human alpha-synuclein (a-Syn) in the midbrain. a-Syn overexpression reduced striatal DAT, impaired motor learning and abolished the learning-induced shift from LTD to LTP, before leading to neurodegeneration and to "dementia-like" onset behavioral dysfunction. This finding identifies a novel molecular and cellular cascade leading to skill learning impairment in the early stages of synucleinopathy.
This newly identified DAT-mediated mechanism of cellular memory, disrupted in the early stage of synucleinopathy, may also underlie habit learning dysfunction in other striatal pathologies, such drug-abuse.

Disclosures: E. De Leonibus: None. **N. Giordano:** None. **A. Iemolo:** None. **M. Mancini:** None. **F. Cacace:** None. **M. De Risi:** None. **E. Latagliata:** None. **V. Ghiglieri:** None. **G. Bellenchi:** None. **S. Puglisi-Allegra:** None. **P. Calabresi:** None. **B. Picconi:** None.

Poster

835. Cognition: Striatal Regions

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 835.07/III26

Topic: G.01. Appetitive and Aversive Learning

Support: NIH Grant DA036737

NIH Grant P51OD011132

Title: Regulation of goal-directed action selection by cocaine, MDMA, and orbitofrontal BDNF-TrkB

Authors: *E. G. PITTS, K. GARZA, S. L. GOURLEY;
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Abstract: Cocaine dependence is characterized by compulsive drug use and maladaptive decision-making. Adolescents are particularly vulnerable to the effects of cocaine; for example, cocaine exposure during adolescence increases the risk of developing lifelong addictions. Previous studies have shown that subchronic cocaine exposure during adolescence, but not adulthood, results in a bias towards stimulus-driven habits in mice, and this bias persists into adulthood. Changes in Brain-derived Neurotrophic Factor (BDNF) in the orbitofrontal prefrontal

cortex (oPFC) could underlie, in part, this habit bias, while strategies that stimulate cortical BDNF systems could be protective. Here we utilized viral-mediated gene transfer to decrease the expression of *Bdnf* and, in separate mice, interfere with the activity of its high-affinity receptor tyrosine kinase receptor B (trkB) selectively in the oPFC. Both manipulations induced habit-like behavior in an instrumental contingency degradation task. Next, we hypothesized that stimulating BDNF expression in the oPFC could block habits by enhancing response-outcome learning and memory. We report that 3,4-methylenedioxymethamphetamine (MDMA) increases BDNF levels in the oPFC, but not the amygdala or dorsal striatum, and also "breaks" habits resulting from adolescent cocaine exposure, as well as oPFC-selective *Bdnf* knockdown. MDMA was delivered immediately following instrumental contingency degradation, suggesting that it enhances the consolidation of new response-outcome learning and memory. Finally, 7,8-dihydroxyflavone (7,8-DHF), a trkB agonist, also reverses cocaine-induced habits, further suggesting that BDNF-trkB systems are a point of intervention in combatting maladaptive decision making following repeated cocaine exposure.

Disclosures: **E.G. Pitts:** None. **K. Garza:** None. **S.L. Gourley:** None.

Poster

835. Cognition: Striatal Regions

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 835.08/III27

Topic: G.01. Appetitive and Aversive Learning

Title: A model-based reinforcement learning model using Rescorla-Wagner principle reproduces Pavlovian-to-Instrumental Transfer

Authors: *K. OKITSU[1], Y. SAKAI[2];
[1]Grad. Sch. of Brain Sci., Tamagawa Univ., Tokyo, Japan; [2]Tamagawa Univ. Brain Sci. Inst., Tokyo, Japan

Abstract: Animal learning behavior has been observed in Pavlovian and instrumental conditionings. Significance of these conditionings has been explained in model-free reinforcement learning using temporal difference (TD) learning. Pavlovian effects can be regarded as state value learning to produce TD error signals, which is used for reinforcement of instrumental effects. Rescorla-Wagner model, a standard model for Pavlovian conditioning, has been often applied to the state value learning in TD learning. However, the simple TD learning can not reproduce Pavlovian-to-instrumental transfer (PIT), in which Pavlovian conditioning affects behavior shaped in instrumental conditioning. To reproduce PIT, we constructed a model-based reinforcement learning model using Rescorla-Wagner principle. We used the Rescorla-

Wagner rule for prediction of stimulus pattern, rather than prediction of value. In our model, outcome is regarded as one of the stimuli presented from outside an organism, and state is defined as compound simulus pattern presented from environment. This state is predicted by the state prediction model which predicts next compound stimulus pattern with current state and action, and learns prediction parameters in manner of Rescorla-Wagner model. For action selection, action with higher state-action value calculated by predicted state is selected more. Through simulations, we confirmed that our model reproduced PIT and typical phenomena of Pavlovian and instrumental conditioning. These results indicate that Rescorla-Wagner type stimulus pattern prediction is the key learning mechanism underlying Pavlovian and instrumental conditioning.

Disclosures: K. Okitsu: None. **Y. Sakai:** None.

Poster

835. Cognition: Striatal Regions

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 835.09/III28

Topic: H.01. Animal Cognition and Behavior

Support: Australian Research Council Grant DP13300101932

National Health and Medical Research Council Grant APP1037746

National Health and Medical Research Council Grant APP1003150

Title: Age-related corticostriatal decline underlies temporal constraints in action execution

Authors: *J. BERTRAN-GONZALEZ[1], Z. SKRBIS[1], M. BAILEY[2], P. BALSAM[2], B. BALLEINE[3], J. GOETZ[1], M. MATAMALES[1];
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Abstract: In a similar way to space, estimates of time are a fundamental component of goal-directed learning, and adjustments of the “time of action” play a crucial role in action sequence formation and automatisation. Aged individuals are known to produce deficient action sequences during the acquisition of skills, a deficit that is attributed to malfunction of cortico-basal ganglia circuits. However, the way these processes relate to deficits in time perception remains unknown. Here we investigated the effect of age on goal-directed performance by studying how deficits during action sequence learning related to impaired corticostriatal function. We first analysed the

detailed structure of behaviour in aged mice engaged in a fully-automated instrumental task and found severe alterations of action structure as compared to younger controls, which were due to their incapacity to produce action sequences longer than two seconds. Importantly, when animals were forced to extend their time of action, aged mice displayed time-locked patterns of behaviour characterised by compressed ultrafast sequences. Surprisingly, introducing an instructive cue signalling the end of each sequence normalised the time of action, but this effect abruptly disappeared as soon as the cue was removed. Finally, using large-scale functional profiling of neurons, we observed that action-timing defects in the aged specifically correlated with incomplete postero-lateralisation of corticostriatal activity, suggesting aberrant automatisation processes. Altogether, our findings reveal major age-related functional deficits in cortico-basal ganglia networks that correlate with shorter patterns of goal-directed action, a process that likely compromises the ability of older individuals to acquire new skills.

Disclosures: **J. Bertran-Gonzalez:** None. **Z. Skrbis:** None. **M. Bailey:** None. **P. Balsam:** None. **B. Balleine:** None. **J. Goetz:** None. **M. Matamales:** None.

Poster

835. Cognition: Striatal Regions

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 835.10/III29

Topic: H.01. Animal Cognition and Behavior

Support: Australian Research Council Grant DP13300101932

National Health and Medical Research Council Grant APP1037746

National Health and Medical Research Council Grant APP1003150

Title: Aging-related dysfunction of striatal cholinergic interneurons produces conflict in action selection

Authors: ***M. MATAMALES**[1], Z. SKRBIS[1], R. HATCH[1], B. BALLEINE[2], J. GOETZ[1], J. BERTRAN-GONZALEZ[1];
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Abstract: For our goal-directed action to remain adaptive, we must constantly acquire new strategies to accommodate environmental changes, a process that largely depends on striatal function. However, it has long been known that, during memory updating, new and old learning

can actively interfere, resulting in conflict and, eventually, forgetting. Although this type of memory interference is a cognitive shortcoming that is particularly common in the elderly, the neural correlates underlying these behavioural deficits are largely unknown. Here, we sought to address the hypothesis that an age-related decline of striatal function affects the capacity of older mice to flexibly adapt to changing environments. Using sophisticated behavioral paradigms in rodent, we found that aged mice were able to encode initial goal-directed learning but failed to adjust this learning when conditions were altered, leading to conflict in action selection and reduced adaptive capacity. Using large-scale functional profiling of neurons, we observed that this deficit was accompanied by reduced cellular activity in the striatal cholinergic system, and that it specifically correlated with defective activation of striatal output neurons, in line with recently proposed models for the flexible control of action. These results demonstrate for the first time an age-related memory interference effect in associative learning, and suggest that such cognitive shortcoming during the integration of goal-directed memories can be particularly detrimental for the flexible adaptation of older individuals to changing environments.

Disclosures: **M. Matamales:** None. **Z. Skrbis:** None. **R. Hatch:** None. **B. Balleine:** None. **J. Goetz:** None. **J. Bertran-Gonzalez:** None.

Poster

835. Cognition: Striatal Regions

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 835.11/III30

Topic: G.01. Appetitive and Aversive Learning

Title: Action and habit in a reward devaluation/inflation paradigm

Authors: *S. E. CONRAD, M. R. PAPINI;
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Abstract: The transition from action to habit is usually thought to occur in sequence, with behavior being guided by outcome expectations early in training and less dependent on current reward value later in training. This sequential transition is thought to be paralleled by a shift of neural control from the dorsomedial striatum to the dorsolateral striatum. Previous research based in autoshaping tested this sequential view using a presession feeding procedure. Lever pressing was reduced when presession feeding occurred early in training, but not after extensive training. Thus, autoshaping can be sensitive to the sequential transition from action to habit. However, this research was based on pairing the presentation of a single lever with food. In this experiment, rats received training with two levers, right and left (R, L) each paired with either 12 or 2 pellets (R12, L2). Reward validity was counterbalanced. Every 7th session, both levers were

paired with the same reward amount, either R2-L2 (R12 to R2 devaluation) or R12-L12 (L2 to L12 inflation) in two independent groups (n=8). In these devaluation/inflation sessions, all reinforced trials involved the presentation of one lever, but the session ended with a nonreinforced choice trial with both levers present. Four such sessions were distributed over the course of 28 daily sessions. In the case of the devaluation manipulation, there was no evidence of differential responding when animals were confronted with a single lever per trial. However, in the same sessions, given a choice between a downshifted lever vs. an unshifted lever, animals avoided the downshifted lever during the first and second choice trials, but not in the third and fourth choice trials. In the case of the inflation manipulation, responding to the lever was nondifferential whether in terms of single-lever or choice trials. Repeated testing tends to weaken control of lever pressing by reward expectancies in the case of devaluation—a result consistent with the sequential view of action-to-habit learning. However, the inflation procedure was ineffective, not surprisingly in view of recent research showing that reward upshifts have, at best, a weak effect on behavior. Animals responded to the downshifted lever just as much as to the unshifted lever when there was only one lever available, but rejected the downshifted lever when they had a choice, at least early in training. Thus, actions may be induced by forcing a simultaneous comparison between alternatives that have different incentive value. Future research will center on understanding the role played by the dorsal striatum in these within-sessions dissociations between actions and habits.

Disclosures: S.E. Conrad: None. **M.R. Papini:** None.

Poster

835. Cognition: Striatal Regions

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 835.12/III31

Topic: H.01. Animal Cognition and Behavior

Support: University of Sydney DVCR-BSG

Title: Chronic consumption of a palatable food increases microglia number and size in the dorsomedial striatum and reduces sensitivity to outcome devaluation.

Authors: *L. H. CORBIT, S. BECCHI, M. KENDIG, J. HOOD;
Univ. of Sydney, Sydney, Australia

Abstract: It is unknown why attempts to lose weight often fail even in motivated individuals. We have recently found that a diet high in sugar and fat promotes habitual control over food-seeking behaviours providing insight into why changing eating behaviours to achieve weight loss

is difficult. Although parallel corticostriatal circuits are known to be involved in goal-directed and habit-based learning, little is known about how experiences that accelerate habit learning, such as drugs and diet, alter activity in these circuits to promote premature habitual control. It is well established that obesity is associated with peripheral inflammation and increasing evidence suggests that obesity also produces inflammation in the brain. It is currently not known how obesogenic diets affect inflammation in brain regions that underlie goal-directed and habitual behavioural control. Microglia and astrocytes can be directly activated by inflammatory mediators including pro-inflammatory cytokines and upon activation undergo morphological changes. This activated morphology allows microglia to impact synaptic plasticity which could alter learning. To begin investigation into the role of microglia in the formation of habits we examined differences in the number and morphology of microglia in the dorsomedial (DMS) and dorsolateral striatum (DLS) from groups of rats receiving either obesogenic or control diets. Rats were given 5 weeks of access to either chow or chow and sweetened condensed milk (SCM) before instrumental training for a distinct food reward. Next, we examined whether goal-directed performance was impaired in these groups using the outcome devaluation task. Control rats reduced responding following devaluation of the earned outcome whereas rats with previous access to SCM responded similarly under the devalued and nondevalued conditions, indicating loss of goal-directed control of responding. Using analyses of 3-D morphological reconstructions of cells we found an increase in microglia number and size, particularly in the DMS, following chronic access to SCM. Pharmacological blockade of microglial activation preserved goal-directed control following chronic SCM. These results indicate that an obesogenic diet can promote microglial activation in decision-making circuits undermining the normal function of the goal-directed DMS system allowing early habitual control mediated by the DLS circuit. These results have important implications for understanding failures of behavioural control and strategies for improving behavioural flexibility.

Disclosures: **L.H. Corbit:** None. **S. Becchi:** None. **M. Kendig:** None. **J. Hood:** None.

Poster

835. Cognition: Striatal Regions

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 835.13/III32

Topic: H.01. Animal Cognition and Behavior

Support: NIH Grant 1P50MH106435

Title: Heterogeneous connectivity indicates pivotal hubs for network communication in the dorsal anterior cingulate cortex: An anatomy-guided discovery

Authors: *W. TANG, S. N. HABER;
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Abstract: An intriguing theory proposes that cortical hubs in the brain connect multiple functional networks and integrate across modalities. The hubs provide a structural basis for the brain to achieve both functional modularity and integration. However, current experimental support for the hub theory mainly comes from neuroimaging data, which indirectly measures neuronal connectivity. Whether anatomical hubs truly exist in the brain remains unclear. Answers to this question would provide not only the ground truth for the neuroimaging findings, but also precise targets for treating various brain diseases. In this study we investigated the dorsal Anterior Cingulate Cortex (dACC), a region known to be active in a variety of cognitive tasks involving reward, motivation, emotion, attention, decision making, social interaction or motor control. The evidence of anatomical hubs would provide a structural basis to account for this multifunctional nature.
We used tract tracing in the Macaque brain and diffusion MRI in both monkeys and humans, looking for whether and where the anatomical hubs exist and what comprises them. Retrograde tracers were injected into the caudal, rostral and ventral parts of anterior area 24 and the rostral part of area 32. Cell labeling in the cortex and amygdala was quantified using stereology. Consistent with the literature, there was a gradual change of connectivity along the dorsal-ventral and rostral-caudal axes, with the ventral and rostral injection sites receiving more inputs from the frontal pole, the ventral medial PFC and area 25, and the dorsal and caudal sites more from the orbitofrontal cortex, the dorsal lateral PFC, the premotor and motor areas. Interestingly, a site at the tip of the rostral area 24 violated this rule: it receives inputs from all of the afore-mentioned cortical divisions, and in addition, from the ventral lateral PFC, the multisensory temporal cortex and amygdala. The extensive inputs make this site stand out as a hub. It has 50% of the inputs coming from 9 different cortical areas, whereas for the non-hub sites this number was only 3 and 4. Next, we applied probabilistic tractography to the monkey diffusion data to show consistency with the tracing result. Finally, we applied analogous analysis on the human diffusion images. The rostral tip of Brodmann area 24 showed the most extensive connections with the PFC, identified as a human homologue to the Macaque hub site.
The results demonstrated the existence of an anatomical hub in dACC. A human homologue was also discovered under the guidance of the anatomy data. These findings bear great potential in advancing target-specific treatment of dACC-related brain dysfunction.

Disclosures: W. Tang: None. **S.N. Haber:** None.

Poster

835. Cognition: Striatal Regions

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 835.14/III33

Topic: H.01. Animal Cognition and Behavior

Support: Croatian Science Foundation HRZZ59443

Title: Regional differences in morphology of the striatal medium spiny neurons

Authors: I. BICANIC[1], D. DZAJA[2], U. BORNSCHEIN[3], *I. I. KOSTOVIC[4], Z. PETANJEK[1]; [1]Dept. of Anat. and Clin. Anat., [2]Sch. of Medicine, Univ. of Zagreb, Zagreb, Croatia; [3]Max Planck Inst. for Evolutionary Anthrop., Leipzig, Germany; [4]Sch. of Med, Univ. of Zagreb, Zagreb, Croatia

Abstract: Medium spiny projection neurons (MSNs) represent the most numerous neurons in the corpus striatum of mammals, birds and reptiles. Similar structure in different species makes them an essential organizational and functional role of the vertebrate brain. In the human brain, dysfunction of the striatal neurons leads to rather complex movement disorders and our complete understanding of the exact pathogenetic mechanisms is still needed. This led to the development of numerous animal models to study principles of striatal organization and pathology. The striatal complex is the site of convergence for a wide range of cortical and subcortical inputs so the dysfunction of any of those pathways can be expressed in various clinical presentations. In the mouse, the rostral part of striatum receives mainly cortical projections from limbic, central part from primary sensory-motor and caudal from associative parieto-occipital regions. We hypothesized that MSNs will show increase in morphological complexity from rostral to caudal part of striatum. Hence, by using Neurolucida system 162 striatal Golgi Cox impregnated MSNs from 15 adult mice where 3D-reconstructed and parameters of dendritic morphology where analyzed. For the purpose of the quantitative analysis neurons in the dorsal part of the central striatum where further divided in medial and lateral part, but no significant differences in dendritic morphology where observed between these two regions. Compared to the central part, MSNs in the caudal striatum had significantly higher tree complexity, 20% more segments and 30 % higher total dendritic length. In addition, the thickness of dendrites was also higher suggesting not only higher complexity but also higher functional activity of caudal MSNs. MSNs of rostral striatum have slightly less segments than in the central part, but have significantly higher total dendritic length (around 20%). Consequently, individual segments were 20-40% longer in the rostral compared to the other striatal regions. This is pointing at morphological specialization of MSNs in the limbic parts of striatum. Obtained data show that despite a uniform structure of mouse striatum there are important regional differences in their micro-circuitry structure. This should be considered in the research using various animal models studying

diseases affecting the striatum. It is likely to expect even more pronounced regional differences in the morphology of MSNs in the human (primate) brain.

Disclosures: I. Bicanic: None. **D. Dzaja:** None. **U. Bornschein:** None. **I.I. Kostovic:** None. **Z. Petanjek:** None.

Poster

835. Cognition: Striatal Regions

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 835.15/III34

Topic: H.01. Animal Cognition and Behavior

Support: H. Lundbeck A/S

Title: Preventing falls in PD in a rat model of impaired cognitive control of complex movements by a pro-cholinergic combination treatment

Authors: *A. J. KUCINSKI[1], I. E. M. DE JONG[2], M. SARTER[1];
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Abstract: Parkinson's disease (PD) patients, in addition to primary motor symptoms resulting from extensive losses of striatal dopamine (DA), suffer from an interrelated group of motor-control symptoms including postural instability, gait deficits, and a propensity for falls. These levodopa-insensitive symptoms are associated with losses of cortically-projecting cholinergic neurons of the basal forebrain (BF), as well as cognitive impairments such as poor attention. Given the high prevalence and severe consequences of falls in levodopa-treated patients, alternative treatment options are urgently needed. To assess potential treatments we have developed behavioral models of falls in rats including a test system (Michigan Complex Motor Control Task, MCMCT) that requires persistent control of gait, limb coordination, and carefully timed and placed steps during traversals of dynamic surfaces (rotating square rods). Rats with bilateral cholinergic lesions of the BF using 192 IgG-saporin and 6-OHDA lesions to the dopaminergic dorsomedial striatum (dual lesions, DL) exhibit falls while traversing rotating rods and these falls correlate with impaired performance of a sustained attention task. DL rats' falls have been hypothesized to result from interactions between disruption of normally cholinergically-driven transfer of extero- and interoceptive cue information from cortex to striatum and impaired striatal action sequencing. Here we tested the hypothesis that falls are reduced by co-treatment with acetylcholinesterase inhibitor donepezil and a 5-HT6 receptor antagonist. This combination treatment was previously reported to exhibit synergistic pro-

cholinergic activity in rats and improved cognition in patients with moderate Alzheimer's disease. Overall, drug-treated rats fell less frequently from the rotating rods and were particularly more efficient at reinstating forward movement after sudden stoppages of forward movement with a passive (doorframe) distractor task. This treatment combination may benefit fall propensity in PD patients via maintaining planned movement sequences in working memory and improving the vigor of executing such movements following brief periods of freezing of gait. The neuropharmacological interactions of this treatment may involve diverse signaling pathways converging onto striatal output neurons. Results from current experiments using microdialysis and HPLC-mass spectrometry to simultaneously assess release of striatal ACh, animo acids and monoamines during rotating rod traversals will assist in elucidating potential targets for therapeutic prevention of falls.
Supported by a grant from H. Lundbeck A/S

Disclosures: A.J. Kucinski: None. **I.E.M. de Jong:** None. **M. Sarter:** B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution; Received grant from H. Lundbeck A/S for drug study.

Poster

836. Models of Memory Consolidation, Protection, and Enhancement

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 836.01/III35

Topic: H.01. Animal Cognition and Behavior

Support: CONACYT CB-167773

Title: Pavlovian learning under enhanced D2-type activity facilitates heterosexual motivation in gonadectomized male rats

Authors: *M. BARRADAS[1,2], M. B. TECAMACHALTZI-SILVARÁN[1,2], L. I. GARCÍA-HERNÁNDEZ[1], P. CARRILLO-CASTILLA[1], J. MANZO-DENES[1], G. CORIA-AVILA[1]; [1]Neurosci., Ctr. De Investigaciones Cerebrales, Xalapa, Mexico; [2]Doctorado en Investigaciones Cerebrales, Univ. Veracruzana, Xalapa, Mexico

Abstract: Neonatally-gonadectomized male rats fail to express sexual motivation and performance in adulthood. We and others, however, have shown that sexual motivation, performance and preference can be modified via Pavlovian conditioning (PC); specially under enhanced D2-type activity. Herein, we explored the effects of PC under enhanced D2 activity on the facilitation of motivation, performance, preference and testosterone (T) levels of neonatally-

gonadectomized male rats. Three groups were formed: Intact , neonatally-gonadectomized (Gx) and Sham. On postnatal day 60 we tested the unconditioned partner preference before two potential partners: one sexually receptive female and one stud male. The groups Intact and Sham expressed an unconditioned sexual preference for the female. However, the Gx group failed to expresse motivation, performance and preference. Then, the three groups were allowed to cohabit with a sexually-receptive female during 24 hrs every four days, for a total of three trials. One minute before cohabitation they received saline or the D2 agonist quinpirole (1.25 mg/kg i.p.). Four days after the last conditioning process they were tested for conditioned partner preference in a drug-free test. The group Gx group expressed a conditioned preference for the female and low T, whereas the groups Intact and sham sensitized such preference and expressed higher T levels after exposure to the scent of receptive females, as compared to controls. These results indicate that cohabitation under enhanced D2-type activity facilitates learning by altering the incentive value of the partner, even in the absence of gonadal hormones. keywords: quinpirole, D2, dopamine, partner preference, sexual motivation, testosterone, gonadectomy.

Disclosures: **M. Barradas:** None. **M.B. Tecamachaltzi-Silvarán:** None. **L.I. García-Hernández:** None. **P. Carrillo-Castilla:** None. **J. Manzo-Denes:** None. **G. Coria-Avila:** None.

Poster

836. Models of Memory Consolidation, Protection, and Enhancement

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 836.02/III36

Topic: H.01. Animal Cognition and Behavior

Support: VIEP-BUAP 2016

CONACyT grants No. 243333 and 243247

Neuroendocrinology BUAP-CA-288

Title: High-yawning rats showed different memory abilities in the object recognition task

Authors: ***J. EGUIBAR**, L. DIAZ, A. UGARTE, A. TRUJILLO, C. CORTES;
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Abstract: We behaviorally selected two sublines from Sprague-Dawley (SD) rats one with a high-spontaneous yawning (HY) with a mean of 20 yawns/h and the other with a low-yawning frequency (LY) with just 2 yawns/h. HY rats are more anxious than low-yawning (LY) and SD subjects when tested in the open-field arena because they ambulated more and had less fecal boluses. We tested 24 subjects (Ss, 8 from each group of rats) which were maintained under

standard animal room conditions and with free access to rodent pellets and purified water all time except during testing conditions. Ss were under 12:12 light-dark cycle (lights on 0700), all experiments were done between 1000 to 1400 in a sound-proof room with a 300 lx illumination. All test were made in an open-field arena with two equidistant objects of the same form and weight (marble cubic) allowing the Ss to freely explore by 5 min, then one the objects was changed with a different form a marble triangular pyramid or a marble cylinder of the same size and weight and equidistant of the first object allowing an additional 5 min exploration time. Our results showed that one min after exposition of the new object only a tendency for higher exploration in the LY subline ($P \leq 0.057$) respect to the other two groups tested. However, memory recall 3 min after the introduction of the new object showed that LY subline significantly spent more time exploring the new object respect to HY and SD female rats ($P \leq 0.001$). Importantly, HY spent more time in vertical exploration, measured as a number of rearings plus wall-leanings, and also had higher number of grooming bouts respect lo LY and SD rats ($P \leq 0.05$). In summary, HY female rats showed different ongoing behavior in the open-field when a novel-object is present. These results imply that learning and memory capabilities differ between sublines, because HY rats explored less the new object but has higher exploration under this memory paradigm.

Disclosures: J. Eguibar: None. **L. Diaz:** None. **A. Ugarte:** None. **A. Trujillo:** None. **C. Cortes:** None.

Poster

836. Models of Memory Consolidation, Protection, and Enhancement

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 836.03/III37

Topic: H.01. Animal Cognition and Behavior

Support: CAPES

SFN

Title: Neuroprotective effect of hypothermia in the behavioral assessment of rats submitted to neonatal anoxia

Authors: *V. VASQUEZ MATSUDA, A. V. MACHADO-NILS, G. F. XAVIER;
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Abstract: Currently, one of the most important causes of brain injury in newborns is neonatal anoxia. This is the most serious problem in many hospitals around the world and even worse in

developing countries due to the lack of required precautions and care. Not long ago, many studies indicated that hypothermia has an important neuroprotective effect, thus could be used as a promising alternative treatment to the damage caused by neonatal anoxia. Although there are several studies demonstrating the neurological neuroprotective action of hypothermia, there is no solid evidence showing the effect of it on behavior, what is extremely important in order to access the effects of this agent completely.
The aim of this study is to evaluate the neuroprotective effect of hypothermia in animals undergoing neonatal anoxia, with a behavioral perspective, considering different functions of spatial memory, fear conditioning and anxiety in rats.
48 male Wistar rats were divided in 4 groups: anoxia control (AC), anoxia with hypothermia (AH), control with hypothermia (CH) and control without hypothermia (CC). The neonatal anoxia protocol started 24 hours after birth, using a semi-hermetic chamber completely saturated with nitrogen gas. The chamber temperature was maintained at 37°C and the time of exposure to anoxic conditions was 25 minutes. Hypothermia treatment was initiated immediately after the anoxia protocol, in a cooled chamber at 30°C, where the newborns remained for 5 hours. At the end of this period, newborns were put in a heated chamber at 37°C for 40 minutes until its recovery. When the animals were 70 days old the elevated plus maze was used to evaluate its anxiety levels. Subsequently, when the animals were 75 days old, a spatial memory tests were started using the Morris Water Maze. Lastly, when the animals were 115 days old, an evaluation of context and the sound fear conditioning were performed using a standard electroshock paired with sound protocol.
Our results on the elevated plus maze showed significant differences between CC and CH groups, demonstrating that hypothermia have an anxiogenic effect in rats. Significant differences between AC and AH groups were observed in the spatial memory tests, thus suggesting that hypothermia mitigates, on the behavioral level, the damage caused by neonatal anoxia. Finally, the results of fear conditioning showed that anoxia decreases the rate of aversive memories extinction, effect that was not observed in hypothermia treated groups. This evidence supports the idea that hypothermia is able to prevent memory damages caused by neonatal anoxia but also seems to have adverse impacts on other behavioral processes such as anxiety.

Disclosures: **V. Vasquez Matsuda:** None. **A.V. Machado-Nils:** None. **G.F. Xavier:** None.

Poster

836. Models of Memory Consolidation, Protection, and Enhancement

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 836.04/III38

Topic: H.01. Animal Cognition and Behavior

Support: Grants-in-Aid for Young Scientists (B, Grant Number 80509266), provided by the Ministry of Education, Culture, Sports

Grants-in-Aid for Young Scientists (B, Grant Number 25830057), provided by the Ministry of Education, Culture, Sports

Title: Alpha2-antiplasmin as a potential mediator contributing to memory function and age-related cognitive decline

Authors: *E. KAWASHITA[1], K. ISHIHARA[1], O. MATSUO[2], S. AKIBA[1];
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Abstract: [Background] Alpha2-antiplasmin (α 2AP), a member of the serine protease inhibitor (serpin) family, is known as a principal physiological plasmin inhibitor. α 2AP is mainly produced by the liver and kidneys, but is also expressed in various parts of the brain including the hippocampus and cortex. Our previous study demonstrated that α 2AP is sufficient to induce the expression of microtubule-associated protein 2, which regulates the development and stabilization of dendrites, and to promote dendritic growth in hippocampal neurons. This suggests that α 2AP could be a potential regulator of morphological plasticity in neurons. However, the roles of α 2AP in brain function have not been sufficiently addressed. [Aims] We investigated the role of α 2AP in memory functions, and the possible factors of the molecular mechanisms controlled by α 2AP. We also investigated the relation of α 2AP to age-related cognitive decline. [Methods] Microarray analysis of genes expressed in the hippocampus and cortex of the α 2AP knockout (α $2AP^{-/-}$) mice and WT mice was performed. The memory functions of the α $2AP^{-/-}$ mice and wild type (WT) mice were examined using the Y-maze test, Morris water maze (MWM) test and fear conditioning test. The effects of intracerebroventricular (icv) injection of an anti-α 2AP-neutralizing antibody or α 2AP on memory functions were evaluated using the MWM test. We also measured the levels of α 2AP in the hippocampus and cortex of young (11-16 weeks) and old (93-138 weeks) mice, and then the association between the levels of α 2AP and cognitive function were investigated using Pearson's correlation analysis. [Results] Microarray analysis identified that 82 genes associated with behavior, memory function or aging were differentially expressed between the α $2AP^{-/-}$ mice and WT mice with a greater than 1.5-fold change. The α $2AP^{-/-}$ mice exhibited impairments in working memory, spatial memory and fear conditioning memory compared with WT mice. Unexpectedly, the icv injection of an anti-α 2AP-neutralizing antibody enhanced the memory formation and retention in the MWM test, while the injection of α 2AP impaired memory retention, but not memory formation. We also found that the levels of α 2AP in the hippocampus and cortex were higher in old mice than in young mice, and had a negative correlation between the levels of α 2AP and cognitive function. [Conclusion] α 2AP is a potential regulator responsible for neuronal plasticity during both brain development and memory function, and may be involved in age-related cognitive decline.

Disclosures: **E. Kawashita:** None. **K. Ishihara:** None. **O. Matsuo:** None. **S. Akiba:** None.

Poster

836. Models of Memory Consolidation, Protection, and Enhancement

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 836.05/III39

Topic: H.01. Animal Cognition and Behavior

Support: Fondation pour la Recherche Médicale

CNES

ANR

CNRS

Aquitaine Region

Title: Deleterious effects of hypertension on the organization of recent and remote memories in the spontaneously hypertensive rat

Authors: A. PULGA, A. HAMBUCKEN, A. COSTET, J.-L. MOREL, *B. BONTEMPI; Inst. of Neurodegenerative Diseases, CNRS UMR 5293, Bordeaux, France

Abstract: While hypertension (HT) is considered a major risk factor for inducing memory impairments or aggravating cognitive decline associated with vascular dementia or Alzheimer's disease, the mechanisms underlying these deleterious effects remain unclear. Here, using the genetic model of spontaneously hypertensive rats (SHRs) which exhibit spontaneous arterial hypertension without developing comorbidity or spontaneous cerebral hemorrhages, we investigated to what extent the organization of recent and remote memory could be altered during the course of this pathological condition. The memory profile of 4- and 6-month old SHRs was established using the social transmission of food preference task in which rats learn about the safety of potential food sources by sampling those sources on the breath of conspecifics. Independent groups of rats were trained and tested for retrieval either 2 days (recent memory) or 30 days (remote memory) following encoding of olfactory associative information. At the age of 4 months, SHRs exhibited an elevated and stabilized blood pressure (BP) compared to age-matched Wistar Kyoto control rats but no memory impairment. In contrast, older SHRs with 2 more months of sustained history of elevated BP as measured by the tail-cuff method showed evidence of time-dependent memory impairment. Remote memory was impaired while recent memory was spared, thus suggesting successful encoding but an inability to adequately stabilize and/or retrieve remotely acquired information. Potential confounding factors such as olfactory sensitivity (odor detection threshold using the paper filter test) and initial memory strength (number and duration of nose contacts during social interaction) were not responsible for this impaired memory profile in SHRs. In addition, chronic treatment with

Losartan (20 weeks; 15.5 mg/kg/day in drinking water, adjusted to normotensive range), an antagonist of angiotensin II receptor type 1, was efficacious in reducing BP and partly rescuing remote memory, indicating that sustained HT is involved in the observed cognitive deficits of SHRs and likely interferes with systems-level memory consolidation. Altogether, these findings point to the SHR model as a valuable tool to examine the relationships between HT, vascular networks and the dynamics of memory formation in the brain. Ongoing experiments are exploring the underlying neurofunctional correlates of memory impairments in SHRs, notably the pattern of neuronal activation (as revealed by Fos protein expression) in hippocampal and cortical regions actively engaged in remote memory formation and the status of vascular networks in these brain regions.

Disclosures: **A. Pulga:** None. **A. Hambucken:** None. **A. Costet:** None. **J. Morel:** None. **B. Bontempi:** None.

Poster

836. Models of Memory Consolidation, Protection, and Enhancement

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 836.06/III40

Topic: H.01. Animal Cognition and Behavior

Support: NIH Grant 5R01MH097695

Title: Deep brain stimulation of the nucleus basalis of meynert improves working memory

Authors: ***R.-F. LIU**[1], J. CRAWFORD[1], P. CALLAHAN[2], A. V. TERRY[2], C. CONSTANTINIDIS[3], D. T. BLAKE[1];
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Abstract: The degeneration of basal forebrain cholinergic neurons is usually coupled with decline of the cognitive functions. Cholinesterase inhibitors are used to treat Alzheimer's Disease by increasing the cholinergic level in the behavior-related brain regions. The prefrontal cortex, which is tightly relevant to the working memory, receives cholinergic projections from the nucleus basalis (NB). Here, we investigated the influence of deep brain stimulation in NB to working memory performance.
Two monkeys were trained to perform a delay-match-to-sample task. During the task, working memory is engaged to remember the color of the sample and select the target sharing the same color. Stimulation electrodes were implanted into NB bilaterally in the monkeys' brains. On some days, donepezil was given before the animals' behavioral session. We collected behavioral

data and analyzed the animals' performance in control condition, NB-stimulation condition, donepezil condition and 'NB-stimulation and donepezil' condition.
We found decrements in animals' behavioral performance when 80Hz continuous pulse stimulation was applied to NB. In contrast, 60Hz intermittent pulse stimulation in NB improved the animals' performances. Through analyzing the correct percentage of trials compared to their positions relative to changes in stimulation condition, we found the effects of stimulation are maximal within at most 3 minutes. We also compared the local field potentials before and after the NB stimulation. Power spectrum analysis shows that stimulation desynchronizes neural activity at frequencies less than 16Hz. To determine the mechanism of the improvement of memory by stimulation in NB, donepezil, a cholinesterase inhibitor, was given to the animal just before testing. The boost of the animal's behavioral performance was dose dependent. In the stimulation+donepezil condition, performance was no longer dose dependent, but performance was significantly
higher than that in control condition. This result implies that the behavioral improvement by NB stimulation and by donepezil share the same neural mechanism.
The results of this study indicate that electrical stimulation of NB decreases neural synchronization in the brain, and the stimulation using an intermittent, but not a continuous, strategy leads to cognitive improvement. This improvement likely utilizes the basal forebrain cholinergic system and its projections to prefrontal cortex.

Disclosures: R. Liu: None. **J. Crawford:** None. **P. Callahan:** None. **A.V. Terry:** None. **C. Constantinidis:** None. **D.T. Blake:** None.

Poster

836. Models of Memory Consolidation, Protection, and Enhancement

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 836.07/III41

Topic: H.01. Animal Cognition and Behavior

Support: NCCIH Center Grant P50 AT008661-01 to GMP

Title: Optogenetic analysis of polyphenol-induced resilience against sleep deprivation-associated cognitive deficits

Authors: *C. SMITH[1,2], T. FROLINGER[1,2], J. WANG[1,2,3], G. M. PASINETTI[1,2,3];
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[3]Geriatric Research, Educ. and Clin. Ctr., James J. Peters Veterans Affairs Med. Ctr., Bronx, NY

Abstract: Sleep deprivation (SD) is a common problem in our society and is linked to a number of physiological and cognitive co-morbidities, including memory impairments. SD disrupts the consolidation period of memory formation and results in downregulation of the cAMP/PKA/CREB signaling pathway, mTOR, and decreased expression of plasticity-related genes including immediate early genes (IEGs) such as c-fos. We have found that treatment with certain bioavailable bioactive phenolic metabolites (BBPMs) provides physiological resilience against SD-induced cognitive deficits, activates the CAMKII and CREB signaling pathways, and induces c-fos expression. To determine the mechanism through which BBPMs provide resilience to SD in neurons activated by behavioral testing, we are using c-fos-tTA transgenic mice to label memory-bearing neurons (tet-labeling) with opsin proteins expressed through a Tetracycline Response Element (TRE), a novel technology that has been used to investigate memory engrams in specific brain regions. Recently, tet-labeling has been used to generate false memories and suppress hippocampal memory engrams in the contextual fear conditioning (CFC) memory test. Ongoing experiments in our labs are testing the feasibility of this approach by injecting mice with a pan-neuronal AAV expressing eNpHR3.0 to silence hippocampal neurons bearing emotional and spatial memories. We will also test the hypothesis that SD impairs memory consolidation through disrupting IEG expression and plasticity-related pathways and BBPMs provide resilience against cognitive impairment through modulating these pathways. The ultimate goal of our studies is to use the c-fos-tTA/TRE-ChR2 model system and to explore the beneficial role of oral administration of BBPMs in cognitive impairment following SD. We hypothesize that optogenetic activation or silencing of memory-bearing neurons in the CFC memory test will cause expression or suppression of fear memory, respectively, allowing for quantification of resilience to SD. Though histological analysis, we will examine the overlap of tet-labeled neurons with IEGs and signaling pathways to determine mechanistically how BBPMs provide resilience to SD. Our ongoing studies will allow the definition of select subpopulations of neurons in brain regions of interest involved in mechanisms associated with cognitive impairment in response to SD. Due to the fact that SD is a common problem in our society, understanding the impact of SD on cognitive function is of great importance.

Disclosures: **C. Smith:** None. **T. Frolinger:** None. **J. Wang:** None. **G.M. Pasinetti:** None.

Poster

836. Models of Memory Consolidation, Protection, and Enhancement

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 836.08/III42

Topic: H.01. Animal Cognition and Behavior

Support: NCCIH Center Grant P50 AT008661-01 to GMP

Title: Gender associated molecular responses in cognitive impairment mediated by chronic sleep deprivation

Authors: *T. FROLINGER[1,2], C. SMITH[1,2], J. WANG[1,2,3], G. M. PASINETTI[1,2,3];
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Abstract: Sleep deprivation (SD) is a common problem in our society. Chronic SD is co-morbid with a number of physiological and cognitive problems, including mental illness and memory deficits. SD is hypothesized to disrupt the consolidation period of memory formation through down regulation of cAMP/PKA/CREB, mTOR signaling pathway, and the expression of immediate early genes (IEGs) and other plasticity-related genes. We found that certain brain bioavailable bioactive phenolic compounds (primarily flavan-3'-ols) provide resilience to acute-SD-mediated cognitive decline in male mice through activation of the CREB, CAMKIIa signaling pathways and induction of IEG expression. Most interestingly, using the novel object recognition paradigm we found a relationship between the estrous cycle phases of low estrogen (metestrus, diestrus, estrus) and; I. Reduced cognitive performance in control females, II. Stress response in sleep deprived females, when compared to male mice in the SD model. This evidence is consistent with the fact that the estrous cycle is accompanied by hippocampal changes that affect memory consolidation, suggesting superiority in learning task performances of proestrus females compared to males. We are currently exploring gender differences in memory performance and gene expression in response to chronic SD, using the c-fos-tTA/TRE optogenetics system to visualize the regional distribution of signaling pathways at molecular level. The study will provide an amenable system to further investigate the potential beneficial role of currently available phenolic metabolites to investigate the molecular relationship between cognitive function and changes in brain gene expression in a gender related fashion. In view of the fact that SD affects more than 70 million Americans, the social implication of this study on cognitive performance is of the foremost importance.

Disclosures: **T. Frolinger:** None. **C. Smith:** None. **J. Wang:** None. **G.M. Pasinetti:** None.

Poster

836. Models of Memory Consolidation, Protection, and Enhancement

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 836.09/III43

Topic: H.01. Animal Cognition and Behavior

Support: Erasmus Mundus Joint Doctorate Programme EUROSPIN

EPSRC Doctoral Training Centre in Neuroinformatics and Computational Neuroscience

Title: Sleep-dependent acquisition and adaptation of neocortical semantic networks - a restricted boltzmann machine model

Authors: *N. DUPUY[1,2], M. VAN ROSSUM[1];
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Abstract: It is widely assumed that new declarative memories are initially stored in the hippocampus, and subsequently slowly consolidated in the neocortex where they are reorganised into semantic networks. Experiments with rodents (Tse et al 2007, 2011) reveal that such neocortical networks can in turn facilitate the acquisition and consolidation of new related information.
The consolidation of declarative memory is sleep-dependent. An emerging idea posits that memories are not equally processed during sleep, but are selectively strengthened according to their "salience tags" (Stickgold & Walker, 2013)(to contrast with molecular synaptic tags)(Stickgold & Walker, 2013). However, the neural mechanisms to create such tags and compute salience remain unclear.
Here we implement a hierarchical computational model of hippocampal-neocortical interaction (Kali & Dayan, 2004) to investigate the formation of semantic networks and their influence on subsequent learning. The model is composed of (1) a Restricted Boltzmann Machine (neocortex) to extract the semantic information and (2) a hippocampal module to support rapid memory encoding and recall. The hippocampus drives the replay of episodes during sleep.
We observe that selective replay during sleep promotes memory consolidation at the expense of overwriting non-replayed memories, and hence governs how semantic networks develop. Our model has a natural way to detect whether an event is familiar, novel but consistent, or novel and conflicting with existing semantic knowledge. We suggest using this signal as the "salience tag" to regulate the replay of a memory. We show that the salience signal becomes stronger as the semantic networks are formed in the neocortex, in line with Richards et al. (2014).
We study how this process allows for the stability-adaptability control of semantic networks depending on the salience of an event. Similar to the findings of Tse et al., the presence of a semantic network improves the consolidation of new consistent memories but not conflicting ones.
However rapid consolidation comes at the cost of greater interference with existing semantic knowledge.

Disclosures: N. Dupuy: None. **M. van Rossum:** None.

Poster

836. Models of Memory Consolidation, Protection, and Enhancement

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 836.10/III44

Topic: H.01. Animal Cognition and Behavior

Support: MEXT KAKENHI 20022012

MEXT KAKENHI 15K12767

MEXT KAKENHI 24227001

Title: SCOP-dependent circadian regulation of memory formation for novel object

Authors: *K. SHIMIZU[1], Y. KOBAYASHI[1], E. NAKATSUJI[1], M. YAMAZAKI[2], K. SAKIMURA[2], Y. FUKADA[1];
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Abstract: Evidence from previous studies demonstrates that circadian rhythms affect memory formation. However, it is not yet clear if the internal clock regulates the efficiency of the memory formation, and there is no molecular-based evidence that connects the memory formation with circadian rhythms. We performed novel object recognition task on mice over the circadian time. Efficiency of long-term memory formation varied in a circadian manner and hence it appears to be controlled by the endogenous circadian clock. In fact, electrolytic lesion of the suprachiasmatic nucleus (SCN), a master *circadian clock in mammals*, disrupted the circadian rhythm of long-term memory formation. Forebrain-specific clock disruption in genetically engineered mice also abrogated the circadian oscillation of long-term memory formation. We focused on SCOP and the related molecules to find a molecular process that connects the circadian clock with memory formation. SCOP is expressed in a circadian manner in the SCN (Shimizu et al. FEBS Lett 1999), and SCOP negatively regulates K-Ras function and its downstream ERK/MAPK pathway (Shimizu et al. JBC 2003). In the hippocampus, SCOP plays a critical role in long-term memory formation for novel objects (Shimizu et al. Cell 2007). These data together suggest that SCOP-K-Ras-ERK pathway plays a key role for the circadian control of long-term memory formation in the hippocampus. We found that SCOP and K-Ras protein levels exhibited circadian variation in the hippocampal membrane rafts. SCOP knockdown in the hippocampus CA1 by shRNA-expressing lentivirus attenuated the circadian oscillation of long-term memory formation for novel objects. SCOP knockout mice showed no significant circadian oscillation in the amount of K-Ras in the membrane rafts and in long-term memory for novel objects. Circadian changes in learning-dependent activation of ERK in the hippocampal CA1 were dependent on the SCOP levels in the membrane rafts, while *Scop* knockout abrogated the activation rhythm. We conclude that circadian regulation of long-term

memory formation for object recognition is mediated by rhythmically expressed SCOP protein in the hippocampal membrane rafts.

Disclosures: K. Shimizu: None. **Y. Kobayashi:** None. **E. Nakatsuji:** None. **M. Yamazaki:** None. **K. Sakimura:** None. **Y. Fukada:** None.

Poster

836. Models of Memory Consolidation, Protection, and Enhancement

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 836.11/III45

Topic: H.01. Animal Cognition and Behavior

Title: Neuroprotective role of intermittent hypobaric hypoxia in unpredictable chronic mild stress induced depression in rats

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Abstract: Hypoxic exposure results in several pathophysiological conditions associated with nervous system, these include acute and chronic mountain sickness, loss of memory, and high altitude cerebral edema. Previous reports have also suggested the role of hypoxia in pathogenesis of depression and related psychological conditions. On the other hand, sub lethal intermittent hypoxic exposure induces protection against future lethal hypoxia and may have beneficial effect. Therefore, the present study was designed to explore the neuroprotective role of intermittent hypobaric hypoxia (IHH) in Unpredictable Chronic Mild Stress (UCMS) induced depression like behaviour in rats. The IHH refers to the periodic exposures to hypoxic conditions interrupted by the normoxic or lesser hypoxic conditions. The current study examines the effect of IHH against UCMS induced depression, using elevated plus maze (EPM), open field test (OFT), force swim test (FST), as behavioural paradigm and related histological and molecular approaches. The data indicated the UCMS induced depression like behaviour as evident from decreased exploration activity in OFT with increased anxiety levels in EPM, and increased immobility time in the FST; whereas on providing the IHH (5000m altitude, 4hrs/day for two weeks) these behavioural changes were ameliorated. The morphological and molecular studies also validated the neuroprotective effect of IHH against UCMS induced neuronal loss and decreased neurogenesis. Here, we also explored the role of Brain-Derived Neurotrophic Factor (BDNF) in anticipatory action of IHH against detrimental effect of UCMS as upon blocking of BDNF-TrkB signalling the beneficial effect of IHH was nullified. Taken together, the findings of our study demonstrate that the intermittent hypoxia has a therapeutic potential similar to an

antidepressant in animal model of depression and could be developed as a preventive therapeutic option against this pathophysiological state and neurological disorders.

Disclosures: **N. Kushwah:** None. **V. Jain:** None. **N. Khan:** None.

Poster

836. Models of Memory Consolidation, Protection, and Enhancement

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 836.12/III46

Topic: H.01. Animal Cognition and Behavior

Support: R01 GM105696

Northwest Mitochondrial Research Guild

Title: Effects of astrocytic and region-specific knock outs of Ndufs4 on volatile anesthetic response

Authors: ***R. RAMADASAN NAIR**, J. HUI, P. G. MORGAN, M. M. SEDENSKY; Developmental Therapeut., Seattle Children's Res. Inst., Seattle, WA

Abstract: Background: The cellular circuitry and the brain regions involved in mediating anesthesia are not well elucidated. Mice featuring global or glutamatergic knock out of the mitochondrial protein NDUFS4 display increased sensitivity to volatile anesthetics (VAs)[1]. Recent research shows that astrocytes may play a role in mediating anesthesia by altering Ca^{2+} transients independent of neuronal activity[2]. In this study, we analyzed the role played by astrocytes and specific regions of the mouse brain in mediating anesthetic sensitivity of *Ndufs4*.
Methods: The SCRI IACUC approved all studies. We constructed a transgenic mouse line *Pgfap-CreERT2*; Ndufs4Δ/lox, which expresses Cre-recombinase in GFAP-expressing cells. For the region-specific knockout (KO), we injected adeno-associated viruses (10^9 pfu) encoding Cre-recombinase or control virus into the vestibular nucleus (VN) and the central medial thalamus (CMT) of *Ndufs4* floxed mice, allowed to recover for 3 weeks. Behavioral testing for sensitivity to anesthesia involved subjection of the mice to isoflurane (ISO) or halothane (HAL) to analyze of the loss of righting reflex (LORR) or response to a tail clamp (TC) as described by Sonner *et al.*[3]
Results: EC_{50}s for each VA were not different between the astrocytic knock-out (KO) and control animals but the dose-response curve for ISO and HAL showed hysteresis (ΔH) between induction and emergence [ΔH for Control – (ISO for TC= 0.26, LORR=0.03 and HAL for TC=0.31, LORR=0.09) and KO (ISO for TC= 0.54*, LORR=0.28* and HAL for TC=0.52*,

LORR=0.43*) p<0.005].
For the region-specific knock-outs, WT-Cre virus injections to the VN increased the EC50s of mice to ISO and HAL [Control – (ISO=1.21, HAL=1.22) and KO (ISO=1.45*, HAL=1.35*)] for TC response. Knocking out *Ndufs4* in the CMT decreased the EC50s for TC to both VAs [Control – (ISO=1.25, HAL=1.30) and KO (ISO=1.00*, HAL=1.00*) p<0.01].
Discussion: Neural inertia/hysteresis between the anesthesia induced loss and regain of consciousness is not explained by pharmacokinetics. Our study shows that astrocytes play a role in generating this inertia. We hypothesize that energy deficits in astrocytes disrupt Ca^{2+} homeostasis, delaying glutamate cycling leading to inability to regain synaptic function in the presence of VAs. Region-specific Ndufs4 KO in the CMT hypersensitize mice to VAs possibly by suppressing glutamatergic relaying to the cortex, while a similar loss in VN confers resistance probably by suppression of inhibitory signaling to the spinal cord.
References: 1. Quintana, A., et al. *PLoS One* **7**, e42904(2012). 2. Thrane, A.S.*, et al. PNAS U S A* **109**, 18974-18979(2012). 3. Sonner, J.M.*, et al. Anesth* **106**, 107-113(2007).

Disclosures: R. Ramadasan Nair: None. **J. Hui:** None. **P.G. Morgan:** None. **M.M. Sedensky:** None.

Poster

836. Models of Memory Consolidation, Protection, and Enhancement

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 836.13/III47

Topic: H.01. Animal Cognition and Behavior

Support: NIH DC007690

Title: Development and structural plasticity of dendritic spines throughout the critical period for imprinting

Authors: *G. BATISTA[1], E. DOMINGUEZ[1], J. JHONSON[2], M. COSTA-MATTIOLI[2], J. L. PENA[1];
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Abstract: Imprinting is a specific form of learning that only occurs during a critical period. The mechanisms underlying the critical period of imprinting remain largely unknown. We approached this question investigating filial imprinting in chickens. Previously, we have found that translational control by eIF2α dephosphorylation mediates auditory imprinting and mTORC1 activation regulates imprinting to sounds and objects. To further understand the role of these two pathways in imprinting we analyzed dendritic spines of imprinted chickens combining

confocal imaging with Diolistic labeling. We found that experience-dependent changes in spine morphology require eIF2α and mTORC1 in a manner consistent with behavioral results. Training increases mushroom spines in the auditory-imprinting area (MNM) and in the visual imprinting area (IMM). This increase is only blocked inhibitors of eIF2α dephosphorylation in the auditory area MNM. On the other hand, blocking mTORC1 with rapamycin abolished structural plasticity in both the auditory and visual regions. In addition, we compared spine morphology and structural plasticity inside and outside the critical period. We found that maturation of spines occurs even in chickens undergoing sensory deprivation. Furthermore, structural plasticity in imprinting areas also exhibits a critical period. Together our results demonstrate that eIF2α and mTORC1 not only are necessary for imprinting but also underlie structural plasticity in imprinting-relevant areas of the brain.

Disclosures: **G. Batista:** None. **E. Dominguez:** None. **J. Jhonson:** None. **M. Costa-Mattioli:** None. **J.L. Pena:** None.

Poster

836. Models of Memory Consolidation, Protection, and Enhancement

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 836.14/III48

Topic: H.01. Animal Cognition and Behavior

Support: Diets and consulting provided by Mead Johnson Nutrition

Title: Young pigs exhibit differential exploratory behavior during novelty preference tasks in response to age, sex, and delay.

Authors: *S. A. FLEMING[1,2], R. N. DILGER[1,2];
[1]Animal Sci., Univ. of Illinois at Urbana-Champaign, Urbana, IL; [2]Neurosci. Program, Urbana, IL

Abstract: Novelty preference paradigms have been widely used in rodent, primate, and human models to study recognition memory and its neural substrates. The pig continues to gain acceptance as an animal model to study neurodevelopment, and as such, tasks that use novelty preference will serve especially useful due to the translatable nature to humans. However, there has been little use of these behavioral paradigms in the pig. Furthermore, previous studies using the novel object recognition paradigm in pigs have yielded inconsistent results. The current study was conducted to determine if young pigs were capable of displaying a novelty preference using the novel object and novel location recognition tasks in pigs younger than 4 weeks of age. In a series of four experiments, 56 pigs (32 female and 24 male) were used to asses performance on

the novel object recognition task and 21 pigs (all male) were used to assess performance on the novel location recognition task at postnatal weeks 3 and 4. Pigs displayed thigmotaxic behavior during the habituation trials ($P < 0.001$) but not during sample ($P = 0.222$) or test trials ($P = 0.301$). In the novel object recognition task, pigs were able to discriminate between novel and sample objects after delays of 2 minutes ($P = 0.004$), 1 hour ($P = 0.025$), 24 hours ($P =0.031$), and 48 hours ($P = 0.001$) when as young as three weeks of age. Four-week-old pigs spent greater time investigating both the novel and sample objects ($P < 0.001$) and habituated to the novel object more quickly than 3 week old pigs ($P = 0.036$). When controlling for sex, 3-week-old female pigs were capable of discriminating between novel and sample objects at 1 and 2 day delays (all $P < 0.031$), while male pigs could discriminate between novel and sample after a 2 day delay ($P = 0.007$), but not after a 1 day delay ($P = 0.347$). Additionally, female pigs habituated to the novel object more quickly than male pigs ($P = 0.026$). Such performance however did not extend towards tests on the novel object location task, as pigs were unable to discriminate between novel and familiar locations after delays of 2 minutes, 24 hours, or 48 hours (all $P > 0.200$). Taken together, we conclude that the novel object recognition paradigm, but not the novel location recognition paradigm, is suitable for use in young pigs, and performance is sensitive to sex, age, and delay.

Disclosures: **S.A. Fleming:** C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Mead Johnson Nutrition. **R.N. Dilger:** C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Mead Johnson Nutrition.

Poster

836. Models of Memory Consolidation, Protection, and Enhancement

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 836.15/III49

Topic: H.01. Animal Cognition and Behavior

Support: Sally McDonnell Barksdale Honors College

Title: The effects of adrenergic receptor antagonists on avain memory

Authors: ***N. J. WEBB**[1], A. HRIBAR[2], J. PEGUES[2], T. WILLIAMS[2], L. DAY[2];
[2]Biolody, [1]Univ. of Mississippi, University, MS

Abstract: In mammals, fear conditioning is influenced by both the adrenergic system as it contributes to consolidation and reconsolidation of memories and the cerebellum as it relates to the consolidation of fear based memories. The arcopallium and posterior pallial amygdala, and cerebellum are thought to be homologs to the mammalian amygdala, and cerebellum

respectively. The adrenergic system appears to have a conserved distribution, but species specializations for cued memory have been found. We have previously shown that several functions of the cerebellum are conserved between mammalian species and the zebra finch. Lesions of the cerebellum result in deficits in spatial learning, postural adjustments, and timing of learned vocalizations. In contrast, we have tested for a conserved role of the adrenergic system in spatial and cued fear conditioning memory and have found no evidence that different doses of adrenergic antagonists that have been given at several time points or chronically during learning affect learning or retention of memory in spatial & cued fear conditioning tasks as they do in rodents. The neural circuitry underlying fear conditioning is well known and because the β-adrenergic receptor system and cerebellum are known to be involved in fear conditioning; we tested whether the β-adrenergic antagonist, propranolol would interfere with retention of fear memories. Cerebellar lesions were investigated to see if it would interfere with fear learning in the zebra finch using a standard fear conditioning chamber adapted for birds. Cerebellar lesions were performed in line with previous experiments in our lab with coordinates at ±1.1, -2.7, -4.6 and birds were tested 48 hours after lesions in the fear conditioning setting. We did not see any behavioral deficits in learning or retention under these conditions. Thus, it appears that the role of the adrenergic system and the role of the cerebellum in fear conditioning are not conserved across species. Propranolol has been shown to reduce immediate-early gene expression in songbird nuclei. However, timing of adrenergic administration and location of lesion placement in the cerebellum can determine whether deficits occur. To avoid repeated testing of various times and lesion locations, we will next examine the location of immediate early genes activation that occurs during fear conditioning with and without adrenergic antagonist. It has previously been shown that when behavioral deficits are not apparent, IEG activation can indicate the effects of antagonists on the brain. These experiments should clearly show the parts of the brain involved in fear conditioning.

Disclosures: **N.J. Webb:** None. **A. Hribar:** None. **J. Pegues:** None. **T. Williams:** None. **L. Day:** None.

Poster

836. Models of Memory Consolidation, Protection, and Enhancement

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 836.16/III50

Topic: H.01. Animal Cognition and Behavior

Support: CNPq

CAPES

FAPITEC

UERN

Title: Behavioral and neurobiological evaluation of memory in the neotropical lizard Tropidurus hispidus

Authors: J. R. SANTOS[1], L. G. SANTOS[2], E. L. SANTOS[2], E. R. SANTOS[2], F. S. GONZAGA[2], L. B. JESUS[2], L. P. M. JESUS[2], R. S. SILVA[2], A. M. GOIS[2], M. MACEDO-LIMA[4], *M. A. FREIRE[5], M. MARCHIORO[3];
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Abstract: In mammals, associations between memory formation and amygdala or hippocampus activation are well established. Neuroanatomical and neurochemical data have suggested homologies between the mammalian hippocampus and amygdala and related structures of the reptile telencephalon. Yet, there is little functional evidence regarding the role of these structures regarding memory formation in reptiles. The aim of this work was to perform a behavioral and neurobiological evaluation of memory in the neotropical lizard *Tropidurus hispidus*. Fifty adult male lizards (CEPA Committee ID #25/2013) were divided into two experiments: Experiment 1 (n=40), aversive memory; and Experiment 2 (n=10), spatial memory. In Experiment 1, the animals were divided into three groups: control (CG), n=8; neutral stimulus (NS), n=16; and aversive stimulus (AS), n=16. While the control group did not participate in the behavioral steps, NS group was exposed to an empty cage, and AS group was exposed to a domestic cat. After, all animals of CG and a half of the animals of both NS and AS groups were perfused with paraformaldehyde 4% for further brain analysis. The remaining animals of NS and AS groups were returned to the accommodation terrarium and after 24 hours have undergone a re-exposure to the same place of the previous stimuli, being then perfused. Brains were collected and subjected to imunohistochemistry to zif-268, a protein involved in mediating plasticity that occurs during memory formation. We found that during exposure to the cat AS group presented a higher freezing time ($p<0.001$), a small number of initiated movements ($p<0.001$) and visited quadrants ($p<0.001$) as compared with NS group. In addition, during the re-exposure to aversive environment, animals of the AS group remained presenting a higher freezing time ($p<0.001$), a small number of initiated movements ($p<0.001$) and visited quadrants ($p<0.001$), suggesting that exposure to the cat acted as aversive stimulus. There also was increase in the number of zif-268-reactive cells in regions of the hippocampus and amygdala in AS group ($p=0.005$ and $p=0.039$, respectively) and also after re-exposure to aversive context ($p=0.001$ and $p=0.009$, respectively). In experiment 2, lizards underwent an adaptation on the Morris water maze, 3 times a day during 19 days, where they performed attempts to find a submerged platform. We found a negative correlation ($p=0.012$) on the time to reach the platform over the days, indicating an improvement in the performance of the lizards in the task. Our results indicate that lizards are able to form aversive and spatial memories, and, at least for the first case, there is an involvement of the hippocampus and amygdala.

Disclosures: **J.R. Santos:** None. **L.G. Santos:** None. **E.L. Santos:** None. **E.R. Santos:** None. **F.S. Gonzaga:** None. **L.B. Jesus:** None. **L.P.M. Jesus:** None. **R.S. Silva:** None. **A.M. Gois:** None. **M. Macedo-Lima:** None. **M.A. Freire:** None. **M. Marchioro:** None.

Poster

836. Models of Memory Consolidation, Protection, and Enhancement

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 836.17/III51

Topic: H.01. Animal Cognition and Behavior

Support: NIH grants R01 MH096120

R01 NS029563

NSF grant IOS 1121690

Title: Dna methylation maintains long-term sensitization in *Aplysia*

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Abstract: Studies in mammals have pointed to a central role for DNA methylation in the maintenance of long-term memory (LTM) (Day and Sweatt, 2010). Moreover, electrophysiological experiments on *Aplysia* sensorimotor cocultures have shown that inhibition of DNA methyltransferase (DNMT) abolished the induction of long-term facilitation (LTF), a cellular analog of long-term sensitization (LTS) in *Aplysia* (Rajasethupathy et al., 2012). Here, we asked whether DNA methylation mediates the consolidation and/or maintenance of LTS of the siphon-withdrawal reflex (SWR) in *Aplysia*. To address this question, we test whether injecting a DNMT inhibitor into *Aplysia* prior to, immediately after, or as late as 5 d after, sensitization training disrupted the LTM for sensitization. The initial, full sensitization training consisted of five spaced bouts of electrical shocks (5X training) delivered to the tail via implanted electrodes. The drug or vehicle solution was injected into the hemocoel prior to, or at various times after, the 5X training. In initial experiments we found that an injection of the DNMT inhibitor RG108 made prior to 5X training disrupted LTM, as assessed by a test of the

SWR at 24 h posttraining. Recently, we demonstrated that truncated sensitization training, comprising three spaced bouts of tail shocks (3X training), could reinstate LTM disrupted by either inhibition of PKM or reconsolidation blockade (Chen et al., 2014). Accordingly, we tested whether 3X training delivered after the 24 h test could reinstate the LTM disrupted by the pretraining administration of RG108. However—unlike in the cases of PKM inhibition and memory reconsolidation blockade—3X training failed to reinstate LTM; thus, pretraining injection of RG108 abolished the induction/consolidation of LTM. In additional experiments we observed that an injection of a DNMT inhibitor, either RG108 or 5-azadeoxycytidine (5aza), could disrupt established LTM when made as late as 5 d after 5X training, and that the LTM could not be subsequently reinstated. Moreover, the elimination of LTM by posttraining DNMT inhibition could not be explained as being due to the disruption of memory reconsolidation. Finally, we found that the memory for LTS could be reestablished following its elimination by DNMT inhibition by retraining animals with five bouts of tail shocks (5X training), which indicated that the memory impairments caused by RG108/5aza could not be attributed to harmful effects of the drugs on the animals' health. Our results suggest that the silencing via DNA methylation of one or more memory canceling genes plays a key role in the acquisition and maintenance of LTM in *Aplysia.*

Disclosures: **K. Pearce:** None. **D. Cai:** None. **S. Chen:** None. **M.E. Kimbrough:** None. **X. Zhao:** None. **E.J. Moc:** None. **V. Kong:** None. **B. Cheema:** None. **S. Apichon:** None. **D. Miresmaili:** None. **R. Sumner:** None. **A. Rangchi:** None. **A. Zobi:** None. **D.L. Glanzman:** None.

Poster

836. Models of Memory Consolidation, Protection, and Enhancement

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 836.18/III52

Topic: H.01. Animal Cognition and Behavior

Support: CIHR Operating grant

Title: Cognitive enhancement requires prenatal diet modification in *Drosophila*

Authors: ***F. V. BOLDUC**[1], C. ROSENFELT[1], S. LANGER[1], D. CHAMBERS[1], A. ANDROSCHUK[1], A. LAU[2], L. SMITHSON[2], P. MANDHANE[2];
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Abstract: BACKGROUND: Abnormal cognitive development has been observed following deprivation of several nutrients in human and animal models. In addition, prenatal

supplementation with folic acid has been shown to reduce the incidence of neural tube defects. Nutritional intake has recently been shown to affect memory formation in Drosophila. But it remains unknown how diet optimization may enhance cognitive performance in human but also model organisms. We recently identified in a large cohort study a cognitive enhancement effect of prenatal fruit intake during pregnancy. We replicated the effect in Drosophila. It remains unknown if prolonged post-natal feeding may also have positive effect on cognition.
METHOD: To assess the impact of specific dietary components on cognition, Drosophila melanogaster (fruit flies) were tested for short and long-term memory using classical olfactory conditioning. Wild type flies born after exposure to regular or fruit supplemented diet were tested for immediate and 1 day memory. The ratio of flies avoiding the odor associated with a footshock is calculated. Statistical analysis using Tukey (multiple planned comparison) or t-test was performed. For neuroimaging, we used adult Drosophila brain immunohistochemistry. We compared the mushroom body structure in flies fed regular versus fruit enriched prenatal diet.
RESULTS: The positive effect of prenatal fruit on cognitive outcome observed in human is conserved with continuous feeding from egg to adult fly stage. Both learning (short-term memory $P<0.001$) and long-term memory ($p<0.5$) were enhanced after prenatal fruit intake. In the other hand, feeding of the same diet with increased fruit after in adult flies did not lead to significant cognitive enhancement at 3 days or 5 days. Next, we assessed if morphological changes could be seen as a result of increased prenatal fruit. We observed no significant changes in the shape or size of mushroom bodies, an essential center for learning.
DISCUSSION: Several studies have shown the effect of nutritional deficit on cognitive outcome. Here we show that prenatal fruit diet can significantly enhance memory performance in wild-type flies. Importantly, the effect seems to depend on prenatal feeding as even prolonged post-natal feeding did not seem to lead to cognitive enhancement. Furthermore, these changes in memory seem not to be associated with gross structural changes in the mushroom body, suggesting that the changes may be in other structures or at the organizational level.

Disclosures: **F.V. Bolduc:** None. **C. Rosenfelt:** None. **S. Langer:** None. **D. Chambers:** None. **A. Androschuk:** None. **A. Lau:** None. **L. Smithson:** None. **P. Mandhane:** None.

Poster

836. Models of Memory Consolidation, Protection, and Enhancement

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 836.19/JJJ1

Topic: H.01. Animal Cognition and Behavior

Support: NIH/NIA Grant 1F32AG046106-01A1

NIH/NIA Grant 2R01AG034446-06A1

Glenn Foundation

Title: A Gαq signaling mutant that extends memory 10-fold via enhanced consolidation

Authors: *R. AREY[1], G. STEIN[2], R. KALETSKY[1], C. T. MURPHY[1];
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Abstract: The ability to form associative memories is one of the most important functions of an organism's nervous system. Identifying molecules involved in these processes is important not only to gain an understanding of normal brain function, but can also lead to an understanding of disease states such as Alzheimer's disease and age-related cognitive decline. Associative memories are generally divided into 3 categories: short-term (STAM), intermediate-term (ITAM), and long-term associative memory (LTAM), based on duration of the memory and the molecular requirements for the formation of each type of memory. We have developed two positive olfactory association assays that pair a conditioned stimulus (CS) with an unconditioned stimulus (US) to measure S/ITAM and LTAM in the nematode worm, *C. elegans*. S/ITAM is induced following 1 CS-US pairing, while LTAM requires 7 CS-US pairings. These behaviors require processes that are conserved in higher organisms: STAM is both transcription- and translation-independent, ITAM is translation-dependent, and LTAM requires translation and CREB-mediated transcription. Using these assays, we identified animals with a mutation in the $G_{\alpha q}$ signaling pathway that exhibit a greater than 10-fold extension of memory following S/ITAM training. This extended memory requires CREB and the AIM interneuron pair, which we previously found to be the site of CREB activity during LTAM formation. These findings suggest that in this mutant, a long-term memory is formed following training that normally results in short- or intermediate-term memory, and that consolidation occurs after a single CS-US pairing, as opposed to the 7 usually required for LTAM formation. We find that increased CREB-dependent transcription mediates this phenotype. Surprisingly, altering $G_{\alpha q}$ signaling in a single chemosensory neuron is sufficient to cause a CREB-dependent memory extension following a single CS-US pairing, indicating a cell non-autonomous role for this pathway in enhancing memory circuit function. We have identified a potential role for octopamine, the invertebrate equivalent of norepinephrine, in this phenotype. These findings provide insight into a novel and conserved pathway that enhances memory consolidation. Understanding mechanisms by which S/ITAM can be converted into LTAM will enhance treatments to prevent or improve impaired memory function, such as age-related cognitive decline, and to prevent deleterious memory consolidation, such as in PTSD.

Disclosures: **R. Arey:** None. **G. Stein:** None. **R. Kaletsky:** None. **C.T. Murphy:** None.

Poster

837. Cognition: Nucleus Accumbens

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 837.01/JJJ2

Topic: G.01. Appetitive and Aversive Learning

Support: DA034021 to RMC

DA037733 to EAW

Title: Prelimbic neurons encode reward predictive cues following reward devaluation

Authors: *E. A. WEST, M. NIEDRINGHAUS, R. M. CARELLI;
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Abstract: Medial prefrontal cortex (mPFC) neurons encode features of stimulus learning and action selection associated with rewards. The mPFC is also necessary for using information about expected outcome values to guide behavior following reinforcer devaluation. Here, we recorded neural activity in the prelimbic cortex (PrL), a subregion of the mPFC, while rats were trained on a pavlovian task (10 daily sessions) and following devaluation. Male Long-Evans rats (n=4) were presented with two distinct cue light patterns as conditioned stimuli (CS+), each predicting a different reward. One CS+ predicted the delivery of a sugar pellet (CS+1) and the other CS+ predicted the delivery of a food pellet (CS+2). Rats were also presented with other cues that did not predict a specific reward (CS-). Following training, rats underwent sugar pellet devaluation procedures. Briefly, rats ate sugar pellets *ab libitum* for 30 minutes followed by a LiCl injection (i.p., 0.3 M; 10 ml/kg) to induce a conditioned taste aversion. The following day, rats were given access to food pellets followed by a saline injection. This LiCl/saline procedure was repeated once, and the reward order was counterbalanced across rats. On a subsequent day, rats were tested on the pavlovian task to evaluate their ability to avoid the devalued outcome and associated CS+. We found that rats ate significantly fewer sugar pellets (3.3 +/- 0.6, devalued) compared to food pellets (10 +/- 0, nondevalued) on the test day demonstrating successful outcome devaluation. Rats also spent significantly less time in the food cup during the CS+ associated with the devalued outcome (13.4% +/- 2.2%) compared to the CS+ that predicted the nondevalued outcome (22.8% +/- 3.2%). On the last day of training, no difference was observed in the strength of phasic responsiveness of PrL neurons (cells that either increased or decreased firing) to the different rewards (sugar vs food) or their associated stimuli (CS+1 vs CS+2). However, following devaluation of the sugar, preliminary findings showed that there was lower magnitude of PrL phasic responding to the now devalued reward (i.e., sugar) and associated cue (CS+1) compared to the nondevalued reward (i.e., food) and its associated cue (CS+2). These findings suggest that PrL neurons encode updated outcome values and their predictive stimuli following devaluation.

Disclosures: **E.A. West:** None. **M. Niedringhaus:** None. **R.M. Carelli:** None.

Poster

837. Cognition: Nucleus Accumbens

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 837.02/JJJ3

Topic: G.01. Appetitive and Aversive Learning

Support: DA034021

DA037733

Title: Oscillatory dynamics in the prelimbic cortex form to a reward-predictive cue following learning

Authors: ***M. NIEDRINGHAUS**, E. A. WEST, D. A. SACKETT, R. M. CARELLI;
Dept. of Psychology and Neurosci., Univ. of North Carolina, Chapel Hill, Chapel Hill, NC

Abstract: Medial prefrontal cortex (mPFC) neurons encode reward-predictive cues. Interestingly, there are distinct patterns in local field activity of mPFC neurons both in anticipation of a reward and at the time of reward delivery; notably, transient changes in oscillatory dynamics at the gamma50 (50Hz) and gamma80 (80Hz) frequency bands. Here, we determined if similar brain activity patterns form in a subregion of the mPFC, the prelimbic cortex (PrL) as animals learn a reward predictive cue. We implanted electrophysiological recording arrays bilaterally into the PrL in Long-Evans rats (4 males and 2 females) and simultaneously recorded neuronal spikes and local field potentials throughout the acquisition of a Pavlovian task. Over 10 daily sessions, rats were presented with either a conditioned stimulus (CS+, 10 seconds) that preceded a food reward or another cue that did not (CS-, 10 seconds). In addition we sought to determine how different reward values affected PrL neural dynamics during learning. Therefore, rats were also trained to an additional CS+ (and CS-) that predicted a sucrose reward. By day 10, all animals spent significantly more time in the food cup during CS+ presentation compared to the CS- (39.9% +/- 3.4 vs. 19.9% +/- 2.3%; $p<0.05$), suggesting the successful formation of cue-outcome associations. As predicted, PrL neurons showed phasic responses (i.e., either increases or decreases in cell firing) to the CS+ following training. Further, changes were observed in local field potential power at distinct frequency bands as rats learned the Pavlovian task. Specifically, prior to learning, all rats demonstrated a significant increase in gamma80 power only at the time of reward delivery accompanied by a significant decrease in gamma50 power. Importantly, after training, there was a sustained increase in gamma80 power throughout the CS+ presentation and during reward delivery. In contrast, during CS-

presentation, there was a brief initial increase in gamma80 power which quickly returned to baseline. Additionally, following training, there was a transient increase in gamma50 power for both the CS+ and CS-. Similar dynamics were found with the CS+ associated with sugar. Ongoing analyses will determine the relationship between these changes in high frequency brain activity patterns and neuronal spiking in addition to examining how other lower frequency patterns (e.g., theta) in the PrL are altered as a function of learning. Taken together, these results suggest that a functional component of learning is the successful development of reward-associated PrL oscillatory dynamics to a reward-predictive cue.

Disclosures: M. Niedringhaus: None. **E.A. West:** None. **D.A. Sackett:** None. **R.M. Carelli:** None.

Poster

837. Cognition: Nucleus Accumbens

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 837.03/JJJ4

Topic: G.01. Appetitive and Aversive Learning

Support: NIH DA034021

T32 DA007244

Title: The role of nucleus accumbens shell versus core in magnitude-based decision making

Authors: *D. A. SACKETT[1], M. P. SADDORIS[2], X. WANG[1], R. M. CARELLI[1];
[1]Psychology and Neurosci. Dept., Univ. of North Carolina At Chapel Hill, Chapel Hill, NC;
[2]Univ. of Colorado - Boulder, Boulder, CO

Abstract: Effective decision making requires organisms to predict reward values and bias behavior toward the best available option. Integral to this decision making process is the mesolimbic dopamine system, including the nucleus accumbens (NAc) and its dopaminergic input. The NAc is divided into two discrete subregions, the core and the shell, believed to differentially process information about reward learning, reward value, and goal-directed decision making. However, the precise role of those subregions in magnitude-based decision making remains unclear. Here, dopamine (DA) release was measured in the NAc shell and core using fast-scan cyclic voltammetry (FSCV) during a magnitude-based decision making task. Male Sprague-Dawley rats (n=15) were trained to press distinct levers following discrete cue lights. On Forced Choice Low Magnitude trials, a cue light predicted the opportunity to press a lever for a small reward (one sucrose pellet). On Forced Choice High Magnitude trials, another

cue light predicted the opportunity to press a different lever for a large reward (two sucrose pellets). Lastly, on Free Choice trials, rats were presented with both cue lights and levers, and could freely choose between both magnitude options. Electrochemical recordings from electrodes in the NAc shell (n=8) and core (n=7) show increases in rapid DA release following presentation of all reward-predictive cues. However, in the NAc shell, peak DA concentrations on forced choice trials were significantly greater during the high, compared to low, magnitude cue. On free choice trials, peak DA to presentation of both cue lights was the same as during the high forced trials, regardless of choice. In the NAc core, DA release was significantly lower overall than shell DA and did not scale to cues predictive of different reward values. These findings implicate DA in the NAc shell, not core, in selectively encoding comparative reward value during magnitude-based decision making. Previous work in our lab (Saddoris et al., 2015) found no casual role of the NAc in magnitude based decision making, but that study did not specifically target the NAc shell. Based on our current FSCV findings, ongoing studies using optogenetics are selectively altering DA release in the NAc shell during our task. Specifically, we are optically stimulating the NAc shell during forced choice low magnitude cues, with free choice trials serving as an indication of choice bias toward the less-preferred, smaller magnitude option. Preliminary results (n=3) indicate no change in low magnitude choice selection, suggesting that DA encodes, but may not causally drive, magnitude-based decision-making.

Disclosures: **D.A. Sackett:** None. **M.P. Saddoris:** None. **X. Wang:** None. **R.M. Carelli:** None.

Poster

837. Cognition: Nucleus Accumbens

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 837.04/JJJ5

Topic: G.01. Appetitive and Aversive Learning

Support: NIDA IRP

Title: Characterizing Fos-expressing neuronal ensembles in the rat nucleus accumbens that are associated with amphetamine sensitization

Authors: *R. V. FALLON[1], F. J. RUBIO[2], B. L. WARREN[2], B. T. HOPE[2];
[1]Cellular, Molecular, Developmental Biol. and Biophysics, Johns Hopkins Univ., Baltimore, MD; [2]NIDA, Baltimore, MD

Abstract: Repeated exposure to drugs reinforces maladaptive behavior through pathologically strong associative learning. Our lab has developed techniques to study neuronal ensembles that express the immediate early gene Fos in response to cell activation. By comparing Fos-

expressing neurons to neighboring inactive neurons, our lab has shown drug-associated behaviors create neuronal ensembles with distinct electrophysiological and molecular properties. We have also shown a causal role for these Fos-expressing ensembles using the Daun02 inactivation procedure that ablates Fos-expressing neurons. However, these important neuronal ensembles are only beginning to be characterized at the molecular and cellular levels. Here, we hypothesize that a small, heterogeneous neuronal ensemble in the nucleus accumbens is recruited during repeated amphetamine exposure to encode amphetamine-sensitized locomotion. In our experimental design, rats are exposed to 5 days of 2mg/kg (ip) amphetamine injections in a novel context for 2 hours daily. One week later, rats are reintroduced to the drug-associated context and rats previously exposed to repeated amphetamine show sensitized locomotion after an acute dose of 1mg/kg (ip) amphetamine compared to the control group injected with saline [$F(1,36)= 5.97$, $p=0.0194$]. Immunohistochemistry in these amphetamine-sensitized rats reveals increased Fos expression in the nucleus accumbens in response to acute amphetamine when compared to control rats [$F(1,36)= 4.542$, $p=0.0400$]. These data suggest that a Fos-expressing neuronal ensemble of the reward circuit supports associative learning of sensitized locomotion in the accumbens. Next, we will use Daun02 to selectively inactivate these Fos-expressing neurons to determine if this neuronal ensemble plays a causal role in the circuit initiating amphetamine-sensitized locomotion. We know from RNAscope in situ hybridization that *Fos*-expressing cells in our ensemble are composed of *D1*- and *D2-receptor* positive medium spiny neurons, as well as other accumbens neurons. We are continuing our experiments to test their selective activation in two different non-home cage contexts as well as unique morphological alterations.

Disclosures: **R.V. Fallon:** None. **F.J. Rubio:** None. **B.L. Warren:** None. **B.T. Hope:** None.

Poster

837. Cognition: Nucleus Accumbens

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 837.05/JJJ6

Topic: G.01. Appetitive and Aversive Learning

Support: University of Sussex Strategic Development Funds

Title: Differential excitability of nucleus accumbens core and shell neuronal ensembles activated by cocaine-associated contexts

Authors: J. J. ZIMINSKI, G. MARGETTS-SMITH, E. KOYA;
Univ. of Sussex, Brighton, United Kingdom

Abstract: Learned associations about drugs of abuse (e.g. cocaine) and the drug administration context play an important role in addiction-related behaviours. Previous studies have shown that these learned associations were mediated by a minority of sparsely, distributed, behaviourally activated neurons called 'neuronal ensembles' in the nucleus accumbens. Moreover, these neurons exhibited distinct synaptic alterations compared to their surrounding counterparts. Although the synaptic properties of these neurons have been characterised, very little is known about the intrinsic excitability properties of these neurons that influence the probability of neuronal firing.
We recently observed that exposure to cocaine-associated contexts elicited robust conditioned locomotion and expression of the activity marker 'Fos' in the nucleus accumbens core and shell. The aim of this study was to examine the excitability properties of accumbens neuronal ensembles that were activated following conditioned locomotion in *Fos-GFP* mice, which express GFP in behaviourally activated neurons. In the accumbens core, but not shell, activated GFP+ neurons exhibited increased excitability compared to their non-activated GFP- counterparts. These results indicate that different neuronal ensemble recruitment strategies exist for the different accumbens subareas. Also, the increased excitability in GFP+ neurons in the accumbens core may be implicated in the storage of cocaine-context associations.

Disclosures: J.J. Ziminski: None. **G. Margetts-Smith:** None. **E. Koya:** None.

Poster

837. Cognition: Nucleus Accumbens

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 837.06/JJJ7

Topic: G.01. Appetitive and Aversive Learning

Support: BBSRC (BB/M009017/1)

University of Sussex Strategic Development Funds

Title: Enhanced excitability of nucleus accumbens, but not orbitofrontal cortex neuronal ensembles following sucrose memory recall

Authors: *S. HESSLER, J. ZIMINSKI, M. C. SIEBURG, G. MARGETTS-SMITH, H. S. CROMBAG, E. KOYA;
Univ. of Sussex, Brighton, United Kingdom

Abstract: Animals utilize cues (e.g. smells) that predict food availability to seek out nutrient sources. If the same cue no longer predicts food availability during extinction learning, animals

rapidly learn to inhibit their food-seeking responses. These Pavlovian cue-outcome associations are encoded by a minority of sparsely distributed, behaviourally-activated neurons coined 'neuronal ensembles'. Alterations in neuronal excitability underlie many learning and memory processes, but little is known about the excitability properties of neurons that are specifically activated during the retrieval of learned associations. In this study, we examined the excitability properties of behaviourally activated orbitofrontal cortex (OFC) and nucleus accumbens neurons following the retrieval of a sucrose memory (elicited by sucrose-associated cues in Pavlovian conditioned mice) or extinction memory. We performed whole-cell recordings on activated (GFP+) and non-activated (GFP-) neurons from the brain slices of Fos-GFP mice that express GFP in strongly activated neurons. Sucrose-associated cues recruited more GFP+ neurons in these areas compared to neutral cues. However, in the accumbens, but not OFC, GFP+ neurons were more excitable than their GFP- counterparts. Following extinction, this excitability difference was abolished in the accumbens, while GFP+ and GFP- OFC neurons continued to display no differences in excitability. These data indicate that sucrose memories are retrieved by recruiting distinct neuronal ensemble phenotypes in the OFC and accumbens, and that sucrose and extinction memories are represented in distinct neuronal ensemble phenotypes within the accumbens.

Disclosures: **S. Hessler:** None. **J. Ziminski:** None. **M.C. Sieburg:** None. **G. Margetts-Smith:** None. **H.S. Crombag:** None. **E. Koya:** None.

Poster

837. Cognition: Nucleus Accumbens

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 837.07/JJJ8

Topic: G.01. Appetitive and Aversive Learning

Support: Sussex Neuroscience

Title: The identification of sucrose cue-evoked corticostriatal neuronal ensemble activity patterns underlying hunger states

Authors: *M. C. SIEBURG, G. MARGETTS-SMITH, S. HESSLER, J. ZIMINSKI, H. S. CROMBAG, E. KOYA;
Sch. of Psychology, Univ. of Sussex, Brighton, United Kingdom

Abstract: In wild animals, learned associations between food and the environmental cues that predict its availability guide appetitive behaviours. Accordingly, in laboratory animals, exposure to food-associated cues elicits conditioned approach behaviours towards the food delivery site.

This evokes activation of motivationally relevant 'neuronal ensembles', a minority of sparsely distributed neurons in corticostriatal brain areas. Little is known about how changes in general internal (energy) states modulate neuronal ensemble activity following exposure to food-associated cues. Therefore, the aim of this study was to examine changes in conditioned approach responses and corticostriatal ensemble activity, using the activity marker 'Fos', elicited by sucrose-associated cues in mice following modulation of overall hunger state.
First, under food-restriction, mice were trained to associate an auditory cue with sucrose delivery. Three days following this acquisition phase, one group of mice were given *ad lib* normal chow (sated group) for 4 days, whereas the other group continued to be food-restricted (restricted group). On test day, 7 days following the last acquisition session, mice were exposed to the cue alone and tested for conditioned approach responses. Surprisingly, these responses did not differ between sated and restricted mice. Preliminary Fos analysis from several prefrontal cortical brain areas suggest that although these groups of mice display similar levels of approach responses on test day, the underlying neuronal ensemble recruitment mechanism may differ. We are currently examining Fos expression patterns in other motivationally relevant striatal areas (e.g. accumbens shell).

Disclosures: M.C. Sieburg: None. **G. Margetts-Smith:** None. **S. Hessler:** None. **J. Ziminski:** None. **H.S. Crombag:** None. **E. Koya:** None.

Poster

837. Cognition: Nucleus Accumbens

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 837.08/JJJ9

Topic: G.02. Motivation

Support: UCONN research foundation

UCONN SURF grant

P1.1B2010-43

Title: Effort-related motivational effects of the proinflammatory cytokine interleukin 6: implications for studies of depression

Authors: *S. E. YOHN[1], Y. ARIF[2], A. HAILEY[2], Y. BAQI[3], C. MULLER[3], N. SAN MIGUEL[4], M. CORREA[2,4], J. D. SALAMONE[2];
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Abstract: Motivational dysfunctions span multiple disorders and constitute a major unmet therapeutic need in psychiatry. Motivational or psychomotor symptoms are frequently observed in patients with depression and other disorders. There is a growing emphasis on studying motivational deficits because these debilitating symptoms are very common, and they adversely affect treatment outcomes. It has been suggested that tasks that measure effort-related choice behavior could be used as animal models of motivational symptoms, which are seen in several patient populations. In rodents, effort-related decision making tasks provide a choice between a more valued reinforcer that can only be obtained by a high degree of effort versus a low effort/low reward option. Regardless of the paradigm used, interference with dopamine shifts choice behavior by decreasing selection of the high effort option and increasing selection of the lower effort alternative. Cytokines are signaling molecules of the immune system that play a critical role in the regulation of physiological responses to infection, injury, and foreign antigens. Pro-inflammatory cytokines play a role in the motivational symptoms of depression such as psychomotor slowing and fatigue. For example, levels of pro-inflammatory cytokines such as IL-6 tend to be elevated in patients with depression compared to the general population. Administration of pro-inflammatory cytokines, a common treatment for cancer and viral infections, can produce side effects such as anergia, fatigue, and amotivation. The present study investigated the behavioral and neurochemical effects of the pro-inflammatory cytokine IL-6 (2.0-8.0 μg/kg) on effort related choice behavior. IL-6 shifted choice behavior, significantly decreasing lever pressing and increasing chow intake. Further experiments showed that the adenosine A_{2A} antagonist MSX-3 and the stimulant methylphenidate attenuated the effort-related impairments produced by IL-6, increasing lever pressing and decreasing chow intake in IL-6 treated rats. Behaviorally active doses of IL-6 did not alter food intake or preference in parallel free-feeding choice studies, demonstrating that these low doses were not altering preference for the high carbohydrate pellets or generally suppressing appetite. Also, IL-6 did not affect body temperature. Microdialysis studies showed that 8.0 μg/kg IL-6 significantly decreased extracellular dopamine in nucleus accumbens core. Thus, dopaminergic mechanisms appear to be involved in the effort-related effects of IL-6. This research has implications for the involvement of cytokines in motivational symptoms such as anergia and fatigue.

Disclosures: **S.E. Yohn:** None. **Y. Arif:** None. **A. Hailey:** None. **Y. Baqi:** None. **C. Muller:** None. **N. San Miguel:** None. **M. Correa:** None. **J.D. Salamone:** None.

Poster

837. Cognition: Nucleus Accumbens

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 837.09/JJJ10

Topic: G.02. Motivation

Support: University of Connecticut Research Foundation

NIH Grant MH094966

Fundació Bancaixa/ U. Jaume I P1.1B2010-43

Title: Blockade of uptake for dopamine, but not norepinephrine or 5-HT, increases selection of high effort instrumental activity: implications for treatment of effort-related motivational symptoms in psychopathology.

Authors: *J. D. SALAMONE[1], S. E. YOHN[2], E. ERRANTE[2], A. ROSENBLOOM SNOW[2], M. SOMMERVILLE[2], K. TOKARSKI[2], N. ZAFAR[2], M. CORREA[2,3];
[1]Dept Psychol, Univ. of Connecticut Dept. of Psychology, Storrs Mansfield, CT; [2]Psychological Sci., Univ. of Connecticut, Storrs, CT; [3]Àrea de Psicobiologia, Univ. Jaume I, Castello, Spain

Abstract: Deficits in behavioral activation, exertion of effort, and other psychomotor/motivational symptoms are frequently seen in people with depression and other disorders. Depressed people show a decision bias towards selection of low effort activities, and animal tests of effort-related decision making are being used as models of motivational dysfunctions seen in psychopathology. Considerable evidence from rodent models and human studies indicates that dopamine (DA) is a critical modulator of effort-based decision making. Recent research has demonstrated that the effort-related effects of the VMAT-2 inhibitor tetrabenazine can be reversed by drugs that block dopamine transport (DAT), but not by drugs that block norepinephrine transport (NET), and serotonin transport (SERT). The present studies investigated the ability of drugs that inhibit DAT, NET, and SERT to increase lever pressing work output in rats responding on a test of effort-related decision making (i.e., a progressive ratio (PROG)/chow feeding choice task). With this task, rats choose between working for a preferred food (high carbohydrate pellets) by lever pressing on a PROG schedule vs. obtaining a less preferred lab chow that is freely available in the chamber. Because of the increasing work-related challenge presented by the PROG schedule, this task generates relatively low baseline levels of lever pressing. This characteristic makes the PROG/chow feeding choice task sensitive to drugs that can increase selection of high-effort activities. The present work focused on the effects of the selective DAT inhibitor GBR12909, the selective SERT inhibitor fluoxetine, and the selective NET inhibitors desipramine and atomoxetine. Both acute and repeated 7-day administration of GBR12909 shifted choice behavior, increasing measures of PROG lever pressing but decreasing chow intake. In contrast, fluoxetine, desipramine and atomoxetine failed to increase lever pressing output, and actually decreased it at higher doses. In the behaviorally effective dose range, GBR12909 elevated extracellular DA levels in accumbens core as measured by microdialysis, but fluoxetine, desipramine and atomoxetine decreased extracellular DA. Thus, blockade of DAT increased selection of the high effort instrumental activity, while inhibition of SERT or NET did not. Clinical studies have reported that commonly prescribed SERT inhibitors (also known as SSRIs) are relatively ineffective at treating motivational symptoms such as fatigue and anergia. Thus, the present results have implications for the use of monoamine uptake inhibitors for the treatment of effort-related psychiatric symptoms in humans.

Disclosures: **J.D. Salamone:** None. **S.E. Yohn:** None. **E. Errante:** None. **A. Rosenbloom Snow:** None. **M. Sommerville:** None. **K. Tokarski:** None. **N. Zafar:** None. **M. Correa:** None.

Poster

837. Cognition: Nucleus Accumbens

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 837.10/JJJ11

Topic: G.02. Motivation

Support: University of Connecticut Research Foundation

NIH Grant MH094966

Fundacio Bancaixa/ U. Jaume | P1.1B2010-43

Title: Behavioral economics and dopamine function: The VMAT2 inhibitor tetrabenazine alters elasticity of demand for food reinforcement, increasing sensitivity to effort related response costs.

Authors: *J.-H. YANG[1], S. E. YOHN[1], M. SOMMERVILLE[1], M. CORREA[1,2], J. D. SALAMONE[1];
[1]Psychological Sci., Univ. of Connecticut, Storrs, CT; [2]Dept. of Psychobiology, Univ. of Jaume I, Castelló, Spain

Abstract: Mesolimbic dopamine (DA), particularly within the nucleus accumbens, is a critical component of the brain circuitry regulating behavioral activation, exertion of effort, and effort-related decision making. Interference with accumbens DA transmission alters response allocation in choice procedures that involve cost/benefit evaluations of reinforcement value and response costs. Accumbens DA depletions produced by local injections of neurotoxic agents such as 6-OHDA make animals more sensitive to work-related response costs, and produce a shift in choice behavior, biasing rats towards low effort alternatives. It has been suggested that these DA-related impairments in effort-based functions that are seen in animals could be analogous to symptoms such as psychomotor retardation, anergia, and fatigue, which are observed in people with depression, Parkinsonism, and other disorders. For that reason, recent studies have investigated the effects of tetrabenazine (TBZ) on effort-related choice behavior. TBZ inhibits the vesicular monoamine transporter 2 (VMAT-2), and is used to treat Huntington's disease. However, TBZ has been shown to produce depressive side effects in some patients, including motivational symptoms such as psychomotor slowing, anergia, and fatigue. Considerable evidence indicates that the vast majority of VMAT-2 binding in nucleus accumbens and striatum

is on DA terminals. TBZ depletes DA in nucleus accumbens at low doses, and blunts post-synaptic DA signaling in accumbens as measured by expression of phosphorylated DARPP-32. Recent papers have reported that TBZ alters effort-related choice behavior at low doses that do not affect food intake, food or sucrose preference, or hedonic reactivity to sucrose. In the present studies, rats were trained on fixed ratio (FR) schedules ranging from FR1 to FR64. Low doses of TBZ (0.5-1.0 mg/kg IP) had no significant effect on FR1 lever pressing, but the effects were substantial when the ratio requirement was higher. These results were analyzed using economics equations that allow for determination of elasticity of demand (i.e., sensitivity to costs, in this case, the response costs from the increasing ratio requirement). Under baseline conditions, demand was somewhat inelastic, but injections of TBZ increased elasticity of demand. These results demonstrate that, in behavioral economic terms, TBZ makes animals more sensitive to the increasing response costs (i.e., the 'price') presented by the higher ratio requirements. These studies provide fundamental information about the functions of brain DA, and may contribute to the understanding of effort-related motivational symptoms in humans.

Disclosures: J. Yang: None. **S.E. Yohn:** None. **M. Sommerville:** None. **M. Correa:** None. **J.D. Salamone:** None.

Poster

837. Cognition: Nucleus Accumbens

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 837.11/JJJ12

Topic: G.02. Motivation

Title: Agomelatine reverses impairments in effort-based decision-making tasks in mice treated with a dopamine-depleting agent: comparison with fluoxetine.

Authors: *M. CORREA[1], C. CARRATALA-ROS[1], N. SAN MIGUEL[1], J. RIBES[1], R. OLIVARES-GARCIA[1], J. ORTET[1], L. LOPEZ-CRUZ[1], C. GABRIEL[2], P. DELAGRANGE[2], J. D. SALAMONE[3];
[1]Psicobiologia. Univ. Jaume I, Castello, Spain; [2]Inst. de Recherches Servier, Croissy-sur-Seine, France; [3]Univ. of Connecticut, Storrs, CT

Abstract: Depression is characterized by emotional symptoms, however, motivational impairments such as anergia and psychomotor retardation are very common. These motivational symptoms are highly resistant to treatment, and antidepressants such as fluoxetine can even exacerbate them. Mesolimbic dopamine (DA) plays an important role in behavioral activation and effort-based decision-making. Thus, DA depletion produces anergia in effort-based choice tasks. Agomelatine is a new antidepressant that acts as a MT_1/MT_2 agonist and 5-HT_{2c} receptor

antagonist (de Bodinat et al, 2010), and has been shown to increase DA in frontal cortex (Millan et al, 2003). In the present work, we evaluated the effect of agomelatine and fluoxetine on anergia induced by the VMAT-2 inhibitor tetrabenazine (TBZ), which depletes DA. Effort-based decision-making was studied in a T-maze-barrier-task with a high effort/high density of reward (HD) option versus a low effort/low reward density (LD) option. CD1 male mice received i.p. vehicle (hydroxyethylcelullose 1%) or agomelatine (25 mg/kg) or fluoxetine (10 mg/kg) during 15 days in the adquisition phase. Two weeks after chronic treatments were removed and behavior was well established, an acute injection of vehicle, agomelatine (25 or 50 mg/kg) or fluoxetine (10 or 20 mg/kg) was administered in TBZ (4 mg/kg)-treated mice. In the first phase (end 2-weeks treatment) as compared to vehicle, while chronic agomelatine showed a tendency to improve latency, and did not affect HD-selection during acquisition, fluoxetine showed a tendency to impair performance. In the second phase (after chronic treatment washout) in vehicle-treated mice, an acute administration of TBZ significantly reduced HD selection. Agomelatine (25 and 50 mg/kg) reversed impairments in HD-selection and shows a tendency to improve psychomotor slowing produced by TBZ. At the opposite, fluoxetine (10 and 20 mg/kg) exacerbated TBZ-induced impairments in HD-selection and speed. Thus, agomelatine improves DA-depletion-induced motivational symptoms of depression in animal models, while SSRIs not only do not improve these symptoms, but can make them worse. In conclusion agomelatine could be beneficial for the treatment of depressed patients with fatigue, loss of energy and apathy.

Disclosures: **M. Correa:** C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); 1Psicobiologia. Universitat Jaume I, Castelló. Spain. **C. Carratala-Ros:** None. **N. San Miguel:** None. **J. Ribes:** None. **R. Olivares-Garcia:** None. **J. Ortet:** None. **L. Lopez-Cruz:** None. **C. Gabriel:** A. Employment/Salary (full or part-time): Unité de Recherche Chimie Neurosciences, Institut de Recherches Servier. **P. Delagrange:** A. Employment/Salary (full or part-time): Unité de Recherche Chimie Neurosciences, Institut de Recherches Servier. **J.D. Salamone:** None.

Poster

837. Cognition: Nucleus Accumbens

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 837.12/JJJ13

Topic: G.01. Appetitive and Aversive Learning

Title: When I wake up, I immediately check the status of my manuscript: Urge to publish predicts striatal reward signal in the prospect of publication

Authors: *S. KRACH[1], L. MÜLLER-PINZLER, 23538[2], L. RADEMACHER[2], F. PAULUS[2]; [1]Luebeck University, Dept. of Psychiatry, Luebeck, Germany; [2]Lübeck Univ., Lübeck, Germany

Abstract: Scientists across the globe consent to short-term, underpaid contracts, cope with rejections and almost always face an unpredictable future in academia. What drives scientists? The nucleus accumbens (NAcc), part of the ventral striatum, is known to influence our actions by coding the expected value of anticipated potential outcomes of our goal-directed behaviors. One of the most powerful incentives for scientists thus is a visible publication in a high-impact journal. In two studies we examined the neural mechanisms of a scientist's reward cycle. We predicted increased goal-directed behavior and stronger NAcc activity with the anticipation of high impact publications and the NAcc's response to be related to real-world metrics for scientific success: the averaged personal journal impact factor (JIF). Also, we predicted that the subjectively experienced “urge to publish” would correlate with the NAcc’s activity. Finally we hypothesized that the NAcc's response would be modulated by the author's position on a high impact publication. With this study we shed light on the neuroscientists' reward structure and the neural pathways linked to the anticipation of the vital parameters in scientific life. 18 neuroscientists participated in two fMRI runs. For both runs we adopted the classic monetary incentive delay task (MID) using title pages of publications as incentives (PID). First, neuroscientists had shorter reaction times and more hits with higher anticipated reward, both during MID as well as the PID and subsequently rated the reward potential of the stimuli accordingly. Second, fMRI results revealed a parametric increase of the bilateral NAcc activation with increasing reward value, both for MID and PID. Notably, we found a significant interaction effect with stronger linear increase of NAcc activation in the PID compared to MID. As predicted, the increase in the NAcc's response in the PID but not the MID was correlated with the averaged personal JIF of the neuroscientists. Also, urge-to-publish, as measured with a newly developed questionnaire, correlated significantly with the increase in NAcc activity in the prospect of publication. Finally, the anticipatory response of the NAcc was larger during the anticipation of a first- compared to a co-authorship on high-impact journals.According to economic theory, human behavior is guided by the expectation that the benefits of one's actions outweigh the costs. The results of this study show how the scientist's brain has adapted to the predominant reward structure in the environment and integrated the essential paradigm of the scientific community to "publish or perish" in the reward system to guide behavior.

Disclosures: S. Krach: None. **L. Müller-Pinzler:** None. **L. Rademacher:** None. **F. Paulus:** None.

Poster

837. Cognition: Nucleus Accumbens

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 837.13/JJJ14

Topic: G.01. Appetitive and Aversive Learning

Support: NIH Grant DA033386

Title: Dopamine's role during the acquisition of conditioned behaviors towards cues signaling different reward sizes

Authors: *M. J. LEFNER, M. J. WANAT;
Biol. Dept. - Neurosciences Inst., The Univ. of Texas At San Antonio, San Antonio, TX

Abstract: Effective decision-making requires both learning the relationship between cues that predict rewarding outcomes and discriminating between cues that signal different rewards. The mesolimbic dopamine system responds to cues to signal an estimation of reward size. However, it is unknown how the dopamine system acquires reward size encoding during early learning in response to cues associated with distinct reward sizes. Furthermore, is the dopamine response between cues influencing behavior during early learning? To address these questions, rats were trained on a Pavlovian conditioning paradigm where distinct audio cues were paired with different reward sizes. We utilized fast-scan cyclic voltammetry to record phasic dopamine release in the nucleus accumbens with chronically-implanted electrodes throughout learning. Preliminary findings illustrate that cue-evoked dopamine release reflects differences in reward size, though this is not related to differences in conditioned responding. These findings highlight a dissociation between cue-elicited dopamine release and cue-elicited behavioral responding.

Disclosures: **M.J. Lefner:** None. **M.J. Wanat:** None.

Poster

837. Cognition: Nucleus Accumbens

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 837.14/JJJ15

Topic: G.02. Motivation

Title: Reduced behavioral activation in the Wistar-Kyoto rat model of depression: neurochemical mechanisms

Authors: *A. M. FARRAR, S. MYRON, A. OMAR, B. ABBOTT, I. TUNCALI, F. DHANG, M. PEREIRA;
Psychological and Brain Sci., Univ. of Massachusetts, Amherst, Amherst, MA

Abstract: Previous work has demonstrated the importance of monoamine neurotransmitters in depression. In particular, dopamine neurotransmission in the nucleus accumbens has been shown to be essential for behavioral activation and expenditure of effort, both of which are commonly impaired in depression. Rodent models of deficits in behavioral activation often assess motivation using food reinforced instrumental tasks, such as the progressive ratio (PR) operant task. The PR task requires animals to increase work output to receive subsequent food reinforcers and is exquisitely sensitive to interference with nucleus accumbens dopamine neurotransmission. The present study compared the performance of male Wistar Kyoto rats, a putative genetic rat model of depression, to male Sprague Dawley rats, which were selected as normative control strain, on the PR task. Initial results indicate that Wistar Kyoto rats exhibit impaired performance on the PR task, in terms of the last ratio completed ("breakpoint"), as well as a reduction in the local rate of responding. At the conclusion of behavioral testing, brain tissue samples were collected from prefrontal cortex, nucleus accumbens and neostriatum to determine intracellular content of monoamine neurotransmitters and their major metabolites. Preliminary neurochemical findings suggest that intracellular levels of dopamine are reduced in nucleus accumbens. The present results represent an important initial step in validating the Wistar Kyoto rat as an endogenous, genetic rat model of depression. In addition to the behavioral and neurochemical phenotyping studies, ongoing work in the laboratory aims to determine the genetic mechanism that underlie the depressive-like behavioral symptomatology.

Disclosures: **A.M. Farrar:** None. **S. Myron:** None. **A. Omar:** None. **B. Abbott:** None. **I. Tuncali:** None. **F. Dhang:** None. **M. Pereira:** None.

Poster

838. Learning and Memory: Molecules and Circuit Dynamics

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 838.01/JJJ16

Topic: H.01. Animal Cognition and Behavior

Title: Memory trace superimposition impairs recall in a mouse model of Alzheimer's disease

Authors: *S. POLL, L. SCHMID, J. STEFFEN, D. EHNINGER, M. FUHRMANN;
German Ctr. for Neurodegenerative Dis. (DZNE), Bonn, Germany

Abstract: The hippocampus is critically involved in learning and memory processes and one of the first regions affected in Alzheimer's disease (AD). Hippocampal CA1 pyramidal neurons substantially contribute to memory acquisition and retrieval. Memory retrieval in part involves the same neuronal ensemble that is active during acquisition - a memory trace. We asked whether memory trace formation was altered in a mouse model of AD. For this purpose we performed repetitive *in vivo* two-photon imaging of individual hippocampal CA1 pyramidal neurons combined with contextual fear conditioning. Neuronal activity was related to the expression of the immediate early gene *c-fos* in a transgenic FosGFP mouse. The mouse model was crossbred to APP/PS1 transgenic mice that served as a model for AD. We revealed decreased FosGFP expression in the proximity to Aß-plaques. Contextual fear learning induced an increased number of FosGFP-positive (FosGFP+) neurons in wildtype and APP/PS1 mice. A minor, but specific subset of these neurons was reactivated during retrieval, potentially representing a memory trace. However, APP/PS1 mice exhibited an increased number of FosGFP+ neurons after retrieval, similar to wildtype mice exposed to a novel context. These data suggest, that excessive activity of CA1 pyramidal neurons during memory retrieval superimposes the memory trace and therefore contributes to memory deficits in APP/PS1 mice and potentially in AD.

Disclosures: S. Poll: None. **L. Schmid:** None. **J. Steffen:** None. **D. Ehninger:** None. **M. Fuhrmann:** None.

Poster

838. Learning and Memory: Molecules and Circuit Dynamics

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 838.02/JJJ17

Topic: H.01. Animal Cognition and Behavior

Support: NSF GRFP

NINDS F30NS090819

NIMH 1R01MH100631

NIMH 1U01NS090583

NIMH 1R01NS094668

Title: *In vivo* imaging of state-dependent modulation of dendritic Ca^{2+} signaling in hippocampal CA1 pyramidal cells

Authors: *S. V. ROLOTTI, N. DANIELSON, M. LADOW, A. LOSONCZY;
Neurosci., Columbia Univ., New York, NY

Abstract: Although it is known that information about internal state as well as external proximal and distal cues is actively integrated in the dendrites of CA1 pyramidal cells (CA1PCs), it remains unclear how the intrinsic properties of CA1PC dendrites interact with those inputs to provide a basis for place field formation and stability. For example, it has been shown that the prevalence of regenerative dendritic events, i.e. branch-spike prevalence (BSP), throughout the basal arbor in response to somatic firing is predictive of place field stability (Sheffield & Dombeck, 2015). Recent work has also demonstrated that backpropagating somatic spikes arising from CA3 inputs to proximal dendrites interact with entorhinal cortical inputs to the distal apical tuft to produce regenerative dendritic plateau spikes that play an important role in potentiating inputs underlying place cell formation and maintenance (Bittner et al., 2015). The mechanisms underlying intra- and intercellular BSP variability remain unknown, and a direct demonstration of plateau-initiated place field formation is still lacking. To pursue this line of inquiry we have explored a variety of *in vivo* sparse labeling techniques including transgenic mouse lines, as well as viral approaches *in utero* and in the adult to accomplish sparse Cre-recombinase expression, paired with Cre-dependent GCaMP6f to yield expression in a subset of CA1PCs in the dorsal hippocampus. Preliminary work using our simultaneous two-photon calcium imaging and behavioral recording apparatus has shown that BSP in the basal arbor of CA1PCs is significantly modulated by the mouse's behavioral state during head-fixed exploration tasks on a novel cue-rich linear treadmill. CA1PC sublayer-specific differences in BSP baseline and modulation were also detected. Using a long-range piezoelectric actuator we have managed to trace CA1PCs out to the apical tuft, and we have begun simultaneous imaging of the tuft and somatic proxies along the apical trunk. Our work focuses on dendritic mechanisms of place cell formation and stability by pairing subcellular imaging with virtual environments to control environment initiation and therefore the timing of place field formation. We also conduct these experiments in random foraging as well as goal-oriented learning tasks to assess the impact of these cell-level mechanisms on the hippocampal network during behaviorally-relevant spatial navigation.

Disclosures: S.V. Rolotti: None. **N. Danielson:** None. **M. Ladow:** None. **A. Losonczy:** None.

Poster

838. Learning and Memory: Molecules and Circuit Dynamics

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 838.03/JJJ18

Topic: H.01. Animal Cognition and Behavior

Support: NIH Grant U01NS090583

Title: Calcium imaging of lfp-related hippocampal ensemble dynamics

Authors: ***A. D. GROSMARK**, G. TURI, M. A. S. LADOW, A. LOSONCZY;
Neurosci., Columbia Univ., New York, NY

Abstract: As a technique two-photon calcium imaging is increasingly utilized as it offers advantages for monitoring neural activity in 1) the recording of large (10^2 to 10^3) numbers of individual neurons, 2) recording these cells stably over the several-day time course relevant to many learning paradigms, 3) affording cellular sub-compartment resolution, and 4) naturally incorporating the genetic tools used for tagging individual cell types. Capitalizing on these advantages calcium imaging has recently been used to track the determinants and evolution of hippocampal ensemble coding of spatial location in various amenable tasks. However, beyond stimulus coding, hippocampal activity is known to be organized by self-generated dynamics. These self-generated dynamics, such as run-related theta-sequences and immobility-related Sharp-wave ripples, are closely associated with local field potential (LFP) biomarkers, which have been the subject of extensive study. In order to more closely examine these self-generated dynamics and how they relate to long-term stimulus encoding we performed simultaneous two-photon calcium imaging and LFP recordings in the CA1 layer of the mouse hippocampus. We report preliminary results regarding how hippocampal ensemble activity as assessed by calcium imaging relates to well-established hippocampal LFP biomarkers.

Disclosures: **A.D. Grosmark:** None. **G. Turi:** None. **M.A.S. Ladow:** None. **A. Losonczy:** None.

Poster

838. Learning and Memory: Molecules and Circuit Dynamics

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 838.04/JJJ19

Topic: H.01. Animal Cognition and Behavior

Support: NSF INSPIRE

Title: The application of a parylene neural probe for *In vivo* recordings from multiple sub-regions of the rat hippocampus

Authors: *H. XU, A. WELTMAN, M. HSIAO, E. MENG, T. BERGER, D. SONG;
USC, Los Angeles, CA

Abstract: The hippocampus is crucial to the formation of long-term memory and declarative memory. Simultaneous recording of unitary activities from main sub-regions which composed the hippocampus can provide helpful insight in the understanding of neuronal circuitry within the hippocampus and the understanding of roles that the hippocampus plays in memory function. In this work, parylene-C, a highly biocompatible and flexible polymer, based multisite neural probes are designed and introduced as a novel interface for long-term recordings from multiple sub-regions of the rat hippocampus. The neural probe is composed of 8 parylene shanks spaced 250 μm apart to span the dorsal hippocampus along it's longitudinal axis. Sixty-four electrical recording sites are micro-machined onto parylene shanks and spaced according to the distribution of hippocampal principal neurons in different sub-regions. The arrangement of recording sites are based on spatial information of the cell body layers gleaned from brain atlas measurement, *in vivo* recordings from different sub-regions of the hippocampus with micro-wire arrays and histology results. Together with our collaborators, we developed and optimized the special implantation approach of the flexible parylene probe and tested the insertion procedure both in brain tissue phantom and *in vivo*. Immunohistochemistry (IHC) staining post-implantation of sham probes were used to verify the location of the probe and to evaluate immune responses to the probe. Unitary activities were also collected during acute implantations. In future studies, the parylene based neural probe will be chronically implanted and neural activities will be recorded and compared with signals obtained with micro-wire arrays.

Disclosures: **H. Xu:** None. **A. Weltman:** None. **M. Hsiao:** None. **E. Meng:** None. **T. Berger:** None. **D. Song:** None.

Poster

838. Learning and Memory: Molecules and Circuit Dynamics

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 838.05/JJJ20

Topic: H.01. Animal Cognition and Behavior

Support: AURIC

Title: Doxorubicin alters mechanisms of memory formation in *Ex vivo* and *In vivo* models of Chemobrain

Authors: *A. H. ALHOWAIL[1], V. SUPPIRAMANIAM[2], R. ARNOLD[2];
[1]Pharmacal Sci., [2]Drug Discovery and Develop., Auburn Univ., Auburn, AL

Abstract: Doxorubicin (DOX), an antitumor drug, plays a major role in cancer chemotherapy. Doxorubicin is effective in the treatment of various types of tumors; however, optimal clinical effectiveness is limited due to secondary effects including cognitive impairment, also known as "chemobrain" or "chemofog." Chemobrain refers to a phenomenon in which cancer survivors exhibit cognitive impairment following chemotherapy treatment. Chemobrain is observed in up to 75% of cancer survivors exposed to chemotherapy, and persistent in 17-34% of cancer survivors. Although the mechanism of cognitive dysfunction is unknown for most of these drugs, some chemotherapeutic agents may trigger cognitive impairment by accessing the brain via the blood-brain barrier. Our previous study has shown that doxorubicin impaired long-term potentiation (LTP - cellular model of memory) in chemobrain animals. To further investigate this aim, we explored the direct effects of doxorubicin on cognitive impairment by incubating brain slices in a concentration of doxorubicin that mimics central DOX exposure from a peripheral injection, which is 250 nM in rats for 4 hours. From these slices, we assessed LTP and long-term depression LTD recordings, hippocampal protein expression through western blot analysis and hippocampal oxidative stress. The results indicated that doxorubicin-incubated slices have reduced in LTP, LTD and basal synaptic transmission as well as a decrease in mitochondrial complex I activity. In addition, we found that phosphorylation of ERK1/2 and lipid peroxidation is increased in doxorubicin-incubated slices compared to control without a change in total protein expression. Therefore, we conclude that doxorubicin directly modulates cognitive function.

Disclosures: **A.H. Alhowail:** None. **V. Suppiramaniam:** None. **R. Arnold:** None.

Poster

838. Learning and Memory: Molecules and Circuit Dynamics

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 838.06/JJJ21

Topic: H.01. Animal Cognition and Behavior

Support: The EPFL Blue Brain Project Fund

The ETH Board Funding to the Blue Brain Project

Novartis Pharma

European Union Seventh Framework Program (FP7/2007-2013) under grant agreement no. 604102 (HBP)

Calculations were performed on the EPFL Blue Brain IV BlueGene/Q supercomputer hosted at the Swiss National Supercomputing Center (CSCS) in Lugano

Medical Research Council (MRC)

Title: Reconstruction and simulation of the hippocampus in the human brain project

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Abstract: We report a first draft digital reconstruction and initial validation of the rodent hippocampus using algorithms, applications and workflows that were developed in the Blue Brain Project (BBP) and made publicly available through the Human Brain Project (HBP) Brain Simulation Platform (BSP). In brief, the reconstruction process began with populating the hippocampal volume, defined by publically available atlases, with a series of reconstructions of well-characterized neuron types according to experimentally measured densities and composition. A connectome was generated as previously described [1], using biological data on bouton densities and synapses per connection. Electrical models of neurons and synaptic physiology were constrained by electrophysiological recordings and published data. Finally, further datasets were used to validate each of the reconstruction steps, and emergent properties of

the complete model. The BSP facilitates this process by providing access to well-defined workflows integrating the multiple components required in a transparent and repeatable way, and works in synergy with the HBP Neuroinformatics (NIP) and the High Performance Analytics and Computing (HPAC) platforms. Furthermore, the BSP enables teams to collaborate on the reconstruction by making the building workflow and validations accessible in a web-based user-oriented interface supported by the HBP "Collaboratory" framework. Indeed, the reconstruction is intended to form part of a larger community initiative involving groups beyond the HBP, and periodic collaborative refinements and regular public releases of the reconstruction are planned. The reconstruction represents a resource for the community to integrate experimental data, perform *in silico* experiments, and test hypotheses on hippocampal function.
[1] Reimann, M. et al. An algorithm to predict the connectome of neural microcircuits. Front. Comput. Neurosci. (2015). http://dx.doi.org/10.3389/fncom.2015.00120

Disclosures: **A. Romani:** None. **N. Antille:** None. **J. Courcol:** None. **A. Devresse:** None. **J. Dynes:** None. **J. Falck:** None. **M. Gevaert:** None. **J. Gonzalo:** None. **A. Gulyas:** None. **S. Jimenez:** None. **S. Kali:** None. **L. Kanari:** None. **S. Lange:** None. **H. Lu:** None. **A. Mercer:** None. **M. Migliore:** None. **J. Palacios:** None. **S. Ramaswamy:** None. **M. Reimann:** None. **R. Riquelme:** None. **C. Rössert:** None. **Y. Shi:** None. **J. Shillcock:** None. **A. Thomson:** None. **W. Van Geit:** None. **L. Vanherpe:** None. **H. Markram:** None. **E. Muller:** None.

Poster

838. Learning and Memory: Molecules and Circuit Dynamics

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 838.07/JJJ22

Topic: H.01. Animal Cognition and Behavior

Support: NIH Grant R01NS085709

NIH Grant P01NS045260

NIH Grant R21HD079823

Title: Spaced training offsets cognitive deficits in Down syndrome model mice

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Abstract: Down syndrome (DS) is a developmental intellectual disability disorder resulting from a full or partial extra copy of chromosome 21. Individuals with DS have deficits in speech and language, and in non-verbal skills including spatial memory. Consistent with this, previous studies in the Ts65Dn mouse model of DS have demonstrated object recognition and object location memory deficits, as well as impaired hippocampal long-term potentiation (LTP) which may contribute to these cognitive deficiencies. Recent work by our group has demonstrated memory and associated synaptic signaling deficits in a mouse model of fragile x syndrome that are offset by spaced behavioral training (Seese et al. *PNAS*, 2014). In the present study, we tested if spaced, as opposed to massed, training could be used to improve long-term spatial memory in the Ts65Dn mouse. Littermate wild-type (WT) and Ts65Dn mice were trained on the hippocampus-dependent, object location memory task: Mice explored a chamber containing two identical objects for 10 continuous minutes for massed training, or in three trials each lasting 3.3 minutes with 60 minutes between trials (this particular spacing was chosen to correspond to parameters of spaced stimulation that augments field CA1 LTP; Kramar et al. *PNAS*, 2012). Memory for object location was then assessed 24 hours later, at which time the mouse was placed in the arena and allowed to explore the same objects with one in the original, and the second in a novel, location; preference for the novel location object denotes learning. Wild type mice learned the task with 10 min massed training, while Ts65Dn mice did not ($p<0.0005$). However, when the same amount of total training was spaced over three trials the Ts65Dn mice learned at levels comparable to wild types. These results demonstrate that a spaced-training regimen can be used to facilitate long-term spatial memory in Ts65Dn mice, and suggest the possibility of a non-pharmacological approach to improve learning and memory in individuals with DS. Ongoing studies are further evaluating the temporal parameters of spaced training that are effective in Ts65Dn mice, the degree to which spacing can facilitate learning in other tasks, and if the restoration of long-term memory in Ts65Dn mice is associated with changes in synaptic signaling.

Disclosures: **A. Le:** None. **B.M. Cox:** None. **J.C. Lauterborn:** None. **J.N. Crawley:** None. **G. Lynch:** None. **C.M. Gall:** None.

Poster

838. Learning and Memory: Molecules and Circuit Dynamics

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 838.08/JJJ23

Topic: H.01. Animal Cognition and Behavior

Support: REPROBESITY, HEALTH–F2–2008–223713

Endofood, ERC–2010– 11 StG–260515

ERC-2014-PoC-640923

FRM DRM20101220445

ANR-13-BSV4-0006

BRAIN ANR-10-LABX-0043

Title: Mitochondrial CB1 signaling in the brain mediates adverse effects of cannabinoids

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Abstract: Understanding the specific mechanisms of cannabinoid effects is mandatory for their safe therapeutic use. The G protein coupled cannabinoid type-1 (CB1) receptor is widely expressed in the brain, where it is present both at plasma and mitochondrial membranes (mtCB1). This study shows that important side effects of cannabinoids can be ascribed to activation of brain mtCB1 receptors. The inhibition of mtCB1 receptor signaling in the substantia nigra reticulata (SNr) blocks cannabinoid-induced catalepsy, but not antinociception. Moreover, we generated a mutant CB1 protein (DN22-CB1) lacking mtCB1 signaling. The viral expression of DN22-CB1 in the SNr specifically prevented the cannabinoid-induced catalepsy. By using similar approaches we observed that hippocampal inhibition of mtCB1 blocked cannabinoid-induced impairment of long-term memory. These data show that mtCB1 receptors mediate important cannabinoid-induced adverse effects, such as catalepsy and amnesia, and provide potential therapeutically relevant approaches for discriminating between desired and undesired effects of cannabinoid drugs.

Disclosures: **E. Soria:** None. **T. Desprez:** None. **L. Bellocchio:** None. **G. Marsicano:** None.

Poster

838. Learning and Memory: Molecules and Circuit Dynamics

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 838.09/JJJ24

Topic: H.01. Animal Cognition and Behavior

Support: HEALTH-603191

ERC–2010–StG–260515

ERC-2014-PoC-640923

DRM20101220445

Title: Astroglial CB1 receptors control memory via D-serine

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Abstract: Bidirectional communication between neurons and astrocytes shapes synaptic plasticity and behavior. Astroglial cannabinoid type-1 receptors (CB1) are key mediators of neuroglial cross-talks, but their physiological role in memory processes is unknown. Using a combination of genetic, behavioral, and in vivo and in vitro electrophysiological approaches, here we show that astroglial hippocampal CB1 receptors are key determinants of learning and memory via D-serine gating of NMDA receptors-dependent synaptic plasticity.

Disclosures: L.M. Robin: None. **J.F. Oliveira da Cruz:** None. **V.C. Langlais:** None. **M. Metna-Laurent:** None. **A. Busquets-Garcia:** None. **E. Soria-Gomez:** None. **T. Papouin:** None. **B. Bosier:** None. **F. Drago:** None. **A. Van Eeckhaut:** None. **I. Smolders:** None. **F. Georges:** None. **A. Panatier:** None. **S.H.R. Oliet:** None. **G. Marsicano:** None.

Poster

838. Learning and Memory: Molecules and Circuit Dynamics

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 838.10/JJJ25

Topic: H.01. Animal Cognition and Behavior

Support: FP7-PEOPLE-2013-IEF-623638

ERC–2010–StG–260515

ERC-2014-PoC-640923

DRM20101220445

ANR-10-LABX-0043

ANR-10-IDEX-03-02

ANR-13-BSV4-0006-02

Title: Pregnenolone prevents cannabinoid-induced psychosis

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Abstract: Cannabis-induced psychosis (CIP) represents a growing health issue and their underlying neurobiological mechanisms are poorly understood. Moreover, current antipsychotic treatments used to treat CIP are limited either by side-effects or by their ability to tackle only certain aspects of psychosis. Thus, safer wide-spectrum treatments are currently needed. Although the blockade of cannabinoid type-1 receptor (CB1) has been suggested as a therapeutical mean, the use of orthosteric CB1 receptor antagonists is strongly limited by undesired side effects. In this regard, the neurosteroid pregnenolone has been recently shown to act as a very potent endogenous signal-specific inhibitor of CB1 receptors. Thus, we tested the possible therapeutic use of pregnenolone against psychotic-like effects of the main psychoactive compound of cannabis Δ^9-tetrahydrocannabinol (THC) in mice. Pregnenolone treatment was able to prevent a wide spectrum of THC-induced endophenotypes typically associated with psychosis, including cognitive, somatosensory gating and negative ones such as decreased social interaction. Moreover, in order to capture positive symptoms of psychotic-like states in mice, we adapted a behavioral paradigm based on associations between different sensory modalities and selective devaluation allowing to study mental sensory representations. Notably, THC impaired mental sensory representations, a hallmark of psychotic-like positive symptoms, in an antipsychotic- and pregnenolone-sensitive manner. Overall, this work reveals that signal-specific inhibitors mimicking pregnenolone effects can be considered as new therapeutic tools to treat CIP.

Disclosures: **A. Busquets-Garcia:** None. **E. Soria-Gomez:** None. **Y. Mackenbach:** None. **G. Ferreira:** None. **P. Piazza:** None. **G. Marsicano:** None.

Poster

838. Learning and Memory: Molecules and Circuit Dynamics

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 838.11/JJJ26

Topic: H.01. Animal Cognition and Behavior

Support: NIH Grant NS078434

NIH Grant MH105427

Title: Excitatory hilar mossy cells are the major local circuit integrators in the dentate gyrus

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Abstract: The dentate gyrus is a critical structure of the hippocampal formation, and considered as the first stage of information processing in the excitatory tri-synaptic circuitry of the hippocampus. The excitatory neuronal types in the dentate gyrus include much-studied dentate granule cells in the fascia dentate, and the mossy cells in the hilus. Hilar mossy cells are the principal and only glutamatergic neurons in the dentate hilus. They were named after their ‘‘mossy’’ appearance due to their relatively large somata and thick bushy proximal dendrites covered by numerous large and complex spines which are the sites of mossy fiber input synapses. Mossy cells receive much attention because of their likely critical roles in cognitive functions that the dentate gyrus serves such as pattern separation. Compared with dentate granule cells, mossy cells do not form recognizable layers with densely packed somata, and they are scattered in the hilar region under the granule cell layer. Partly due to technical difficulty for targeting mossy cells for circuit mapping and their relative lack of ordered ultrastructure, the circuitry inputs to these neurons remain largely uncharacterized. To better understand how mossy cells interact with dentate granule cells and other neuronal types to modulate functional circuit operations of the dentate gyrus, we have used new viral genetic and functional circuit mapping approaches to map and compare local and long-range circuit connections of mossy cells and dentate granule cells. Selective viral genetic systems were combined with monosynaptic rabies retrograde tracing of synaptic connections to uncover previously unidentified circuits to hilar mossy cells and dentate granule cells which provide a new view of information flow through these cells. We then functionally confirmed these new anatomical features of the mossy cell and dentate granule cells with photostimulation-based circuit mapping via fast voltage sensitive dye imaging and whole cell recordings in brain slices. Together, these results show that the great majority of inputs to mossy cells consist of two parallel inputs from within the dentate gyrus, with dentate granule cells providing strong excitatory inputs along with inhibitory neurons in DG molecular layer and hilus providing predominant inhibition. There is also significant CA3 input and long range septal cholinergic input to the hilus mossy cells along with a very minor entorhinal cortex input. Together, the anatomical and functional evidence reveals that mossy cells are a major locus of integration in the dentate gyrus that utilize feedback modulation of activities of DG granule cells as well as its upstream CA3 region.

Disclosures: **X. Xu:** None. **Y. Sun:** None. **T. Ikrar:** None.

Poster

838. Learning and Memory: Molecules and Circuit Dynamics

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 838.12/JJJ27

Topic: H.01. Animal Cognition and Behavior

Support: AIHS

NSERC

CFI

CIHR

LCIA

Title: The activity of ryanodine receptor calcium release channel is a critical determinant of long term potentiation in hippocampus

Authors: *F. HIESS[1], J. YAO[1], R. WANG[1], J. MICLAT[2], S. CHEN[1];
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Abstract: The type 2 ryanodine receptor (RyR2) is most abundantly expressed in the heart and brain. RyR2 is located in the sarco(endo)plasmic reticulum (SR/ER) membrane and functions as an intracellular calcium release channel. In the brain, RyR2 is thought to play a role in learning and memory, but its cellular/subcellular distribution and the mechanisms of its actions in the brain remains largely undefined. We have recently generated a knock-in mouse model that expresses a green fluorescence protein (GFP)-tagged RyR2. This GFP-RyR2 mouse model allows us to directly and specifically monitor the cellular/subcellular distribution and expression of RyR2 in various cells and tissues. To improve the detection of GFP, we have also developed novel GFP-specific probes based on anti-GFP single domain antibodies (inanobodies). High-resolution confocal imaging of intact GFP-RyR2 brain sections revealed widespread distribution of RyR2 in various brain regions, most prominently in regions involved in spatial learning and memory, such as the hippocampus. To define the functional role of RyR2 in this region, we performed electrophysiological studies using hippocampal slices prepared from knock-in mice harboring RyR2 mutants with increased (R4496C) or decreased (E4872Q) store luminal calcium sensitivity. We found that enhanced RyR2 activity (R4496C) reduces long-term potentiation (LTP), while suppressed RyR2 function (E4872Q) increases in Schaffer collaterals. Thus, RyR2 plays a critical role in LTP. Behavioral studies on these RyR2 mutant mouse models will be conducted to further assess the role of RyR2 in learning and memory (Supported by AIHS, NSERC, CFI, CIHR, and LCIA).

Disclosures: **F. Hiess:** None. **J. Yao:** None. **R. Wang:** None. **J. Miclat:** None. **S. Chen:** None.

Poster

838. Learning and Memory: Molecules and Circuit Dynamics

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 838.13/JJJ28

Topic: H.01. Animal Cognition and Behavior

Support: NIH P01-AI102852

NIH P01-AI073693

Title: Sepsis leads to impaired contextual memory and abnormal hippocampal ensemble dynamics

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Abstract: Sepsis is a condition in which the immune system reacts excessively to infection, leading to body-wide inflammation. Long-term survivors of sepsis often display neurological dysfunction, leading to cognitive impairment and encephalopathy. Using a mouse model for sepsis with cecal ligation and puncture (CLP), we ask whether contextual fear memory and the network dynamics of the hippocampus show abnormalities in sepsis survivors. Young adult mice (Balb/Cj, male, 3-mo old) underwent CLP (n = 20) or SHAM (n = 15) laparotomy surgeries and, after 6 weeks of recovery, were subjected to delay fear conditioning (FC) with 3 episodes of tone (80 dB, 15-sec) followed by shock (1 mA, 1 sec). Mice were tested for contextual memory (10 min in FC chamber) and tone memory (3 tones in novel chamber). Freezing was analyzed by software (Freeframe). We find that CLP mice freeze significantly less during the contextual memory session (CLP, 23.77±2.3, SHAM, 35.16±3.44, P = 0.007, t = 2.75, t test), but the CLP group shows comparable freezing to SHAM mice in the tone memory test. After FC, in a select group of mice (CLP, n = 6; SHAM, n = 6), a microarray with 3 tetrodes and 2 single electrodes (50μm) was implanted into the CA1 region for in vivo recordings performed over the course of 2 days in an open field (2 square chambers, 20 cm and 60 cm on the side), interspersed by rest periods (home cage). We recorded network oscillations and CA1 place cells (software: Cheetah, Neuralynx, NeuroExplorer, Matlab, Spike2). We find that freely moving CLP mice have distinct oscillations in dorsal CA1 during exploration of a novel environment (new chamber) and in the presence of novel objects. However, theta frequency power and theta-gamma coupling are significantly diminished when compared to SHAM mice, particularly during exposure to novelty. Moreover, CLP mice exhibit severely diminished pyramidal cell activity compared to

SHAM animals. For instance, in a 1-h session (including chamber and home cage), we find that CLP mice have 19.82±7.9 spikes per cell compared to 441.62±193.34 spikes per cell in SHAM mice. Place cell activity is also greatly affected in sepsis survivors (peak firing rate: CLP = 0.50±0.11 Hz, SHAM = 2.39±0.31 Hz) with place fields covering extremely small areas and lacking a normal maturation process. We conclude that sepsis survivors display impaired contextual fear memory and CA1 neural ensembles with striking abnormalities in the cell spiking characteristics and the formation of robust place fields. Therefore, sepsis can affect spatial cognition by altering the function of the hippocampus.

Disclosures: **J.J. Strohl:** None. **T.S. Huerta:** None. **A. Sabharwal:** None. **P.T. Huerta:** None.

Poster

838. Learning and Memory: Molecules and Circuit Dynamics

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 838.14/JJJ29

Topic: H.01. Animal Cognition and Behavior

Support: KU YW02-15

Title: The effect of developmental vitamin d deficiency on spatial learning and memory in wistar rats

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Abstract: Vitamin D deficiency is widespread in the Middle East. Recent evidence suggests that vitamin D is involved in brain development and function. Low plasma vitamin D has been associated with poor cognitive function in adults but the effect of developmental vitamin D deficiency (DVD) on cognitive function and brain development has not been well-established. We determined the effect of DVD on spatial learning and memory in Wistar rats. Rats were divided into four groups: C (control), dG (deficient during gestation only), dL (deficient during lactation only), dGL (deficient during gestation and lactation). Learning and spatial memory was measured by Morris water maze (MWM) test at postnatal day (PND)-24 and -45. Number of synapses in the molecular layer of hippocampus was counted at PND-32 and -63 (the day animals were sacrificed after MWM test). Repeated measure ANOVA revealed that at PND-24 the dGL group learned significantly slower compared to all the groups. At PND-45, however there were no significant differences in escape latencies among the four groups indicating that learning was not affected by DVD at this age. Probe test was performed after 2 days of learning sessions for Short Term Memory (STM) and after 10 days for Long Term Memory (LTM).

Neither STM nor LTM were affected by DVD at both PND-24 and -45. The number of synapses at PND-32 was not significantly different between groups C and dGL (15.1±7.0 vs 14.5±7.0). On the other hand, at PND-63 the number of synapses was significantly lower ($p < 0.001$) in the dGL group (11.8±6.0) than group C (23.0±6.1). In the control group the number of synapses significantly increased from PND-32 to PND-63 ($p < 0.001$), whereas, it did not change in the dGL group. Our results suggest that DVD during a particular developmental window of the brain development may have more severe consequences of learning impairment, but once learning has occurred, DVD has no significant effect on memory.

Disclosures: **A. Al-Harbi:** None. **A. Rahman:** None. **K.M. Khan:** None.

Poster

838. Learning and Memory: Molecules and Circuit Dynamics

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 838.15/JJJ30

Topic: H.01. Animal Cognition and Behavior

Support: NIH Grant NS078434

Title: Circuit connection and function of the subicular neurons that project to hippocampal CA1

Authors: ***Y. SUN**, X. XU;
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Abstract: The hippocampal formation is traditionally viewed as having a feed-forward, unidirectional circuit organization which promotes propagation of excitatory processes. While the substantial forward projection from hippocampal CA1 to the subiculum has been very well established, accumulating evidence supports the existence of a significant back-projection pathway comprised of both excitatory and inhibitory elements from the subiculum to CA1 (Sun et al., 2014). Such a back projection could serve to modulate information processing in hippocampal CA1 (Jackson et al., 2014; Xu et al., 2016). To better understand the circuit mechanism and function of this pathway, in the present study, we test whether CA1-projecting subicular neurons are a unique neuronal group that has distinct circuit connections compared to other subicular neuron types. Combinatorial viral tracing approaches are used to map the input connections of CA1-projecting subicular neurons in the mouse. Canine adenovirus type 2 (CAV2) expressing Cre-recombinase is injected in the CA1; retrograde Cre expression selectively labels CA1-projecting subicular neurons. Cre-dependent monosynaptic rabies tracing is followed in the subiculum to map direct synaptic connections of CA1-projecting subicular neurons in the intact brain. We found that CA1-projecting subicular excitatory neurons were

innervated by CA1 excitatory pyramidal neurons (60.0% of total labeled cells), and a considerable number of inhibitory interneurons in CA1 stratum oriens (16.1%). These subicular neurons received some inputs from the neocortex such as visual cortex and auditory cortex, but little input from the entorhinal cortex. In comparison, subicular excitatory neurons targeted by using the Camk2a-Cre mouse received nearly 90% of the total inputs from CA1 pyramidal neurons and 2.2% of inputs from CA1 inhibitory neurons. Notably, subicular excitatory neurons in the Camk2a-Cre mouse received relatively strong inputs from perirhinal, entorhinal, and temporal association cortices. Thus, our data support that the CA1 projecting subicular excitatory neurons differ from overall subicular excitatory neurons in terms of their circuit input patterns, and these non-canonical projecting neurons provide feedback regulation of CA1 activity independent of entorhinal influence. We are currently addressing what roles subiculum-CA1 projections may play in hippocampus-associated learning and memory behaviors through targeted inactivation of CA1-projecting subicular neurons.

Disclosures: **Y. Sun:** None. **X. Xu:** None.

Poster

838. Learning and Memory: Molecules and Circuit Dynamics

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 838.16/JJJ31

Topic: H.01. Animal Cognition and Behavior

Title: Comparing memory models with and without dendrites

Authors: *G. C. MEL[1], B. W. MEL[2];
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Abstract: Neurally-inspired models of online recognition memory generally operate by modifying synapses as input patterns are sequentially presented to the network, where the goal is to encode a memory trace of each stored pattern that survives as long as possible. Architecturally, these systems fall into two main categories -- single layer networks, whose inputs act directly on a (virtual) classifier unit through modifiable synaptic weights (eg. Fusi and Abbott, 2007; Lahiri and Ganguli, 2013) and two-layer networks, whose inputs form modifiable synaptic connections onto a layer of nonlinear dendritic subunits, whose outputs then converge onto a classifier unit (Wu and Mel, 2009). It has been difficult to compare these two types of architectures in terms of storage capacity, robustness, scalability, and biological plausibility, as they have also differed in their synaptic learning rules (e.g, deterministic vs. stochastic changes, relative roles of LTP and LTD), synaptic parameters (e.g., number and type of internal states), assumed sparsity of input patterns (e.g. sparse vs. dense), and so on. In this poster we sort

through these issues in the attempt to clarify the role that active dendrites and complex synapses may play in online memory formation in the brain.

Disclosures: **G.C. Mel:** None. **B.W. Mel:** None.

Poster

838. Learning and Memory: Molecules and Circuit Dynamics

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 838.17/JJJ32

Topic: H.01. Animal Cognition and Behavior

Support: ANR-12-BSV4- 0021-01

ANR-13-JSV4-0002-01

Ville de Paris

Title: Hippocampal area CA2 properties under enhanced cholinergic tone and influence of supramammillary inputs on this physiological state

Authors: *V. ROBERT, L. THERREAU, V. CHEVALEYRE, R. PISKOROWSKI; CNRS UMR8118, Paris, France

Abstract: Hippocampal network theta and gamma rhythms are critical for learning and memory. These oscillatory states can arise under conditions of enhanced cholinergic tone provided by extra-hippocampal structures such as the septum. While oscillatory patterns of activity have been extensively studied both *in vivo* and *ex vivo* in hippocampal areas CA1 and CA3, area CA2 has rarely been examined. Recently, *in vivo* recordings (Kay et al., Nature 2016) revealed that hippocampal physiology during immobility is dominated by a unique pattern of activity that originates in area CA2. Hence, information regarding the cellular and local network mechanisms enabling this phenomenon in area CA2 is required to understand the hippocampal physiology in those states. Further, hippocampal oscillations are tuned by several extra-hippocampal structures including the supramammillary nucleus (SuM) which could influence this activity pattern through its direct projections onto area CA2/CA3a. Using a pharmacological *ex vivo* approach combined with electrophysiology, calcium imaging and optogenetics, we investigate the mechanisms and control of area CA2 oscillatory properties. Patch-clamp recordings of CA2 pyramidal neurons in acute hippocampal slices have revealed their ability to rhythmically fire bursts of action potentials upon application of the muscarinic agonist carbachol. Although this intrinsic burst firing persists in absence of synaptic transmission, our preliminary experiments using calcium imaging suggest that synchrony can emerge amongst clusters of CA2 pyramidal

neurons in an intact network. Given the importance of synaptic inputs for this synchronization, we currently ask whether additional perisomatic inhibition recruited by SuM projections to area CA2/CA3a can influence rhythmogenesis in this region.

Disclosures: V. Robert: None. **L. Therreau:** None. **V. Chevaleyre:** None. **R. Piskorowski:** None.

Poster

838. Learning and Memory: Molecules and Circuit Dynamics

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 838.18/JJJ33

Topic: H.01. Animal Cognition and Behavior

Support: NSERC #222912

Savoy Foundation Studentship

Title: Intrahippocampal infusions of the extracellular matrix protein reelin ameliorates fear memory impairment associated with kindling of the basolateral amygdala

Authors: *J. J. BOTTERILL[1], N. NOGOVITSYN[2], H. J. CARUNCHO[3], L. E. KALYNCHUK[4];
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Abstract: Temporal lobe epilepsy is associated with a myriad of behavioral and cognitive comorbidities. Unfortunately, effective treatment options for these comorbidities remains a major challenge in the field. Here, we used the kindling model of temporal lobe epilepsy to characterize interictal behavioral comorbidities and test novel therapeutic approaches from a preclinical perspective. Kindling refers to the gradual progression and intensification of elicited motor seizures resulting from repeated electrical stimulation of a discrete brain region. We have previously reported that 99 kindling stimulations of the basolateral amygdala (BLA) impairs hippocampal-dependent fear conditioning and reduces the number of hippocampal cells expressing reelin. Interestingly, reelin has broad effects on synaptic plasticity in the adult brain by enhancing long-term potentiation, stimulating dendritic spine formation, and improving cognition through NMDA receptor-dependent mechanisms. The goal of this study was to determine whether acute intrahippocampal infusions of reelin could ameliorate the cognitive deficits associated with kindling. All rats received 99 electrical or control stimulations over 6.5 weeks. Upon completion of kindling, all rats were subjected to a 4-day hippocampal-dependent

fear conditioning paradigm comprising habituation, training, and testing (tone and context, respectively). A subset of BLA-kindled rats with a cannula located in the ipsilateral dorsal hippocampus (i.e., stimulated hemisphere) received two intrahippocampal reelin infusions (spaced 24 hours apart) prior to the fear training session. All rats were sacrificed 1 hour after the final memory test (i.e., context) and their brains were prepared for immunohistochemistry. We found that kindling and reelin infusions had no effect on baseline behaviors or the acquisition of fear conditioning. However, the BLA-kindled rats were significantly impaired on subsequent tests of tone and context memory. Interestingly, the BLA-kindled rats that received intrahippocampal infusions of reelin were comparable to control rats on both tests. Next, we analyzed the behaviorally-relevant neural activity marker Fos in the dentate gyrus. We found that the BLA-kindled rats had fewer Fos immunoreactive cells than control and BLA-kindled rats that received reelin, which indicates that reelin partially restores kindling-induced reductions of neural activity in hippocampal memory circuits. Collectively, our results suggest that acute intrahippocampal infusions of reelin can restore cognitive deficits associated with kindling of the basolateral amygdala.

Disclosures: J.J. Botterill: None. **N. Nogovitsyn:** None. **H.J. Caruncho:** None. **L.E. Kalynchuk:** None.

Poster

838. Learning and Memory: Molecules and Circuit Dynamics

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 838.19/JJJ34

Topic: H.01. Animal Cognition and Behavior

Title: Hippocampal ensemble dynamics timestamp events in long-term memory

Authors: *A. RUBIN, N. GEVA, L. SHEINTUCH, Y. ZIV;
Weizmann Inst. of Sci., Rehovot, Israel

Abstract: The capacity to remember temporal relationships between different events is essential to episodic memory, but little is currently known about its underlying mechanisms. Recent work has revealed that in familiar environments hippocampal place cell activity is dynamic over timescales that range from minutes to weeks. Here, we asked to determine whether such dynamics could contribute information about the temporal relationship between different events by providing a unique code that functions as a “timestamp”. We analyzed the ensemble activity dynamics of CA1 pyramidal cells in mice exploring two familiar environments. Using calcium imaging we were able to record repeatedly from hundreds of cells in each mouse over more than two weeks. Longitudinal analysis exposed ongoing environment-independent evolution of

episodic representations, despite stable place code and constant remapping between the two environments. To determine to what extent can the dynamics in the representations of the two environments infer the time in which episodes occurred we constructed neuronal "time decoders". The decoders could successfully estimate the day of the experiment from which test data were taken, indicating that the observed dynamics time-stamped experienced events via neuronal ensembles that had cellular composition and activity patterns unique to specific points in time. Temporally close episodes shared a common timestamp regardless of the spatial context in which they occurred. Temporally remote episodes had distinct timestamps, even if they occurred within the same spatial context. Overall, our results suggest that days-scale hippocampal ensemble dynamics could support the formation of a mental timeline in which experienced events could be mnemonically associated or dissociated based on their temporal distance.

Disclosures: **A. Rubin:** None. **N. Geva:** None. **L. Sheintuch:** None. **Y. Ziv:** None.

Poster

838. Learning and Memory: Molecules and Circuit Dynamics

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 838.20/JJJ35

Topic: H.01. Animal Cognition and Behavior

Support: CAS Grant Y3F9060901

Title: A competitive network model for cognitive map in large scale environments

Authors: S. LIU[1,2], *B. SI[3], Y. LIN[2];
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Abstract: Cognitive map representations in the brain are important for tasks like food-searching and homing especially in large environments (Tsoar et al., 2011). Experimental studies revealed that in large environments, place cells express more firing fields than in typical-sized environments tested in laboratories (Fenton et al., 2008). The formation of place fields of each place cell can be described by an independent Poisson process (Rich, Liaw, & Lee, 2014). We study the formation of efficient cognitive map representations of large environments in a competitive network model. In the model, each place unit receives spatial inputs from grid units in the medial entorhinal cortex as well as non-spatial inputs from the units in the lateral entorhinal cortex. The non-spatial inputs are modelled by random activities across units but are

constants within the same environment. Hebbian learning of the connections between grid units and place units drives place units to compete in field formation, and produces population codes that are determined together by the co-activation of grid cells and the strength of non-spatial inputs. We found that place units form multiple place fields in the environment. The inter-field intervals follow an exponential distribution. In the population level, the recruitment curve of place units is sub-linear and memoryless. If the non-spatial inputs to the place units are inactivated, the place units only form single firing fields, and the recruitment curve of place units becomes linear with respect to the sizes of the explored environment. These results explain the observed statistics of the hippocampal population codes, and predict that interruption of the non-spatial inputs from the lateral entorhinal cortex and other related areas would alter the statistics and efficiency of spatial representations in large environments.

References:
Fenton, A. A., Kao, H.-Y., Neymotin, S. A., Olypher, A., Vayntrub, Y., Lytton, W. W., & Ludvig, N.(2008). Unmasking the CA1 ensemble place code by exposures to small and large environments: more place cells and multiple, irregularly arranged, and expanded place fields in the larger space. The Journal of Neuroscience, 28(44), 11250-11262.
Rich, P. D., Liaw, H.-P., & Lee, A. K. (2014). Large environments reveal the statistical structure governing hippocampal representations. Science, 345(6198), 814-817.
Tsoar, A., Nathan, R., Bartan, Y., Vyssotski, A., DellOmo, G., & Ulanovsky, N. (2011). Large-scale navigational map in a mammal. Proceedings of the National Academy of Sciences, 108(37), E718-E724.

Disclosures: **S. Liu:** None. **B. Si:** None. **Y. Lin:** None.

Poster

838. Learning and Memory: Molecules and Circuit Dynamics

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 838.21/DP09 (Dynamic Poster)

Topic: H.01. Animal Cognition and Behavior

Support: NIH T32 MH015174-37

NINDS-NIH R01 NS075222

NIH R01 DA07418

NIH R01 DA010154

HHMI

Burroughs Wellcome Fund Postdoctoral Enrichment Program

Henry M. Jackson Grant

Title: Dopamine is co-released from the locus coeruleus into the dorsal hippocampus.

Authors: *K. A. KEMPADOO, E. V. MOSHAROV, S. CHOI, D. L. SULZER, E. R. KANDEL;
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Abstract: Dopamine signaling in the hippocampus mediates aspects of attention and arousal, however the site of dopamine release that drives the selective attention underlying spatial learning and memory is largely unexplored. We attempt to address this question by utilizing optogenetics to selectively stimulate dopamine release from the ventral tegmental area (VTA) to the hippocampus (HPC). Our immunohistochemistry results indicated that the locus coeruleus (LC), not the VTA, may provide the main source of dopamine to the HPC. We utilized HPLC with electrochemical detection and were able to directly measure co-release of norepinephrine and dopamine in the hippocampus following optogenetic LC axon stimulation. We therefore assayed the function of LC catecholamine release in the HPC during a learning and memory task. Photostimulation of the LC-to-hippocampus catecholamine pathway enhanced performance in a spatial recognition task via the dopamine D1/D5 receptor, but not via the beta-adrenergic receptor. These findings indicate that dopamine is co-released from LC neurons and provide a framework for further exploring catecholamine anatomy and function in the hippocampus.

Disclosures: K.A. Kempadoo: None. **E.V. Mosharov:** None. **S. Choi:** None. **D.L. Sulzer:** None. **E.R. Kandel:** None.

Poster

838. Learning and Memory: Molecules and Circuit Dynamics

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 838.22/JJJ36

Topic: F.02. Behavioral Neuroendocrinology

Support: St. Norbert Collaborative: Center for Undergraduate Research

Title: Insulin receptor labeling in zebra finch brain as revealed by confocal microscopy

Authors: A. T. HON, *D. J. BAILEY;
Biol., St. Norbert Col., De Pere, WI

Abstract: Insulin is a peptide hormone most studied for its role in the regulation of blood glucose. The action of insulin in the brain has centered on the hormone's role in nutrient homeostasis, reproduction, and memory. For example, in rodents, hippocampal insulin receptors are upregulated post-training in a Morris water maze task. Additionally, insulin receptors decrease in the hippocampus in aged rodents, and this correlates with hippocampal-dependent memory impairment. Songbirds are important model systems in behavioral neuroendocrinology in regard to brain sexual differentiation, learning and memory, and responses to acute and chronic stress, yet few studies have examined the presence or role of insulin receptors in brain tissue. Levels and activity of a related heterotetrameric glycoprotein receptor, the insulin-like growth factor receptor, have been examined in birds, with most studies aimed at determining their role in development, axon guidance, and neuronal turnover. We examined the extent and distribution of insulin receptor immunoreactivity in male songbird (zebra finch, *Taeniopygia guttata*) brain tissue. Adult birds were euthanized and transcardially perfused with paraformaldehyde. Tissue sections underwent immunohistochemical labeling with an antibody directed toward an epitope of the beta subunit of the insulin receptor, followed by a TRITC-conjugated secondary antibody, tyramide signal amplification, and counterstaining. Confocal microscopy revealed pronounced labeling in the hippocampus. In the ventral subdivision, there was a high number of immunopositive neuronal somata and diffuse immunoreactivity in the neuropil, the latter of which is suggestive of localization of these receptors in axon terminal membranes. Labeling was similar in the dorsolateral subdivision, but there was limited immunoreactivity in the dorsomedial portion. Dense immunoreactivity in the neuropil was found in the caudomedial nidopallium, while staining in the caudomedial mesopallium was sparse. Elsewhere in the telencephalon, labeling in nucleus taeniae was almost exclusively restricted to neuronal somata. In the diencephalon, insulin receptor immunoreactivity was most pronounced in the ventromedial hypothalamus. Further research will examine whether insulin receptor labeling is sexually dimorphic, and if antagonism of the receptor impairs spatial memory in this species. Determination of the localization and action of these receptors in the zebra finch brain will increase our understanding of the contribution of insulin to cognitive processes like learning and memory in songbirds.

Disclosures: **A.T. Hon:** None. **D.J. Bailey:** None.

Poster

839. Modulation of Cognition and Behavior II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 839.01/JJJ37

Topic: H.01. Animal Cognition and Behavior

Support: NHMRC Grant APP1070081

Title: The role of vitamin D in the adult brain

Authors: *T. H. BURNE, J. MCGRATH, N. GROVES;
Queensland Brain Inst., Brisbane, Australia

Abstract: Vitamin D deficiency is prevalent throughout the world and there is growing evidence to support a requirement for optimal vitamin D levels for the healthy developing and adult brain. There is accumulating evidence that low vitamin D levels may compromise the ability of the brain to recover after various stressors or may leave that individual more vulnerable to later environmental exposures (e.g. cannabis use, trauma, social stress). The focus of our recent work has been on a mouse model to examine the mechanism by which Adult Vitamin D (AVD) deficiency affects behavioural and neurochemical responses of relevance to schizophrenia. We feed adult BALB/c mice a vitamin D-deficient diet for 10 weeks prior to testing. Under these conditions the animals have normal calcium levels for at least 20 weeks on the vitamin D-deficient diet. We have assessed a wide range of neurochemical and behavioural outcomes with a particular focus on neuroprotective pathways and neurochemical dysfunction, using high performance liquid chromatography and LS-MS/MS to assess the proteome. Behavioural analysis has focused on social, cognitive and depressive-like behaviours. Our data suggest that vitamin D deficiency is associated with an altered balance of excitatory and inhibitory neurotransmitters. Neurochemical analysis of brain tissue showed that AVD-deficient mice had a significant reduction in the levels of glutamine and glutamate and a significant increase in the levels of GABA and glycine. In addition we have shown that vitamin D deficiency is associated with changes in pathways related to protein transport, cell surface receptors, glutathione metabolism and amino acid metabolism. With respect to cognition, we showed that there was no association between diet and performance for stimuli of long duration (2-5s) using the 5-CSRTT. However, when the task was made more difficult, the stimulus was on for a brief duration (0.6-1s), AVD-deficient mice made significantly fewer correct responses ($p<0.05$). We have also shown that AVD-deficient mice have delayed learning on a hippocampal-dependent active place avoidance task. These findings provide compelling evidence that low concentrations of vitamin D impact on brain neurochemistry and behaviour in adults. In particular our data suggest that vitamin D deficiency may exacerbate underlying brain disorders, and increase risk of cognitive impairment across multiple domains. This research has implications for a wide range of adverse psychiatric and neurological outcomes.

Disclosures: **T.H. Burne:** None. **J. McGrath:** None. **N. Groves:** None.

Poster

839. Modulation of Cognition and Behavior II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 839.02/JJJ38

Topic: H.01. Animal Cognition and Behavior

Title: Effects in anxiety behaviour after consumption of vegetal shortening or soy oil in 45 days age old Wistar rats.

Authors: *A. G. MARTINEZ[1], T. NERI-GOMEZ, Miss[2], R. E. JIMENEZ-LÒPEZ[3], A. SÀNCHEZ-CHINCHILLAS[4], R. BUSTAMANTE-GARCÌA[5];
[1]Fac Quimica, UNAM, Mexico City, Mexico; [2]Lab. de Patología Mol., CENTRO MEDICO SIGLO XXI. IMSS., MEXICO CITY, Mexico; [3]Biotecnology and Food Chem., UNAM, MEXICO CITY, Mexico; [4]Biotecnology and Food Chem., UNAM, MEXICO CITY, Moldova, Republic of; [5]BIOLOGY, UNAM, MEXICO CITY, Mexico

Abstract: Many studies support the hypothesis that the structure and function of the brain may be modulated by specific aspects of diet, including frequency, content and total energy intake throughout life of the organism. It is know that almost all foods are important in brain tissues, but certain mental faculties require more of certain nutrients for restoration, especially the lipids. The aim of this study was to evaluate two lipid diets, from different sources a vegetable lipid (soybean oil), animal origin (lard) and determine if these modify animal's behavior after 21 days of administration, since the variation of any nutrient could can lead not only physiological but also behavioral disorders, such as anxiety, depression, obsessive compulsive disorders or impaired memory. For this purpose Wistar rats were used (45 ± 50 g), divided into 5 groups (n=6 per group), and were placed in a rack individually, with the following diets: A = Reference diet, B = vegetal shortening, C= soy oil, after 21 days animals were evaluated with the task of marble burying behavioral that evaluates anxiety like behavior. We observed that the diet with soy oil the rats show an anxiogenic effect compared with control diet. When we evaluate the vegetable shotering we did not observe any significant change. This data suggest that some kind of lipids can alter the anxiety like behavior and at a long term affect the process of satiety that could affect the memory and learning process causing a degenerative disease

Disclosures: **A.G. Martinez:** A. Employment/Salary (full or part-time): UNAM. **T. Neri-gomez:** Other; IMSS. **R.E. Jimenez-lòpez:** Other; student. **A. Sànchez-Chinchillas:** A. Employment/Salary (full or part-time): UNAM. **R. Bustamante-garcìa:** A. Employment/Salary (full or part-time): UNAM.

Poster

839. Modulation of Cognition and Behavior II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 839.03/JJJ39

Topic: H.01. Animal Cognition and Behavior

Support: NIH-NIA Grant 1R21AG046875-01A1

Title: Sparsely-activating dentate granule cells decode hippocampal experience to promote neurogenesis

Authors: *G. W. KIRSCHEN[1], J. SHEN[1], B. SCHROEDER[2], G. MAN[1], S. GE[1];
[1]Neurobio. & Behavior, [2]Biomed. engineering, Stony Brook Univ., Stony Brook, NY

Abstract: The continuous generation of new dentate granule cells, exquisitely regulated by brain activity, renders the hippocampus plastic. However, how adult brain decodes its activities to impact neurogenesis remains largely unknown. In this work, we first mapped brain activity using c-fos labeling and *in vivo* Ca^{2+} imaging under control and enriched environments, the latter of which is known to promote neurogenesis. We for the first time found that sparsely-activating suprapyramidal dentate granule cells responded to enrichment by increasing their firing instead of recruiting more neurons. The potentiated firing dampened gradually to the basal level around 60 minutes in the same enrichment. Using a newly-developed non-head-fixed and running-trackable virtual reality system, we found that frequently changed environments with similar complexity further enhanced neurogenesis. Furthermore, optogenetic silencing of mature dentate granule cells perturbed the enrichment-induced neurogenesis. Together, our study shows that sparsely-activating dentate granule cells convey the enrichment through increased firing to regulate hippocampal neurogenesis.

Disclosures: G.W. Kirschen: None. **J. Shen:** None. **B. Schroeder:** None. **G. Man:** None. **S. Ge:** None.

Poster

839. Modulation of Cognition and Behavior II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 839.04/JJJ40

Topic: H.01. Animal Cognition and Behavior

Support: Academy of Finland Grant 274098

Title: Startle habituation and prepulse inhibition in rats selectively bred for endurance capacity

Authors: *J. WIKGREN[1], M. UTRIAINEN[2], S. LENSU[3], M. S. NOKIA[2], H. VALLI[2], E. MÄKINEN[3], S. L. BRITTON[4], L. G. KOCH[4], H. KAINULAINEN[3];
[1]Univ. Jyvaskyla, Jyvaskyla, Finland; [2]Psychology, [3]Biol. of Physical Activity, Univ. of Jyväskylä, Jyväskylä, Finland; [4]Anesthesiolgy, Univ. of Michigan Med. Sch., Ann Arbor, MI

Abstract: Aerobic fitness has in many studies been linked with cognitive skills. In a previous study (Wikgren et al, 2012), we showed that rats selectively bred for low endurance running capacity were compromised in a task that requires flexible cognition. The use of selectively bred animals allows for elimination of typical confounders in this kind of research, i.e., enrichment and stimulation related to physical activity by which the aerobic fitness is acquired. However, a number of factors might lead to this learning deficit in the animals with predisposition to low aerobic capacity. It might be that the genes that code for aerobic capacity are directly related to cognition in which case the difference should be present already at young age. On the other hand, it might be that animals with low aerobic capacity develop, among other detrimental health conditions, neuropathology, which then leads to cognitive deficits.
In this study, we aimed at 1) determining whether intrinsic aerobic capacity affects lower level of cognition (sensorimotor gating) and 2) whether this difference exists already at a very young age or whether it develops as a function of aging. We subjected both juvenile (8 weeks old) and adult (10 months old) rats from the High or Low Capacity Runner (HCR/LCR) strains to startle habituation and prepulse inhibition procedures. The actual experimental protocol involved three blocks of trials: 1. 10 startle alone trials, 2. 10 startle alone trials + 40 trials with startle tone preceded by a prepulse tone with either 30, 60, 100, or 200 ms lead interval, and 3. 10 startle alone trials.
We found that while startle amplitudes were higher in young HCR rats, the amount of habituation (from block1 to block 3) was similar. In older rats, the habituation was clearly more prominent in the HCR rats. Prepulse inhibition with short lead intervals was similar between the strains in young animals, but already at the 100 ms lead interval the PPI effect disappeared in HCR, indicating faster processing. In old animals, the PPI effect was larger in the HCR also in short lead interval trials. These results imply that automatic auditory processing is more efficient in young animals with better intrinsic aerobic capacity. Further, poor aerobic capacity seems to disrupt the low-level cognition at adult age. It would be of interest to see whether aerobic exercise would be able to reverse such a development.

Disclosures: **J. Wikgren:** None. **M. Utriainen:** None. **S. Lensu:** None. **M.S. Nokia:** None. **H. Valli:** None. **E. Mäkinen:** None. **S.L. Britton:** None. **L.G. Koch:** None. **H. Kainulainen:** None.

Poster

839. Modulation of Cognition and Behavior II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 839.05/JJJ41

Topic: H.01. Animal Cognition and Behavior

Title: Gladiolus dalenii van geel lyophilisate reverses scopolamine induced amnesia and improves oxidative stress damage in rat

Authors: *G. T. NGOUPAYE[1,2], D. B. PAHAYE[3], F. T. DJANKPA[4], J. L. NGONDI[5], E. NGO BUM[3];
[1]Univ. of Dschang-Dschang Cameroon, Dschang, Cameroon; [2]Sch. of Lab. Med. and Med. Sci., Univ. of KwaZulu-Natal, Durban, South Africa; [3]Dept. of Biol. Sci., Univ. of Ngaoundéré, Ngaoundere, Cameroon; [4]Program in Neurosciences, Uniformed Services Univ. of the Hlth. Sci., Bethesda, MD; [5]Dept. of Biochem., Univ. of Yaounde 1, Yaounde 1, Cameroon

Abstract: Background
Dementia is a syndrome of progressive deterioration of cognitive abilities associated with psychiatric and behavioral disturbances which affects millions of people all over the world, due to either neurodegenerative diseases or brain injury. Learning and memory are the most important executive functions performed by the human brain, the loss of which is a prominent feature in dementia. *Gladiolus dalenii* is an ornamental plant, and its bulbs are traditionally used to treat a number of illnesses such as epilepsy and schizophrenia in Cameroon. Previous studies have shown antidepressant and anticonvulsant properties of the aqueous macerate of this plant. This study aims to investigate the anti-amnesia effect of *Gladiolus dalenii* in scopolamine induced amnesia in rats and its possible antioxidant properties in this model.
Methods
Morris water maze, novel object location and recognition task were used to assess the spatial and the working memory. Male rats were treated for 12 days with saline, *Gladiolus dalenii* and tacrine. Animals were co-treated with scopolamine once daily every day from day 9 to day 12. The rats were decapitated on day 12 after the last behavioral testing. Prefrontal cortex and hippocampus was removed for acetylcholinesterase, malondialdehyde and gluthation for anti oxidant properties using standard biochemical procedures.
Results
Gladiolus dalenii reversed the memory impairment induced by scopolamine in the Morris water maze as well as novel object location and recognition task. It decreased acetyl cholinesterase in the hippocampus and prefrontal cortex. It also decreased the level of Malondialdehyde and increased the level of gluthation in the hippocampus showing that *Gladiolus dalenii* may exhibit a therapeutic effect on short- and long-term memory deficits related to Dementia.
Significance:

The results of this study suggest that *Gladiolus dalenii* ameliorate the cognitive impairment induced by scopolamine, through it inhibition of oxidative stress and enhancement of cholinergic neurotransmission activity. It can be therefore useful for conditions associated with memory dysfunctions seen in dementia.
Key word: *Gladiolus dalenii,* amnesia, acetylcholinesterase, anti-oxydant, scopolamine.

Disclosures: G.T. Ngoupaye: None. **D.B. Pahaye:** None. **F.T. Djankpa:** None. **J.L. Ngondi:** None. **E. Ngo Bum:** None.

Poster

839. Modulation of Cognition and Behavior II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 839.06/JJJ42

Topic: H.01. Animal Cognition and Behavior

Support: Innovation Fund Denmark

Karen Elise Jensen's Foundation

Title: Acute dosing of vortioxetine strengthens event-related brain activity associated with engagement of attention and cognitive functioning in rats

Authors: *B. LAURSEN[1], C. H. BUNDGAARD[3], C. GRAVERSEN[4], M. GRUPE[1], C. SANCHEZ[2], S. C. LEISER[2], H. B. D. SORENSEN[3], A. M. DREWES[4], J. F. BASTLUND[1]; [1]Synaptic Transmission In vivo, [2]Brintellix Sci. Team, H. Lundbeck A/S, Valby, Denmark; [3]Dept. of Electrical Engin., Tech. Univ. of Denmark, Kgs. Lyngby, Denmark; [4]Mech-Sense, Dept. of Gastroenterology and Hepatology, Aalborg Univ. Hosp., Aalborg, Denmark

Abstract: Objective: Studies of the multimodal antidepressant drug vortioxetine have demonstrated beneficial effects on cognitive dysfunction associated with depression. We aimed to elucidate how vortioxetine modulates neuronal activity during engagement of attention and cognitive processing in rats performing an auditory discrimination task. Methods: Evoked neuronal activity in target vs. non-target tone responses was investigated after vehicle administration using electroencephalographic (EEG) recordings. Additionally, task performance and EEG changes of target tone responses of vortioxetine (3 and 10mg/kg) vs. controls were characterized. Traditional quantification of grand average event-related potentials (ERPs) was supplemented with time-frequency analyses of spectral power and inter-trial phase-locking. Evaluated brain regions included prelimbic cortex, the hippocampus, and mediodorsal thalamus. Results: As compared to correct rejection of non-target tones, correct target tone responses

elicited increased EEG power in all brain regions. Furthermore, neuronal synchronization was increased in vehicle-treated rats during both early and late ERP responses to target tones. These findings suggest a significant consistency of local phases across trials during conditions of high attentional load. During the early auditory response, vortioxetine increased EEG power in all measured regions. Additionally, vortioxetine increased prelimbic and thalamic synchronized gamma band activity during early sensory processing. Finally, the amplitude of late hippocampal P3-like ERPs, the proposed rodent correlate of the human P300 ERP, was enhanced by vortioxetine. Conclusion: The present findings suggest differential effects of vortioxetine during early sensory registration and late endogenous processing of auditory discrimination. Strengthened P3-like ERP response may be related to the pro-cognitive profile of the antidepressant. Further investigations are warranted to explore the mechanism by which vortioxetine increase network synchronization during attentive and cognitive processing. Also, future investigation is warranted to elucidate the functional relevance and the translational validity of vortioxetine's effect on rodent P3-like potentials and neuronal oscillations in comparable clinical setups.

Disclosures: **B. Laursen:** A. Employment/Salary (full or part-time): H. Lundbeck A/S. **C.H. Bundgaard:** None. **C. Graversen:** None. **M. Grupe:** A. Employment/Salary (full or part-time): H. Lundbeck A/S. **C. Sanchez:** A. Employment/Salary (full or part-time): H. Lundbeck A/S. **S.C. Leiser:** A. Employment/Salary (full or part-time): H. Lundbeck A/S. **H.B.D. Sorensen:** None. **A.M. Drewes:** None. **J.F. Bastlund:** A. Employment/Salary (full or part-time): H. Lundbeck A/S.

Poster

839. Modulation of Cognition and Behavior II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 839.07/JJJ43

Topic: H.01. Animal Cognition and Behavior

Title: Dissociative effects of memantine in two operant behaviors as trained in different regimens

Authors: S.-F. CHEN[1], *R.-K. CHENG[4], R.-M. LIAO[1,2,3];
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Abstract: Although memantine (MEM) has been used to treat dementia and drug relapse, the neurobehavioral mechanisms underlying these clinical treatments remains under dispute. The present study investigated the effects of MEM on the two distinct operant behaviors maintained

on fixed-interval 30 sec (FI 30-s) and differential reinforcement of low-rate response of 10 sec (DRL 10-s) schedules, respectively, in the rat. To further examine how these drug effects could be influenced by the training history, the subjects of each operant behavior were divided into two subgroups (n=6 each) for receiving different training regimens: the continuous and the intermittent, respectively. The continuous operant training was conducted in 15 successive daily sessions, whereas the intermittent one was run by arranging an average of 3 no-training days inserted in the every other day(s) over the 15-session operant training. The rats acquired FI 30-s and DRL 10-s behaviors, but in distinct profiles from different training history. The DRL behavior after intermittent training regimen showed a lower bi-modal inter-response time (IRT) distribution than that after continuous training regimen. Similarly, the FI responding trained in intermittent training regimen was significantly less than that in continuous one. Via MEM dosing (0, 1.25, 2.5, 5 & 10 mg/kg), DRL behavior was more sensitive to this drug treatment than FI behavior in general. Regardless the training history, the 10 mg/kg of MEM was the only dose that decreased the total responses of DRL behavior. Conversely, the lowest dose (1.25 mg/kg) of MEM significantly increased total responses of DRL behavior trained from the intermittent, but not continuous, regimen. Effects of MEM on the microstructure of FI behaviors were depended by the dosing and training history. The aforementioned operant behavioral changes by MEM were independent to motor dysfunction. An interesting finding that 5 mg/kg MEM increased the responses on the bins of 9-11-s of DRL IRT curve reflects a timing process being “sharpened”. Together, these data indicate that operant behaviors trained in different regiments are affected by MEM in distinct profiles. MEM treatment given at certain dosage may have a cognitive enhancement effect on operant behavior.

Disclosures: **S. Chen:** None. **R. Cheng:** None. **R. Liao:** None.

Poster

839. Modulation of Cognition and Behavior II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 839.08/JJJ44

Topic: H.01. Animal Cognition and Behavior

Support: Grant-in-Aid for JSPS Fellows

Title: Hyper-hippocampal glycogen deposit induced by preloading of exercises and high carbohydrate diet: A possible strategy to enhance memory function

Authors: ***M. SOYA**[1,2], T. SHIMA[1], T. MATSUI[1], H. SOYA[1];
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Abstract: Hippocampal glycogen (Gly) localized in astrocytes would play a critical role in memory function as a source of lactate, neuronal energy source and/or neuromodulator. However, physiological strategies to enhance memory functions targeting hippocampal Gly are still unknown. In the sport science field, muscle Gly loading (GL), pretreatment of exercises with high carbohydrate (Carb) diet for 7 days, is a well known short-term method to enhance endurance with hyper-muscle Gly deposit, which could be realized by potentiating muscle Gly replenishment to above the basal level (supercompensation) after exercise. Since we have found hippocampal Gly supercompensation following exhaustive exercise (Exh-exer) (Matsui *et al.,* J Physiol, 2011; 2012), it is hypothesized that GL induces hyper-hippocampal Gly similarly to muscle Gly, which may potentiate hippocampus-related memory functions. We here, as a first step, examined whether GL increases hippocampal Gly similarly to muscles by using a GL model for rats and high-power (10 kW) microwave irradiation to accurately detect brain Gly levels. First, we compared Gly levels in the muscle and brain (the hippocampus, cerebellum, brainstem, cortex, and hypothalamus) at pre- and post-GL with 70% of high Carb diet and exercises (day 1: Exh-exer (20 m/min until exhaustion), day 2-4: moderate exercise (20 m/min, 30 min/day), day 5-7: sedentary). GL induced hyper-Gly in the muscle and also in the hippocampus and hypothalamus. Next, we examined peak of Gly levels during GL in the muscle, hippocampus and hypothalamus, and found that it was day 7 in all detected tissues. Furthermore, we investigated the effects of Carb intake during GL on hippocampal Gly levels, by using different Carb proportions of the diets (low: 5%, middle: 35%, and high: 70%). Carb intake increased depending on Carb dose in diets and muscle Gly increased associating with Carb intake, but hippocampal Gly was unchanged. Finally, we elucidated the effects of exercise conditions (Exh-exer and moderate exercise, Exh-exer, moderate exercise, and sedentary) on hippocampal Gly levels during GL with commercial diet (61% of Carb). Muscle and hypothalamic Gly were unchanged in all groups but hippocampal Gly increases in 2 groups performed Exh-exer. Our results demonstrate that GL induces hyper-hippocampal Gly like muscle Gly, supporting our hypothesis for GL as a physiological strategy enhancing memory function. During 7 days of GL, Exh-exer on day 1 (not high Carb diet) is essential to maximize the levels of hyper-hippocampal Gly deposit, suggesting a possible underlying mechanism of Exh-exer-activated/Carb intake-independent Gly synthesis in the hippocampus.

Disclosures: **M. Soya:** None. **T. Shima:** None. **T. Matsui:** None. **H. Soya:** None.

Poster

839. Modulation of Cognition and Behavior II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 839.09/JJJ45

Topic: H.01. Animal Cognition and Behavior

Title: Chronic effects of the 'biased' 5-HT_{1A} receptor agonists F13714 and F15599 on object pattern separation, hippocampal plasticity and 5-HT_{1A} receptor density in rats

Authors: *B. T. VAN HAGEN[1], N. P. VAN GOETHEM[1], R. SCHREIBER[2], A. NEWMAN-TANCREDI[3], M. VARNEY[3], J. PRICKAERTS[1];
[1]Dept. of Psychiatry & Neurosci., Maastricht Univ., Maastricht, Netherlands; [2]Suadeo Drug Discovery Consulting LLC, Watertown, MA; [3]Neurolixis, Dana Point, CA

Abstract: Pattern separation; the formation of distinct representations out of similar inputs, is an important hippocampal process implicated in memory formation. Impairments in pattern separation are present in multiple psychiatric disorders like dementia and schizophrenia. Based on the distribution of the serotonin 1A receptor (5-HT_{1A}R), and its molecular and cellular mechanisms, we hypothesized that it could be important for pattern separation processes. We have previously presented that *chronic* treatment with the 'biased' 5-HT_{1A}R agonist, F15599 (or NLX101) which preferentially activates postsynaptic heteroreceptors, improved rat performance in a spatial object pattern separation (OPS) task. While F13714, which preferentially activates presynaptic autoreceptors, impaired OPS performance *acutely*, but after *chronic* treatment this impairment was ameliorated. Core body temperature measurements were included as a mechanistic readout of postsynaptic 5-HT_{1A}R activation. A drop of one degree celcius from treatment day 4 onwards, in the F13714 group, implied rapid desensitization of presynaptic 5-HT_{1A}Rs (van Hagen et al., 2014. *Soc. Neurosci. #265.13*). Herein, we study the mechanisms underlying the effects of this chronic 5-HT_{1A}R stimulation on OPS performance in rats. We hypothesized that, the increase in OPS performance is supported by 5-HT_{1A}R mediated adult neurogenesis in the hippocampus. Furthermore, desensitisation of autoreceptors in the dorsal raphe nucleus (DRN) decreases serotinergic inhibition, which leads to increased postsynaptic 5-HT_{1A}R signalling. 48 male Wistar rats were treated daily with either 0.32 mg/kg F15599, 0.02 mg/kg F13714 or vehicle. OPS performance was measured on day 1, 8 and 24h after day 14 of treatment. After the last OPS test, half of the animals were sacrificed and hippocampal brain tissue was snap frozen for biochemistry, the remaining rats were perfused for immunohistochemistry (IHC). Westernblot analysis of plasticy markers and IHC analysis of DCX and Ki-67 were performed to evaluate hippocampal plasticity and neurogenesis. Furthermore, 5-HT_{1A}R IHC was performed on DRN and hippocampal sections to visualise receptor density. Preliminary results show that F15599 treated animals show more DCX positive cells and higher level of BDNF in the dorsal hippocampus, supporting the hypothesis that post-synaptic 5-HT_{1A}R stimulation can lead to an increase in neuronal plasticity which could underlie the improvement on OPS performance. Ongoing 5-HT_{1A}R density analysis will provide insight into the mechanism of desensitisation and the effects of chronically stimulating the 5-HT_{1A}R sub-populations.

Disclosures: **B.T. Van Hagen:** None. **N.P. van Goethem:** None. **R. Schreiber:** None. **A. Newman-Tancredi:** None. **M. Varney:** None. **J. Prickaerts:** None.

Poster

839. Modulation of Cognition and Behavior II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 839.10/JJJ46

Topic: H.01. Animal Cognition and Behavior

Support: LH14053 KONTAKT ll

PRVOUK P34

GACR P303/12/1464

GACR 14-03627S

AZV 15-34524A

GACR P304/12/G069

NIMH-CZ project ED2.1.00/03.0078

Title: Spatial and timing strategy in active place navigation task on rotating arena

Authors: *T. NEKOVAROVA[1,2], K. MALENINSKA[2], K. VALES[1,2], A. STUCHLIK[2,1];
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Abstract: Time and space are two domains intrinsically forming our experience and perception of reality. During navigation we perceive both spatial and temporal cues; every movement in space thus becomes inherently also a movement in time.
To develop behavioral test which separate temporal and spatial strategies in navigation we modified active place avoidance task in carousel arena for rats. The arena contains 60-deg to-be-avoided sector. The sector is defined by extra-maze cues; i.e., it is stable in room coordinate frame while the arena rotation continuously displaces intra-maze cues. Animal can use both spatial (extra-maze visual cues) and temporal strategies to solve the task in the classical version of the task. To distinguish these strategies, we trained the rats (adult male Long Evans from IPHYS breeding) in the light and dark conditions. We assume that during light conditions, the rats would use predominantly spatial cues, whereas during dark they would rely on timing strategy.
After the training, we applied *d*-amphetamine (0.5mg/kg) and THC (tetrahydrocannabinol; 0.5mg/kg) to affect timing strategy. Preliminary results showed that amphetamine distorted performance during dark periods, whereas performance during light periods remained intact. THC at this dose had affected performance only in the first session after application, in subsequent sessions when THC was applied, there was no effect.

We discuss the hypothesis that rats use different cognitive strategies to solve this version of active place avoidance task in light and in dark and that the performance may be affected in different way.
Acknowledgements:
This work was supported primarily by a MSMT grant entitled LH14053 KONTAKT ll awarded to AS and Warren H Meck. Additional support came from GAČR 14-03627S, AZV 15-34524A, GAČR P304/12/G069, PRVOUK P34 of Charles University in Prague, Czech Republic, GACR P303/12/1464, and from "National Institute of Mental Health NIMH-CZ)", grant number ED2.1.00/03.by the ERDF, and by
the project "Sustainability for the National Institute of Mental Health", grant number LO1611, with a financial support from the MŠMT under the NPU I program.

Disclosures: T. Nekovarova: None. **K. Maleninska:** None. **K. Vales:** None. **A. Stuchlik:** None.

Poster

839. Modulation of Cognition and Behavior II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 839.11/JJJ47

Topic: H.01. Animal Cognition and Behavior

Title: Novel small molecule-disease-modifying therapy for alzheimer's and other neurodegenerative diseases

Authors: R. TAYLOR, 98195, W. WALKER, K. CHURCH, *L. H. KAWAS, J. HARDING; Integrated Physiol. and Neurosci., M3 Biotech. Inc., Seattle, WA

Abstract: Aging populations will face an increasing neurodegenerative disease burden, and all neurodegenerative diseases result from a combination of diminished synaptic connectivity and neuron loss. Therefore, an effective treatment would be expected to augment synaptic connectivity, protect neurons from insult, and stimulate the replacement of lost neurons from pools of neural stem cells. These clinical endpoints can all be achieved by therapeutic use of neurotrophic factors, and one particularly attractive neurotrophic factor, hepatocyte growth both neurons and synaptic connectivity due to accumulation of toxic protein plaques, and HGF has shown promise as a potential treatment of AD and other neurodegenerative diseases. Limitations of stability and CNS bioavailability prevent the direct application of HGF in patients, but M3 Biotechnology, Inc. has developed a novel HGF mimetic (NDX-1001) that is inherently blood-brain barrier permeant and stimulates the HGF signaling cascade $\sim<$ 1nM concentrations in cell culture. The hippocampus is deeply affected by AD neurodegeneration, but NDX-1001 is a

potent stimulator of hippocampal synaptogenesis in vitro and in-vivo. Furthermore, NDX-1001 is able to reverse cognitive deficits in scopolamine and aging models of dementia, and exhibits profound neuroprotective activity. Most relevant, however, is NDX-1001's ability to restore cognitive function in behavioral models of neurodegenerative disease. Additionally, motor neurons of the peripheral nervous system can be protected from degeneration in genetic and chemical models of disease. Current treatment schemes for neurodegenerative diseases like AD focus on symptom amelioration, but NDX-1001 is under development by M3 Biotechnology, Inc. to become the first genuine therapeutic agent of AD that may promote protection of healthy connectivity and restore degenerated neural tissue.

Disclosures: R. Taylor: None. **W. Walker:** None. **K. Church:** None. **L.H. Kawas:** None. **J. Harding:** None.

Poster

839. Modulation of Cognition and Behavior II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 839.12/JJJ48

Topic: H.01. Animal Cognition and Behavior

Title: Effects of early-adolescent, mid-adolescent, or adult stress on morphine conditioned place preference

Authors: C. SHIELDS, S. BECKER, *L. BAKNER;
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Abstract: Early-life stress is correlated with a range of negative mental health outcomes including illicit drug abuse. One mechanism that may contribute to drug abuse is stress-induced elevation of drug reward. Place conditioning paradigms, an experimental animal model of drug reward, show that exposure to uncontrollable stress as an adult enhances opiate-induced conditioned place preference, CPP (Der-Avakian et al., 2007; Will, Watkins, and Maier, 1998). The present work addressed whether early-adolescent, mid-adolescent, or adult stress amplifies morphine CPP in adulthood. Although maternal separation stress increases morphine CPP in adulthood (Michaels and Holtzman, 2008), the current work adapts a novel adolescent stress paradigm that elevates aggression in adulthood (Marquez, et al., 2013) to study selective effects of stress experienced at distinct phases of development on morphine-induced CPP.
Male Sprague-Dawley rats (n=48) arrived at P20 and were randomly assigned to one of three groups (early-adolescent, mid-adolescent, or adult) designating the period of development when subjects were exposed to stressors. Animals were further divided into Stress (S) or No Stress (NS) conditions. Beginning on P21 (early-adolescent group), P35 (mid-adolescent group), or P60

(adult group), S subjects were exposed to an unpredictable stress procedure (NS animals remained in homecage). The stress procedure consisted of two stressors, synthetic fox odor (trimethylthiazoline, TMT) and elevated platform (EP). Stressor exposure occurred over 8 days: day one (EP), day two (EP, TMT), day three (TMT, EP), day four (TMT only), day five (none), day six (EP), day seven (EP, TMT), and day eight (EP). Morphine place conditioning commenced on P70 with a 15-min pre-test to determine the initially non-preferred side of the apparatus (black/grid or white/hole). After pre-test were 8 conditioning days where each animal received either morphine (15 mg/kg, IP) on the initially non-preferred side or saline (1 ml/kg, IP) on the initially preferred side, alternating by day. A post-test identical to the pre-test was conducted after conditioning concluded. Time on the non-preferred side served as the primary dependent measure.
A 2 (S/NS) x 2 (pre-/post-test) x 3 (early-adolescent/mid-adolescent/adult) mixed ANOVA revealed a significant main effect of test, $F(1,42)=115.90$, $p<.001$, and an interaction between test and age, $F(2,42)=4.59$, $p<.05$. Post hoc tests revealed statistically significant differences between pre- and post-test, robust CPP regardless of age or stress condition, and no selective effect of stress on opiate reward as measured by place conditioning techniques.

Disclosures: C. Shields: None. **S. Becker:** None. **L. Bakner:** None.

Poster

840. Human Cognition and Memory VI

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 840.01/JJJ49

Topic: H.02. Human Cognition and Behavior

Support: NIMH Grant NIMH K01MH104348

Title: Anticipatory brain activation, and current depression and mania symptoms predict subsequent recognition of emotional faces in depressed individuals with bipolar disorder, depressed individuals with major depressive disorder and healthy controls

Authors: *A. MANELIS, T. LIU, H. A. SWARTZ, M. L. PHILLIPS;
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Abstract: Due to the higher prevalence of depressive over hypomanic symptoms, reliably differentiating unipolar from bipolar depression remains challenging in clinical practice. Therefore, understanding the range of functional psychopathology in these disorders is especially important. Neuroimaging studies using dimentional approach to examine *depressed individuals with bipolar disorder* (BDD) and *depressed individuals with major depressive disorder* (MDD)

may help to understand neural mechanisms underpinning impairments in emotion and cognitive processing, and to identify neurobiological diagnostic markers of these disorders. According to previous studies, depressive episodes are characterized by altered anticipation of positive and negative events. In this study, we have examined how current and life-time depression and mania symptoms together with anticipatory activation during preparation to processes emotional faces affect subsequent recognition of emotional faces in BDD, MDD and healthy controls (HC). Thirty-five individuals (BDD=9, MDD=15, HC=11) were presented with fear, happy, and neutral faces and had to identify the gender of the person on the picture. Each face presentation was preceded with an anticipatory cue that indicated the emotional valence of the upcoming stimulus with a symbol. A surprise memory test was conducted outside the scanner to test subjects' memory for faces. We found that lower anticipatory activation preceding presentation of happy faces in the right middle frontal gyrus, right intraparietal gyrus (RIPS) and left middle temporal gyrus was related to better subsequent recognition of happy faces. A follow-up step-wise regression analyses with anticipatory brain activation, and current and life-time depression and mania symptoms showed that anticipatory activation in the RIPS, and current depression and mania severity explained 34% of variance in recognition of happy faces. The same analysis conducted across patients (n=24) confirmed that greater anticipatory RIPS activation and greater current mania severity reduced recognition of happy faces. The IPS is involved in preparatory control. Excessive preparatory control before processing of happy faces and increased manic symptoms (e.g., irritability, impulsivity) could inhibit formation of memory representation for happy faces. These findings suggest that previously reported memory impairments in BDD and MDD may be related to aberrant anticipatory brain functioning and current manic symptoms and highlight the importance of studying anticipatory processes to better understand emotion and cognitive impairments in mood disorders.

Disclosures: **A. Manelis:** None. **T. Liu:** None. **H.A. Swartz:** None. **M.L. Phillips:** None.

Poster

840. Human Cognition and Memory VI

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 840.02/JJJ50

Topic: H.02. Human Cognition and Behavior

Support: NMRC/STaR/0015/2013

Title: Degraded perceptual representation contributes to memory encoding deficits following total sleep deprivation

Authors: *J.-H. POH[1,2], M. W. L. CHEE[1];
[1]Ctr. for Cognitive Neurosci., Duke-NUS Grad. Med. Sch., Singapore, Singapore; [2]NUS Grad. Sch. for Integrative Sci. and Engin., Natl. Univ. of Singapore, Singapore, Singapore

Abstract: Sleep is essential for optimal encoding, consolidation and retrieval of memory. While impairments of encoding following sleep deprivation (TSD) have largely been attributed to depressed hippocampal function, defective perceptual processing is a relatively unexplored source of encoding failure. This led us to predict that items encoded in TSD, would show reduced quality of information even when successfully remembered. Specifically, we hypothesized that: i) impaired memory following TSD would be associated with reduced stability in neural activation patterns and ii) even for remembered items, distinctiveness of activation patterns would be lower in TSD.

Participants performed an incidental encoding of scene images while undergoing fMRI, after a night of normal sleep (RW) or TSD. An hour following the scan, they performed a recognition task, identifying scene images which were previously presented. Neural representation of each stimulus was computed from voxels within functionally defined PPA, RSC and TOS. 'Stability' of representation was determined by pairwise correlation of activation patterns across repetition (within-item PS). 'Distinctiveness' was defined as the difference of within-item PS and between-item PS, indicating the relative similarity in activation between repetition of an exemplar, and similarity across exemplars of the same category (Fig 1A).

Recognition was significantly poorer following sleep deprivation. The TSD group also showed lower stability of neural activation patterns across repetition (Fig 1B). RW but not TSD participants showed greater stability in neural activation patterns for Remembered items. This suggests that stability of PPA activation contributes to subsequent memory performance. Remembered items elicited more distinct activation patterns in the RW group than in the TSD group (Fig 1C) suggesting that in TSD, encoded items carry less distinct information relative to other items of the same category.

Collectively, these findings provide a finer grained account for understanding why memory encoding is impaired following TSD.

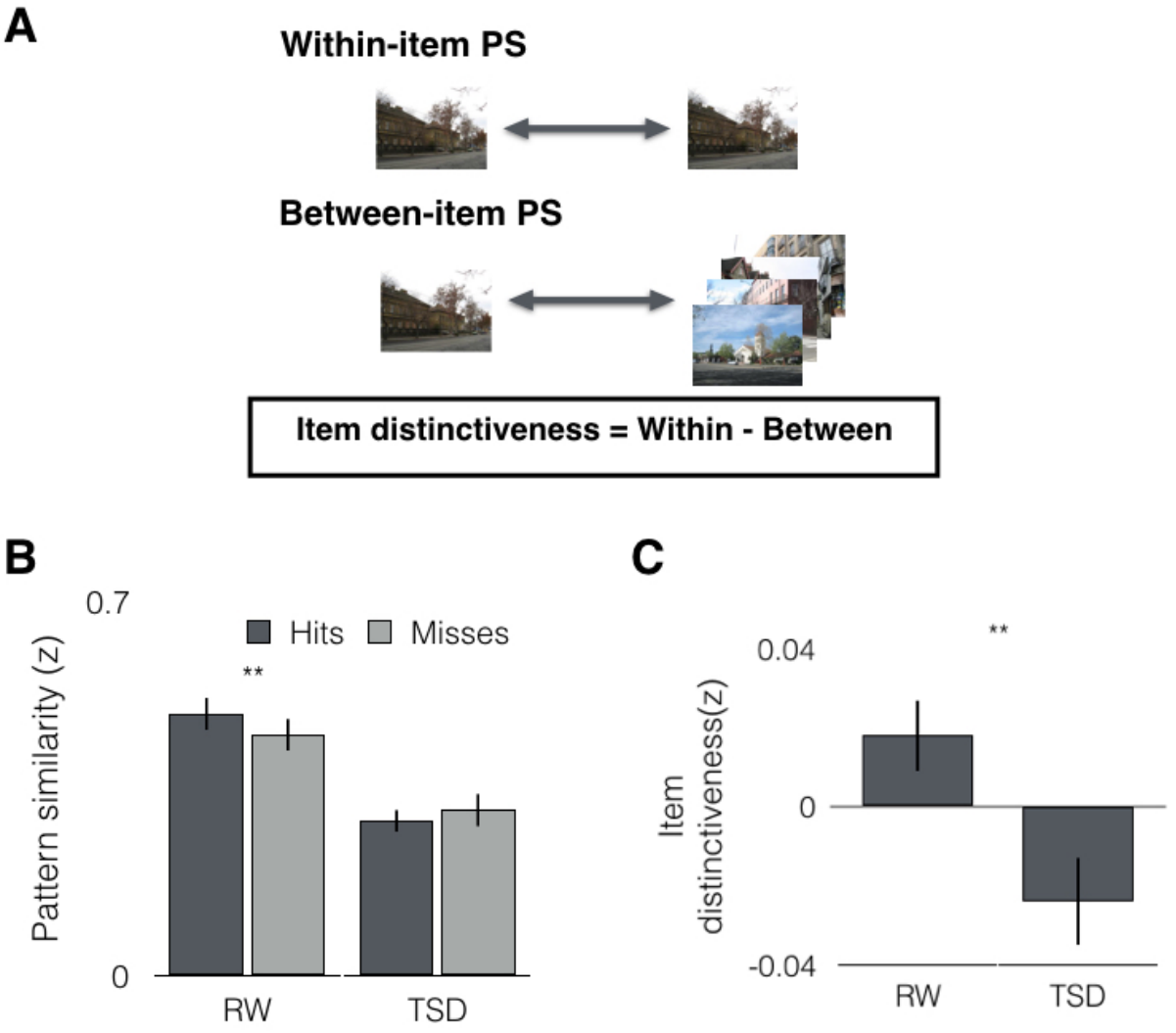

Figure 1. A) Item distinctiveness was defined as the difference between the within-item pattern similarity and across-item similarity (including only items within the same category). B) Pattern similarity for subsequently remembered items was greater in the PPA for the RW group but not in the TSD group. C) Item distinctiveness was greater in RW than TSD for Remembered items. Error bars indicate +/- 1 SEM. ** $p < .01$.

Disclosures: **J. Poh:** None. **M.W.L. Chee:** None.

Poster

840. Human Cognition and Memory VI

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 840.03/JJJ51

Topic: H.02. Human Cognition and Behavior

Support: Wellcome Trust (101759/Z/13/Z)

Wellcome Trust (091593/Z/10/Z)

Title: vmPFC and autobiographical memory consolidation: Two windows to the past

Authors: ***D. N. BARRY**[1], M. J. CHADWICK[2], E. A. MAGUIRE[1];
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Abstract: Remote autobiographical memories are more strongly represented than recent memories in the ventromedial prefrontal cortex (vmPFC), implicating this region in memory consolidation at the systems level. However, the precise time-scale of vmPFC involvement in the consolidation process has not been identified. Here, we combined high-resolution functional MRI and Representational Similarity Analysis to characterise the evolution of vmPFC recruitment during the recall of individual autobiographical memories over the course of time. During experiment 1, participants recalled memories which varied in age from less than one month up to two years, alongside remote memories from five years previously. The similarity of neural patterns during repeated retrieval of the same memory compared to different memories was used as an indicator of the strength of the representation of individual memories. Our analysis revealed two separate time-windows during the observed consolidation period within which autobiographical memories were detectable in the vmPFC, the first from four months to 16 months, and the second from two years to five years. The most recent one-month old memories and those from the intervening period between the two time-windows were not strongly represented in vmPFC. In order to confirm this sensitivity of vmPFC activity to memories of a particular age, we conducted a follow-up experiment eight months later. Participants from experiment 1 returned and were scanned while recalling the same memories again, which allowed us to track the consolidation of individual memories over time. Autobiographical memories entering for the first time either of the time-windows identified in experiment 1 were now detectable in the vmPFC. Conversely, previously well-represented memories which now fell between these two time-periods were no longer detectable. These findings are supportive of a role for the vmPFC in systems-level consolidation of

autobiographical memory beginning as early as four months following an event. Moreover, they suggest that increases in neocortical recruitment over the course of consolidation may occur in a nonlinear manner.

Disclosures: **D.N. Barry:** None. **M.J. Chadwick:** None. **E.A. Maguire:** None.

Poster

840. Human Cognition and Memory VI

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 840.04/JJJ52

Topic: H.02. Human Cognition and Behavior

Support: NIH R01AG049424

NIH R21AG041071

Title: Internal attention training improves working memory and distractor suppression in young adults.

Authors: ***S. N. SKINNER**[1], A. J. SIMON[1], D. A. ZIEGLER[1], A. GAZZALEY[2];
[1]Neurol. & Ctr. for Integrative Neurosci., [2]Neurology, Physiology, & Psychiatry, Univ. of California, San Francisco, San Francisco, CA

Abstract: Attention training studies have typically focused on training attention to external stimuli. Fewer studies have investigated if training attention to an internal stimulus (e.g., breath) has similar beneficial effects on internally-oriented attention. We designed a mobile meditation-inspired training app (MT) that draws from focused-attention meditation practices, such as directing attention to breath sensations and awareness of distracting thoughts. We hypothesized that MT would improve participants' attention, supporting the ability to maintain information in working memory (WM) while regulating internal distractions and avoiding external distractions. To test this question, healthy young adults performed an attention-demanding task requiring high and low load visual WM and distractor filtering (Filter Task) before and after 6-weeks of training with MT (n = 18, 8F) or an active placebo control program (n = 18, 11F). Both training programs were completed on a mobile platform (iPad), 5 days per week, with an average training time of 25 minutes per day. Training sessions were divided into trials of variable duration contingent upon whether the participant reported that their attention remained on their breath (longer subsequent trial), or if distracting thoughts diverted their attention (shorter subsequent trial). The active placebo training consisted of 30 minutes total training with three commercial apps (Logic Games, guided Tai Chi, and language learning). We selected these apps based on a

previous study that surveyed participants on commercial apps and MT to identify placebo apps that matched MT in expectation for improvement on the study's outcome measures.
To test for training effects, we performed an ANCOVA on Filter Task accuracy at post-testing with pre-testing included as a covariate. We found that participants who completed training with MT showed significantly improved accuracy compared with placebo on both Filter Task conditions with low WM load (Set 1, distractors present, $p = 0.04$; Set 1, no distractors present, $p = 0.03$). MT participants also showed trend level improvements in accuracy compared with placebo during conditions with high-load WM (Set 3) with no distractors present ($p = 0.10$). These results show that 6-weeks of MT improves visual WM and distractor suppression under low WM load. Future directions include examining longitudinal EEG and fMRI data to investigate the neural underpinnings of improvements in WM and distractor suppression.

Disclosures: S.N. Skinner: None. **A.J. Simon:** None. **D.A. Ziegler:** None. **A. Gazzaley:** None.

Poster

840. Human Cognition and Memory VI

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 840.05/JJJ53

Topic: H.02. Human Cognition and Behavior

Support: R01 EY021755

R01 MH069456

Title: Differentiation of incorrectly predicted memories after restudy

Authors: *G. KIM[1], K. A. NORMAN[1,2], N. B. TURK-BROWNE[1,2];
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Abstract: We can often predict what will happen next in the world, but these predictions are sometimes incorrect. What happens to the memory of an item when it is mispredicted? In a previous study (Kim et al., 2014, PNAS), we found that the incorrect prediction of an item in a familiar context weakens subsequent memory of that item. Through this process, the brain can prune memories that correspond to irrelevant or unstable aspects of the environment. However, an item that turns out to be irrelevant in one situation might be relevant or stable in another situation. What happens to previously weakened memories if we later reencounter them? Based on our previous neural network modeling work, we hypothesized that the brain differentiates the neural representation of the previously mispredicted item from its initially associated context when it is reencountered. Specifically, the initial misprediction weakens connections between the

mispredicted item and initial context and — upon restudy — the mispredicted item becomes linked to new features that were not shared with the initial context (Hulbert & Norman, 2015, Cerebral Cortex). We tested this hypothesis in an fMRI study. Observers were exposed to a continuous sequence of scenes and faces, which was, unbeknownst to them, generated from pairs (AB). In the "violation" condition, pairs repeated three times, but upon the fourth repetition, the B item was replaced by a new stimulus X to create a prediction error. Crucially, the B item was subsequently restudied without its preceding context (A) item, which was followed by one more cycle of violation and restudy trials (AB-AB-AB-AX-B-AY-B). We hypothesized that the weakened representation of B from violation trials would be incrementally differentiated from A after subsequent restudy opportunities. We tracked this representational change in hippocampal subregions by measuring the pattern similarity of A and B items before and after exposure. Consistent with our hypothesis, in left CA2/3/DG, we found greater neural differentiation between A and B items compared to a control condition in which violations were omitted (AB-AB-AB-B-B) and differentiation was thus not expected. To more directly test the idea that incorrect prediction led to differentiation, we measured the degree to which the (missing) B item activated on violation trials, and then correlated this prediction strength with A-B differentiation (across items, within subjects). Supporting our hypothesis, stronger prediction led to greater neural differentiation between A and B items. These findings indicate how the brain adaptively organizes competing memories based on relations with their temporal context.

Disclosures: **G. Kim:** None. **K.A. Norman:** None. **N.B. Turk-Browne:** None.

Poster

840. Human Cognition and Memory VI

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 840.06/JJJ54

Topic: H.02. Human Cognition and Behavior

Support: NIH Grant R01NS076665

Title: Research assistant

Authors: *Z. HU[1], S. E. MARINO[3,4], S. V. PAKHOMOV[3,5], J. CIBULA[2], M. DING[1];
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Abstract: Working memory capacity (WMC) measures both an individual's capacity for storing information as well as the capacity for sustaining attention to the stored information in the face

of interference or distraction. Higher WMC enables better performance in a variety of cognitive tasks, including working memory, attention, reading comprehension, planning, and problem solving. There is evidence suggesting that higher WMC even confers the individual with the ability to better resist cognitive impairments in brain disorders. A different line of work has examined the cognitive side effects of many commonly used central nervous system (CNS) drugs and an individual's susceptibility to such cognitive impairments. Here we hypothesized that WMC enhances an individual's ability to resist drug-induced cognitive impairments. To test this we recruited healthy volunteers to participate in a double- blind, crossover, and placebo controlled study. During the drug session, each subject received a single, 100- mg oral dose of topiramate (TPM), an antiepilepsy drug also indicated for migraine prophylaxis but known to cause cognitive impairments. Applying an innovative System for Automated Language and Speech Analysis (SALSA) coupled with standard neuropsychological measures of generative verbal fluency, working memory, and attention, we found that (1) TPM decreased cognitive performance compared with placebo and baseline, and (2) TPM-induced cognitive impairments were modulated by WMC, such that low WMC individuals were more susceptible to the detrimental effects of TPM than high WMC individuals. These results enrich the existing accounts of the importance of WMC and suggest that interventions that improve WMC can yield both cognitive and clinical benefits.

Disclosures: Z. Hu: None. **S.E. Marino:** None. **S.V. Pakhomov:** None. **J. Cibula:** None. **M. Ding:** None.

Poster

840. Human Cognition and Memory VI

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 840.07/JJJ55

Topic: H.02. Human Cognition and Behavior

Support: BBSRC Grant BB/M010732/1

Title: Pinging the brain reveals hidden states for working memory guided behaviour

Authors: *M. WOLFF[1], J. JOCHIM[2], T. BUSCHMAN[3], E. G. AKYÜREK[1], M. G. STOKES[2]; [1]Univ. of Groningen, Groningen, Netherlands; [2]Univ. of Oxford, Oxford, United Kingdom; [3]Princeton Univ., Princeton, NJ

Abstract: Recent theoretical work suggests that (visual) WM content is maintained in an activity silent neural state (Sreenivasan, Curtis, & D'Esposito, 2014) through short-term synaptic plasticity (Mongillo, Barak, & Tsodyks, 2008), and that a neutral stimulus results in a WM

dependent impulse response. This raises an important methodological challenge - how to measure hidden neural states. We have recently shown that working memory (WM) content can be revealed in EEG by 'pinging' the visual WM network: The visual evoked response from a neutral stimulus presented in the delay of a WM task could be used to decode the WM item (Wolff, Ding, Myers, and Stokes, 2015). Here, we report two experiments that explore the specificity of the impulse response to attended, unattended and forgotten WM content. In the first experiment, participants were instructed to memorize two simultaneously presented gratings. A subsequent cue indicated that one of those items could be dropped from memory. The evoked response by the following "impulse" stimulus contained information only about the relevant but not the irrelevant item. Furthermore, the decodable pattern was related to WM performance both within and across participants. These results provide clear evidence that the impulse response is specific to WM, and is important for WM-guided behaviour. In the second experiment, participants maintained two WM items, which were tested serially. One of the items was in the focus of attention in the first delay, while the other was attended to in the second delay. An impulse stimulus presented in the first delay could be used to decode both the attended and the unattended item. An impulse presented in the second delay, after the first item had been already tested and could thus be forgotten, only reflected the attended item. These results suggest that both attended and unattended items are represented in silent WM neural states as long as they are still relevant.

Mongillo, G., Barak, O., & Tsodyks, M. (2008). Synaptic Theory of Working Memory. Science, 319(5869), 1543-1546.
Sreenivasan, K. K., Curtis, C. E., & D'Esposito, M. (2014). Revisiting the role of persistent neural activity during working memory. Trends in Cognitive Sciences, 18(2), 82-89.
Wolff, M. J., Ding, J., Myers, N. E., & Stokes, M. G. (2015). Revealing hidden states in visual working memory using electroencephalography. Frontiers in systems neuroscience, 9.

Disclosures: **M. Wolff:** None. **J. Jochim:** None. **T. Buschman:** None. **E.G. Akyürek:** None. **M.G. Stokes:** None.

Poster

840. Human Cognition and Memory VI

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 840.08/JJJ56

Topic: H.02. Human Cognition and Behavior

Title: Using targeted memory reactivation to induce forgetting

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Abstract: Recent studies demonstrate memory improvement following targeted memory reactivation (TMR) using associated sounds or odors during sleep (see Oudiette & Paller, 2013 for review). TMR can also diminish fear conditioning (Hauner, Howard, Zelano, & Gottfried, 2013) and implicit social biases (Hu et al., 2015). Here we investigate whether TMR can induce forgetting in episodic memory. Eighteen participants completed two learning tasks prior to sleeping. In the first task, participants experienced a directed-forgetting task with words. Participants saw 46 words, with half followed by a 'forget' tone. For the second task, participants saw 28 novel object-location pairs. Objects were paired with their associated sounds. From these objects, we randomly chose five for reactivation and five for controls. At night, during the first period of slow wave sleep, we reactivated the five objects with the forget tone 20 times. One week later we tested participants memories of the objects and words using free-recall and recognition. Participants recalled fewer reactivated than control objects ($t(1,17)=3.682$ $p = .002$, Cohen's $d = 1.23$). Of the reactivated objects that were not recalled, participants were also less likely to remember their spatial locations ($t(1,15) = -2.132$ $p = .05$, Cohen's $d = .764$) and had lower confidence in their answers ($t(1,15) = -5.558$ $p > .001$, Cohen's $d = 1.983$).We demonstrate proof of concept that TMR can be used to reduce memory for objects one week later. Participants are less likely to recall the objects, and are also less likely to correctly locate those they successfully forgot. Future studies will determine whether TMR-forgetting can reduce stronger or more emotional memories, paving the way for novel therapeutic treatments for disorders including PTSD or phobias.

Disclosures: K.C. Newman-Smith: None. **R. Gomez:** None. **L. Nadel:** None.

Poster

840. Human Cognition and Memory VI

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 840.09/JJJ57

Topic: H.02. Human Cognition and Behavior

Support: SFB grant 874

Title: Basic visual working memory functions and their relation to perceptual and long-term memory functions in the medial temporal lobe

Authors: *S. SCHENK, R. K. LECH, B. SUCHAN;
ICN, Neuropsychology, Ruhr Univ. Bochum, Bochum, Germany

Abstract: The current study used functional magnetic imaging (fMRI) to investigate basic visual working memory functions and their relation to perceptual and long-term memory functions in the medial temporal lobe. The aim of our study was to shed light on the interplay of these three functions and their related activations in the medial temporal lobe. Therefore, a modified n-back task in combination with a perceptual discrimination task and a long term memory recognition task were combined. Two different stimuli types were used in all three experiments: landscapes and objects. The n in the n-back conditions has been varied to focus on the critical aspects of medial temporal lobe involvement. All items that have been presented twice in the n-back condition were presented after a delay of one week, to analyze long term memory related activations in the medial temporal lobe. The analysis focused on the activation pattern from visual discrimination as well as working and long-term memory related activations and their possible overlap. It has been suggested that the medial temporal lobe, which plays a prominent role in long-term memory, may also be involved in perceptual processing and working memory. The analysis of the imaging data showed an involvement of medial temporal lobe structures during all three tasks with no spatial overlap. The results of our study yield evidence that sensory integration in the medial temporal does not overlap with respect to the time point of first and second presentation and also with respect to recognition and perceptual functions.

Disclosures: **S. Schenk:** None. **R.K. Lech:** None. **B. Suchan:** None.

Poster

840. Human Cognition and Memory VI

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 840.10/JJJ58

Topic: H.02. Human Cognition and Behavior

Support: NIH Grant NS086085

NIH Grant MH105625

Title: Dynamic brain states in working memory

Authors: ***W. CAI**[1], J. TAGHIA[2], S. RYALI[1], T. CHEN[1], V. MENON[1];
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Abstract: The human brain is thought to be a flexible system that can rapidly switch between different states to meet moment-to-moment fluctuations in cognitive demands. Brain activation and regional interaction patterns have been shown to change with conscious states (1) and cognitive demands (2) to allow flexible integration and segregation of information across brain

regions. While most functional neuroimaging research assumes a stationary brain state during an experimental task or condition, emerging evidence points to dynamic brain mechanisms characterized by fluctuating patterns of functional connectivity between distributed brain regions over time (3). However, little is known about dynamic brain states during cognitive processes, such as working memory, and how such dynamic brain states might be related to task performance.

Here we use a novel Switching Autoregressive Factor Analysis (SAFA) approach to investigate brain state dynamics during an N-back working memory task from Human Connectome project. SAFA assumes that data observed at a given time is generated from hidden states which follow a first-order Markov process. Within each state, it is further assumed that data are generated from a first-order autoregressive process. The hidden states capture the underlying temporal dynamics and underlying correlation structure of the data. We use SAFA to determine time-varying brain states from the time series of 11 "task-positive" and "task-negative" regions in prefrontal, parietal and cingulate cortices.

We found that each task block (0-back or 2-back) contains multiple brain states. The dominant brain states in the high-load working memory condition (2-back) was characterized by greater and more extensive directed connectivity between task-positive regions, when compared to states in the low-load or resting conditions (p<0.05 corrected). Importantly, the state occupancy ratio of the dominant brain state in the high-load working memory blocks was significantly correlated with performance accuracy in this task condition (p<0.001). Taken together, our study provides the first evidence for dynamic brain states and a fundamental network mechanism underlying human working memory performance and individual abilities.

Reference

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Disclosures: **W. Cai:** None. **J. Taghia:** None. **S. Ryali:** None. **T. Chen:** None. **V. Menon:** None.

Poster

840. Human Cognition and Memory VI

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 840.11/JJJ59

Topic: H.02. Human Cognition and Behavior

Support: NRF 2015-R1A2A2A04006136

Title: The functional connectivity patterns during post-encoding vary over contextual factors

Authors: ***J. H. PARK**[1], Y. NAH[1], N.-Y. SHIN[2], S.-K. LEE[3], S. HAN[1];
[1]Yonsei Univ., Seoul, Korea, Republic of; [2]Ewha Womans Univ. Sch. of Med., Seoul, Korea, Republic of; [3]Yonsei University, Col. of Med., Seoul, Korea, Republic of

Abstract: Episodic memory contains various kinds of contextual factors. The role of medial temporal lobe (MTL) regions in contextual representations during encoding and post-encoding has become increasingly evident. Using high-resolution functional MRI, we explored the para/hippocampal seeded connectivity patterns during the encoding and post-encoding of five different contextual factors: spatial, temporal, social, behavioral and intentional context. Participants (n = 19) encoded each type of contextual factor while looking at the simple event with two faces and one object on the screen and then had a short post-encoding period (7.5s) in each trial. To acquire sub-regional clusters, hippocampus and parahippocampal cortex was segmented along its longitudinal axis using hierarchical clustering algorithm, and the beta-series connectivity was measured between MTL and other cortical regions during encoding and subsequent post-encoding period. The link strength was differed by each type of contextual encoding processes. In social context, the enhancement during post-encoding in links within MTL was observed, whereas the links between MTL and angular gyrus decreased. The temporal context also required increase of links within MTL, but the increase range was rather small relative to social contexts. The spatial contextual processing recruited the overall enhancement in link strength between perirhinal cortex and inferior parietal lobule. In behavioral contextual processing, the connectivity between posterior perirhinal cortex and hippocampal clusters have enhanced while ventrolateral prefrontal regiosn to hippocampal clusters showed a decreased connectivity. Lastly, the intentional context recruited the stronger connections between posterior hippocampus and dorsolateral prefrontal, while perirhinal cortex to parietal link was weakened during post-encoding period. In addition, the connectivity-based multivariate pattern analysis was conducted which allowed us to demonstrate distinguishable networks involved across contextual memory conditions.

Disclosures: **J.H. Park:** None. **Y. Nah:** None. **N. Shin:** None. **S. Lee:** None. **S. Han:** None.

Poster

840. Human Cognition and Memory VI

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 840.12/JJJ60

Topic: H.02. Human Cognition and Behavior

Support: BBSRC MIBTP studentship

Title: Deconstructing episodic memories to track their reconstruction in EEG time courses

Authors: *J. LINDE DOMINGO, M. WIMBER;
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Abstract: Episodic memory refers to our ability to store and to recall our personal experiences. These memories build our personal history, binding together specific details about our past: where, how and what happened in our life. Despite the importance of episodic memory, how the brain manages to bring back our memories is still unknown. Current studies in neuroscience focus on detecting the similarities between the brain pattern elicited during the encoding of an event and its subsequent retrieval, understanding episodic memory as a static "snapshot" of past episodes. Despite valuable results made following this point of view, this approach does not capture the reconstructive nature of our memories and the temporal dynamics of those elements that constitute them. We here present electrophysiological work, in combination with multivariate pattern analysis techniques, to provide a novel perspective onto the temporal dynamics of memory reconstruction processes, decomposing memory's architecture into relevant sub-components and tracking their re-emergence across the time course of retrieval. The paradigm involves electroencephalography (EEG) recording during the learning (encoding) of novel object-context associations, and the subsequent mental reconstruction of these object-context events. The critical aspect of this paradigm is that the episodes were configured on the basis of three predefined dimensions. The learned events shared a perceptual feature (pictures or drawings of objects), a conceptual relationship (the semantic category to which the objects belongs, e.g. fruits), or a contextual aspect (we used two main categories of context, displaying outdoor and indoor pictures). Using representational similarity analysis and machine learning algorithms, this configuration allowed us to detect at which specific moments across the EEG time course an episode's sub-components are reactivated during retrieval, creating a temporal mapping of perceptual, semantic and contextual features during memory reconstruction. Together, our EEG results suggest that perceptual, semantic and contextual information are recovered at distinct time points after the presentation of a reminder.

Disclosures: J. Linde Domingo: None. **M. Wimber:** None.

Poster

840. Human Cognition and Memory VI

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 840.13/JJJ61

Topic: H.02. Human Cognition and Behavior

Title: Bidirectional modulation of episodic memory for words by repeated focal stimulation of Broca's area using a new wearable magnetic brain stimulator

Authors: *S. A. HELEKAR[1], R. J. ALCAZAR-FELIX[2], B. S. JOHN[1], H. U. VOSS[3]; [1]Dept. of Neurol., Houston Methodist Res. Inst., Houston, TX; [2]Escuela de Medicina del Tecnológico de Monterrey, Monterrey, Mexico; [3]Dept. of Radiology, Weill Cornell Med., New York, NY

Abstract: Functional neuroimaging studies have suggested that left inferior prefrontal cortex plays a critical role in episodic memory formation. Evidence from transcranial magnetic stimulation of this brain region has led to the proposal that it is causally linked to the encoding of words. In the present study we tested the hypothesis that Broca's area is responsible for this verbal memory-related function. We used a new wearable focal brain stimulator called transcranial rotating permanent magnet stimulator (TRPMS) to achieve targeted localized stimulation of the pars triangularis part of Broca's area in 7 right-handed and 1 left-handed subjects (19 - 24 year-old, 5 males, 3 females). The TRPMS device developed in our laboratory consists of a cap with wirelessly controlled, Android app-driven, magnetic microstimulators attached to desired target locations. We conducted synchronous stimulation at F7 and F5 international 10-20 system electroencephalographic electrode sites. A total of 200 stimuli of 100 ms duration were delivered at 5 s inter-stimulus intervals each day on 5 week days over 2 weeks, with sham stimulation and active stimulation being carried out during the first and second weeks, respectively. On the first and the fifth day of each week we administered a word memory test on an Android tablet. The test involved sequential presentation of different sets of 200 nouns from the MRC Psycholinguistic Database (Version 2) one by one every 5 s during 3 phases, namely before, during and after stimulation, followed 4 hours later by a set of 200 nouns consisting of 101 new nouns and 33 previously presented nouns from each phase. Subjects had to indicate whether they have seen each noun in prior presentations or not. The data obtained from this study show that: 1) the mean number of errors committed in recalling words presented during stimulation on the first day of each week was significantly lower with active stimulation compared to sham stimulation (Student's two-tailed paired t test, $p < 0.05$); and 2) the mean numbers of errors corresponding to before and after stimulation on the fifth day were significantly higher with active stimulation than with sham stimulation, with no significant difference in errors during stimulation. These findings indicate that TRPMS stimulation of Broca's area during encoding of words facilitates word memory. In contrast, chronic repeated stimulation of this area at rest in the absence of word memorization disrupts it. We conclude that, first, Broca's area appears to be causally involved in the verbal memory encoding process, and second, our new wearable TRPMS stimulator is effective in modulating this higher cortical function.

Disclosures: **S.A. Helekar:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Houston Methodist Hospital. **R.J. Alcazar-Felix:** None. **B.S. John:** None. **H.U. Voss:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Weill Cornell Medicine.

Poster

840. Human Cognition and Memory VI

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 840.14/KKK1

Topic: H.02. Human Cognition and Behavior

Title: Oscillatory EEG networks predict visual short-term memory retention on individual trials

Authors: *A. WODEYAR, R. SRINIVASAN;
Cognitive Sci., Univ. of California, Irvine, Irvine, CA

Abstract: We carried out an experiment to understand the effects of attention and coherent oscillations, measured using electroencephalograpy (EEG), on short term memory. Our objective was to determine if the variation in performance across trials on a delayed match-to-sample task could be accounted for by trial-to-trial variability in attention during encoding, or by trial-to-trial variability in alpha (8-13 Hz) and theta (4-7 Hz) oscillations that have been implicated in working memory function.
Participants had to remember the orientations of two high contrast Gabors, presented one in each visual field, and embedded in noise. After a one second exposure to encode the Gabor orientation, there was a random delay interval between .5 to 3 seconds. During the response interval a test Gabor was presented in either the left or right visual field location. Participants had to discriminate if the test Gabor was rotated clockwise or counter-clockwise. Accuracy at this task ranged from 65-80%, independent of the length of the delay interval.
During the encoding interval, each of the Gabors was flickered at 24 and 40 Hz, while the background noise changed at 30 Hz, in order to generate stimulus-specific steady state visually evoked potentials (SSVEP). We quantified SSVEP signal strength by the phase locking index which was significant ($p<.05$) in some subset of channels over occipital and parietal cortex for all subjects. We obtained single-trial measures of the SSVEP as an index of attention. We built a logistic regression model to predict performance on individual trials (correct/incorrect) from the SSVEP. We found that we were only able to achieve 55-60% accuracy suggesting at most a weak effect of attention on working memory, at least for the supra-threshold Gabor stimuli used in this experiment.
In previous studies, theta and alpha oscillations have been linked to memory load and successful memory maintenance. EEG coherence during the last 500 ms of the encoding period and the first 500 ms of the delay interval revealed networks observed through high coherence in the alpha and theta band with hubs at frontal, parietal and occipital electrodes. We estimated the strength of this global oscillatory network on individual trials, and used a Partial-Least Square Discriminant Analysis to predict retention in memory. We found that this model was capable of predicting memory retention with up to 70 % accuracy. This is the first study as far as we know to show that on any individual EEG trial, there's sufficient signal to measure the oscillatory network that

helps sustain the central-executive function involved in the maintenance of a visual image in short term memory.

Disclosures: **A. Wodeyar:** None. **R. Srinivasan:** None.

Poster

840. Human Cognition and Memory VI

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 840.15/KKK2

Topic: H.02. Human Cognition and Behavior

Support: DOD W81XWH-12-1-0081

NIMH R34 MH089299

Title: The neural underpinnings of visuospatial working memory in neurofibromatosis type 1

Authors: ***A. IBRAHIM**[1], C. MONTOJO[2], K. H. KARLSGODT[3], K. HAUT[4], C. E. BEARDEN[3];
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Abstract: Neurofibromatosis Type 1 (NF1) is a monogenic disorder occurring in approximately 1 in every 3000 births. The NF1 cognitive profile is characterized by marked impairments in frontally-mediated cognitive functions, particularly working memory. Currently, little is known about the neural underpinnings of these deficits. In the current study, we utilized functional MRI to assess differences in neural activity and functional connectivity between NF1 patients and healthy controls during performance on a spatial capacity working memory task (SCAP).
23 NF1 patients (61% female, mean age 32.69) and 25 (64% female, mean age 33.08) demographically matched healthy controls underwent BOLD fMRI scans while completing the SCAP task. SCAP is a visuo-spatial working memory task (adapted from Glahn et al, 2002) in which participants are presented with a target array including one, three, five, or seven circles in various locations, followed by a probe after a variable delay. The participant must decide whether the probe is presented in the same location as a previously presented target item. BOLD fMRI data was analyzed using a voxel-wise general linear model in FSL. We conducted whole brain analysis as well as psycho-physiological interaction (PPI) analyses to examine functional connectivity during task performance. Specifically, we used the posterior cingulate (PCC), right parietal (rpar), and left parietal (lpar) as seeds in the PPI analysis.
Across all memory loads combined, whole brain analyses revealed greater activation in healthy

controls relative to NF1 patients in the right intraparietal sulcus and left middle frontal gyrus, whereas no regions of increased activation were observed in NF1 patients relative to controls. In addition, NF1 patients evidenced significant differences in task-related connectivity between regions. PPI analyses reveled that healthy controls exhibited greater task-related connectivity than NF1 patients between the PCC seed and left superior temporal gyrus, as well as left fusiform gyrus. In contrast, NF1 patients showed greater connectivity than controls between the lpar seed and the left secondary visual cortex, left premotor cortex, and left associative area; between the rpar seed and the primary visual cortex and left associative visual cortex; and between the PCC seed and the cerebellum, right inferior temporal gyrus, right precentral gyrus, and the left premotor cortex. Our findings demonstrate hypoactivation of working memory circuitry in NF1 patients, as well as altered patterns of connectivity, relative to healthy controls during visuo-spatial working memory performance.

Disclosures: **A. Ibrahim:** None. **C. Montojo:** None. **K.H. Karlsgodt:** None. **K. Haut:** None. **C.E. Bearden:** None.

Poster

840. Human Cognition and Memory VI

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 840.16/KKK3

Topic: H.02. Human Cognition and Behavior

Support: NIH R01MH074368

Title: Neural mechanisms of HIV-associated working memory.

Authors: ***S. N. SIEGEL**, Y. ZHU, H. HUANG, R. COHEN, M. DING;
Univ. of Florida, Gainesville, FL

Abstract: Brain dysfunction continues to be highly prevalent among HIV-infected people, with working memory among the cognitive functions most commonly affected. We employed functional magnetic resonance neuroimaging imaging (FMRI) to investigate the neural bases of HIV-associated working memory deficits during performance of a verbal n-back paradigm (n = 0, 2). Participants were 24 HIV seropositive and 27 seronegative adults (mean age: 46 + 45 years respectively). All of the HIV seropositive participants were treated combined ant-retroviral therapy (cART) and had suppressed HIV-RNA viral load and CD4 > 100. A battery of neuropsychological tests was also administered. Activation in the task-positive frontoparietal areas, including anterior cingulate cortex, dorsolateral prefrontal cortex, and inferior parietal lobule, was greater among the HIV seropositive participants on the 0-back condition relative to

resting their state. In contrast, activation of these same brain regions was reduced during the 2-back condition. These differential response responses on FMRI corresponded with reduced accuracy of working memory and longer response times on both the 0- and 2-back tasks, and suggests that compensatory frontoparietal activation occurring among HIV seropositive participants in the performance of relatively simple attention (0-back) is no longer effective in the face of 2-back working memory demands, leading to reduced activation of this network as well as reduced performance and significant slowing. HIV-associated working memory deficits were associated with lower performance on neuropsychological tests including the Stroop test. Differences in frontoparietal activation during the 0-back and 2-back tasks predicted Stroop performance for the HIV seropositive individuals, but not for the seronegative controls, suggesting shared neural substrate in executive dysfunction.

Disclosures: **S.N. Siegel:** None. **Y. Zhu:** None. **H. Huang:** None. **R. Cohen:** None. **M. Ding:** None.

Poster

840. Human Cognition and Memory VI

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 840.17/KKK4

Topic: H.02. Human Cognition and Behavior

Support: KAKEN 16H01494

KAKEN 26119532

Title: Change in effects of odor contexts over time that modify memory in relation to order of remote and recent past episodes

Authors: ***M. ABE**[1], Y. UGAWA[2];
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Abstract: Humans often have an incorrect impression from memory that they might have experienced past events a moment or a long ago that had occurred years or minutes ago in real world, when they are currently under the situations the same as or different from ones in which these events had really occurred. Thus contexts which consist of background of situations can modify order of past events in memory representations in respect to which events preceded or followed. Memories are dynamically altered over hours or days. Whether contextual effects on memory in respect to order of past events would change over time is unknown. Here, we

demonstrated different effects of context on order of past events in memory immediately and hours after end of events. Young, adult, healthy volunteers participated in this study. Different lists of English words were visually presented in two sessions separated by a 10-min interval. While subjects judged whether presented words belonged to living or nonliving things, different odors were administrated in each session. After one or 6 hours delay, subjects were asked to choose which words were presented in the second session (i.e. recent past) or in the first session (i.e. remote past), under conditions in which odors the same as ones exposed in the first or second session, or different new ones (i.e. control) were administrated. Performance errors were measured in three odor contexts. At one hour, subjects made more incorrect responses that they might have seen words in the second session (i.e. recent past) that were physically presented in the first session (i.e. remote past) when the same odor conditions as ones exposed in the first session were applied, compared with other two contexts. At 6 hours, subjects made more incorrect responses to recall that they might have seen words in the first session (i.e. remote past) that were physically presented in the second session (i.e. recent past) when the same odor conditions as ones exposed in the second session were applied, compared with two other contexts. These results revealed different effects of odor contexts on memory in respect to order of past events at 1 hr and 6 hr time points. We conclude that effects of odor contexts on memory in respect to order of past events dynamically change, probably through progressive processes of memory formation.

Disclosures: **M. Abe:** None. **Y. Ugawa:** None.

Poster

840. Human Cognition and Memory VI

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 840.18/KKK5

Topic: H.02. Human Cognition and Behavior

Support: Network on Culture, Brain, and Learning: The Wallenberg Network Initiative

Title: A causal role for theta-phase alignment during episodic memory encoding

Authors: ***A. GONZALEZ**, V. Y. VILDAVSKI, A. M. NORCIA, A. D. WAGNER; Stanford Univ., Stanford, CA

Abstract: Animal models of hippocampal oscillatory dynamics suggest that theta oscillations are critical for successful memory encoding. In particular, extant data suggest that distinct phases of theta oscillations are markers of the hippocampal circuit being in a state optimal for encoding or, alternatively, retrieval. Hippocampal theta oscillations are also thought to be phase-locked with

the dorsomedial prefrontal cortex during successful encoding. Here, in healthy human participants, we tested the causal role of theta-phase alignment during episodic memory encoding using transcranial alternating current stimulation (tACS). tACS allows the creation of an experimentally controllable, exogenously generated theta rhythm. Using a closed-loop protocol, individual stimuli (faces/scenes) were presented at specific phases of a transcranially imposed 6Hz-theta oscillation. Stimulation was applied over the Fz site (10-20 system) at 1.2 mAmps, with four surrounding return electrodes (0.3 mAmps each) to achieve focal stimulation. We hypothesized that, through attractor dynamics, Fz stimulation would phase-lock the hippocampal circuit, enabling a test of the relationship between stimulus/theta-phase alignment at encoding and later memory performance. To test subsequent memory, subjects made recognition memory decisions (without stimulation). During analysis, encoding trials were sorted based on subsequent memory (hits / misses) and encoding stimulation theta phase. For each subject, we computed the mean vector across trials, separately for hits and for misses, and then examined the theta phase difference between these subsequently remembered and subsequently forgotten vectors. Results indicated that in all subjects there was an ~180 degree difference between the theta-phases associated with subsequent remembering vs. forgetting. Moreover, the deviation from a 180-degree phase difference was smaller for individuals who showed greater mean vector lengths. These results provide evidence for a causal role for stimulus/theta-phase alignment in effective episodic encoding, and further suggest that stimuli that are experienced completely in phase with an individual's preferred encoding phase are more likely to be later remembered.

Disclosures: A. Gonzalez: None. **V.Y. Vildavski:** None. **A.M. Norcia:** None. **A.D. Wagner:** None.

Poster

840. Human Cognition and Memory VI

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 840.19/KKK6

Topic: H.02. Human Cognition and Behavior

Title: Weakening memories through closed-loop modulation of perceptual distraction

Authors: *A. C. MENNEN[1], J. POPPENK[2], M. T. DEBETTENCOURT[1], K. A. NORMAN[1]; [1]Princeton Neurosci. Inst., Princeton Univ., Princeton, NJ; [2]Queen's Univ., Kingston, ON, Canada

Abstract: Prior work from our laboratory indicates that moderate activation of a memory can lead to weakening of that memory (Newman & Norman, 2010; Detre et al., 2013; Kim et al.,

2014; Lewis-Peacock & Norman, 2014). This suggests that, in principle, it should be possible to design therapies that weaken maladaptive memories by deliberately eliciting moderate activation of those memories. However, in practice, eliciting moderate levels of memory activation can be extremely difficult to accomplish in a reliable fashion, due to variance in memory strength and the efficacy of retrieval cues.

To address this problem, we developed a closed-loop neurofeedback procedure that allows us to measure the strength of memory activation, and -- based on this measurement -- adaptively titrate perceptual distraction in real time to manipulate retrieval strength. This study builds on prior work from our lab (Poppenk & Norman, 2014, SfN) that used a dot tracking task as a distractor to disrupt memory retrieval. We found that the difficulty of dot tracking influenced memory retrieval strength such that more distraction resulted in lower evidence of memory retrieval. Additionally, memories that were retrieved during dot tracking were on average weaker than baseline as assessed by recall tests before and after dot tracking.

In the present study, we extend our prior work by "closing the loop" and using our neural measure of memory activation to directly control the difficulty of the distractor task. If memory activation is too high, we increase dot task difficulty in order to reduce memory activation; if memory activation is too low, we reduce dot task difficulty. The overall goal is to use these adjustments to actively drive memory activation into the moderate range that (we predict) will cause memory weakening.

We will present preliminary results from a pilot study where subjects learn word-scene associations. Then subjects imagine the scenes associated with centrally-presented words while tracking multiple dots moving in the periphery. To track memory retrieval, we will employ an fMRI pattern classifier trained to detect scene recall. We will compare the closed-loop manipulation described above with a yoked control where a given participant's dot-task difficulty is governed by a yoked participant's classifier output. We hypothesize that the closed-loop procedure will more reliably yield moderate memory activation and thus will result in more memory weakening than the control. Successful demonstration of memory weakening here could motivate new neurofeedback therapies that induce moderate activation to weaken maladaptive memories.

Disclosures: A.C. Mennen: None. **J. Poppenk:** None. **M.T. deBettencourt:** None. **K.A. Norman:** None.

Poster

840. Human Cognition and Memory VI

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 840.20/KKK7

Topic: H.02. Human Cognition and Behavior

Support: DFG HA 5622/1-1

Title: The temporal dynamics of human memory replay

Authors: ***S. MICHELMANN**[1], B. GRIFFITHS[1], B. STARESINA[1], M. WIMBER[1], R. CHELVARAJAH[2], D. ROLLINGS[2], V. SAWLANI[2], H. HAMER[3], S. GOLLWITZER[3], G. KREISELMEYER[3], H. BOWMAN[1,4], S. HANSLMAYR[1];
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Abstract: When we remember dynamic events from our past (e.g. driving to the beach last summer), we can vividly replay specific events in front of our mental eye in a temporally structured way. It remains however largely unexplored how the brain orchestrates the replay of dynamic memories, and in particular what the mental chronometry of such dynamic replay is. Recent evidence suggests that oscillatory activity in the alpha rhythm plays an important role in the temporal organisation of neural representations and that decreases in power relate to this phenomenon. We therefore set out to clarify the neural temporal dynamics of memory replay and their relation to the alpha frequency. In one study we used Magnetencephalography (MEG) and participants were asked to associate a word to one of three scenes within a video clip. Later during memory retrieval subjects were asked to tell in which scene they saw the word. Importantly, to answer this question subjects had to mentally replay the video in order to know the temporal position of the word. In a parallel version of this experiment we recorded electrophysiological activity from patients suffering from intractable epilepsy. These patients were undergoing intracranial recordings for diagnostic purposes. Patients were instructed to associate a word with one of two scenes within a video. At retrieval they were also asked in which scene they remembered the word. To help memory performance the same associations were repeated three times. Crucially in both experiments we presented (and subjects remembered) the same videos several times but associated with different words. This enabled us to use representational similarity analysis (RSA) in order to track the replay of individual scenes. In both experiments we found sustained power decreases in the alpha frequency range to be associated with successful memory. Studying the time course of replay for different scenes provided new indications on how dynamic memories are replayed, how their neural representations unfold over time.

Disclosures: **S. Michelmann:** None. **B. Griffiths:** None. **B. Staresina:** None. **M. Wimber:** None. **R. Chelvarajah:** None. **D. Rollings:** None. **V. Sawlani:** None. **H. Hamer:** None. **S. Gollwitzer:** None. **G. Kreiselmeyer:** None. **H. Bowman:** None. **S. Hanslmayr:** None.

Poster

840. Human Cognition and Memory VI

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 840.21/KKK8

Topic: H.02. Human Cognition and Behavior

Title: The role of posterior parietal activity in episodic retrieval

Authors: *M. FIATI, P. BRIGHT;
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Abstract: Increasingly findings from the memory literature have implicated the posterior parietal cortex (PPC) in the memory operations which occur at the time of episodic retrieval. Involvement of the PPC has been found to support fine multi-sensory recollection of features within episodic memories, and has also been suggested to reflect binding of such contextual information within an episode. In the current study, participants performed a multisensory episodic retrieval task in which they first identified previously studied (Old) faces, and subsequently made context-based source judgements denoting the spatial location (left/right), voice (male/female), and study task (pleasantness rating/celebrity judgement) that they had associated with each face at study. The ERPs for presentations of Old faces were separated according to the accuracy of source judgements for the different contexts, and were compared to ERPs of new faces. Source recollection was associated with a late positivity (450ms-800ms) maximal over centro-parietal sites. The prediction that the magnitude of the parietal positivity reflected successful binding at retrieval was tested by comparing ERPs according to the number of accurate source memory judgments for each face. Findings suggested that the differences between parietal ERPs co-varied with number of source retrievals, supporting predictions, and furthermore they did not vary with the sensory modality of retrieved contexts. In order to evaluate the causal relationship of this activity with episodic retrieval transcranial direct current stimulation (tDCS), was employed. Participants underwent tDCS at the site of maximal peak activity in the left PPC (P3) before performing the source retrieval task. The performance following excitatory anodal tDCS for 15 participants, and inhibitory cathodal tDCS for 15 participants, was compared to sham tDCS. Excitatory stimulation was not found to lead to greater retrieval of multimodal contexts than sham stimulation overall. Inhibitory stimulation however was found to decrease the number of episodic contexts retrieved compared to sham stimulation. The findings indicate that the binding of different sensory features of an episode at retrieval is decreased by reductions in activation of the PPC, and recruitment of this region therefore may mediate the richness of episodic retrieval.

Disclosures: M. Fiati: None. **P. Bright:** None.

Poster

840. Human Cognition and Memory VI

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 840.22/KKK9

Topic: H.02. Human Cognition and Behavior

Support: NIH R01 EY021755

Title: Narrative coherence and temporal structure in the posterior medial network

Authors: *M. ALY, J. CHEN, N. B. TURK-BROWNE, U. HASSON;
Princeton Univ., Princeton, NJ

Abstract: Brain activity can reflect information at multiple timescales, including events that occurred seconds or minutes ago. Regions in the posterior medial network integrate information over particularly long timescales. The studies that provided evidence for this used naturalistic stimuli such as movies, and interpreted long-timescale integration as reflecting the relevance of past events for ongoing narratives. However, movies are special not only because of narrative coherence, but also because they contain predictable temporal structure. Although narrative coherence and temporal structure are often confounded, they can be distinguished: an arbitrary but repeated sequence can afford learning of regularities even if it is narratively incoherent. Here we investigated the role of such temporal structure in integration and prediction. Participants watched three 90-s clips from "The Grand Budapest Hotel" during fMRI. Each clip was viewed 6 times. One clip was a continuous segment (Intact). Another was divided into segments lasting 2-5s; segment order was scrambled for the first presentation but this order was used again for subsequent repetitions (Scramble-Fixed). The final clip was also divided into segments, but their order was scrambled independently for all repetitions (Scramble-Random). Thus, Intact and Scramble-Fixed clips contained predictable temporal structure over repetitions, but only the Intact clip was narratively coherent. We hypothesized that narrative coherence would consistently engage posterior medial regions, resulting in more highly correlated activity within these regions across repetitions of Intact vs. Scramble-Fixed clips. In contrast, learning of temporal regularities in Scramble-Fixed clips may enhance coordinated communication between posterior medial regions across repetitions. Indeed, activity in the precuneus was more highly correlated between the first and last repetitions of Intact clips, as compared to its correlation between the first and last repetitions of Scramble-Fixed clips or Scramble-Random clips. However, functional coupling between precuneus and other posterior medial regions (hippocampus, retrosplenial cortex, angular gyrus) increased from the first to last repetition for Scramble-Fixed clips but not Intact or Scramble-Random clips. Finally, repetitions of the Intact clip also resulted in neural prediction: multivoxel patterns of activity at a given moment came to resemble future, expected events. Together, these results show that temporal structure is an

important determinant of posterior medial function, and that this temporal structure need not be narratively coherent.

Disclosures: **M. Aly:** None. **J. Chen:** None. **N.B. Turk-Browne:** None. **U. Hasson:** None.

Poster

840. Human Cognition and Memory VI

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 840.23/KKK10

Topic: H.02. Human Cognition and Behavior

Support: NIH R01MH063901

NIH F32MH106280

Title: Hippocampal-targeted theta-burst transcranial magnetic stimulation enhances associative memory

Authors: ***A. TAMBINI**, D. E. NEE, M. D'ESPOSITO;
Helen Wills Neurosci. Inst., UC Berkeley, Berkeley, CA

Abstract: Transcranial magnetic stimulation (TMS) has been used in cognitive neuroscience to causally manipulate the activity of individual brain regions on the cortical surface. In addition to superficial sites, TMS has been used to indirectly target subcortical structures by stimulating cortical regions with anatomical connections to subcortical sites of interest (e.g. Strafella et al., 2003). Recently, this approach has been used to target the hippocampus via TMS over inferior parietal cortex (IPC; Wang et al., 2014, 2015). In this work, both behavioral and neural measures of hippocampal function (associative memory performance and hippocampal resting connectivity) were enhanced after a chronic, 5-day TMS protocol. However, the lengthy 5-day protocol practically limits further exploration using this paradigm. Moreover, it is unclear based upon this work whether TMS over IPC affects encoding or retrieval. Given that IPC activity is associated with retrieval success (Kim, 2013), but is not typically related to encoding (Uncapher & Wagner, 2009; Kim, 2011), isolating an influence during encoding would reinforce the notion that resultant effects are due to distal influences of TMS on the hippocampus rather than the proximal influence of TMS on IPC. Here, we sought to determine whether: 1) one session of hippocampal-targeted continuous theta-burst TMS (cTBS) is sufficient to modulate associative memory and 2) whether TMS that influences only initial memory encoding, but not retrieval, is sufficient to influence subsequent associative memory performance. To this end, participants encoded unique object-spatial location associations, with cTBS to IPC (defined based resting

hippocampal connectivity) or to a control site (primary somatosensory cortex, S1) performed before encoding, in a repeated-measures design. Memory for individual objects and their associated spatial locations was tested approximately 2 - 5 hours later, after the influence of TMS had dissipated. Object-location associative memory performance was significantly enhanced for hippocampal-targeted cTBS versus S1, while memory for individual objects did not reliably differ between TMS sites. IPC cTBS also enhanced the confidence of spatial location judgments. Together, these results indicate that a single session of cTBS administered before memory encoding is sufficient to enhance a behavioral signature of hippocampal function, associative memory formation. More broadly, these results support the notion that TMS can be used to indirectly target hippocampal function via IPC, paving the way for future causal examinations of hippocampal function.

Disclosures: A. Tambini: None. **D.E. Nee:** None. **M. D'Esposito:** None.

Poster

840. Human Cognition and Memory VI

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 840.24/KKK11

Topic: H.02. Human Cognition and Behavior

Support: UT Brain Seed Grant #366582

Title: Modulation of oscillatory power and connectivity in the human posterior cingulate cortex supports the encoding and retrieval of episodic memories

Authors: *J. W. GERMI[1], B. LEGA[1], M. RUGG[2];
[1]Neurolog. Surgery, Univ. of Texas Southwestern, Dallas, TX; [2]Ctr. for Vital Longevity, Univ. of Texas at Dallas, Dallas, TX

Abstract: The role of the posterior cingulate cortex in episodic memory has not been described using intracranial EEG. Existing evidence has led researchers to posit that the PCC supports mnemonic processes: it exhibits degeneration in memory disorders, and fMRI investigations have demonstrated memory-related activation during both encoding and retrieval of memory items. Using data gathered from 21 human participants who underwent stereo electroencephalography for seizure localization, we characterized oscillatory patterns in the posterior cingulate cortex during the encoding and retrieval of episodic memories. We describe for the first time a subsequent memory effect during item encoding characterized by increased gamma band oscillatory power and a low frequency power decrease. 14 participants had stereotactic electrodes located simultaneously in the hippocampus and PCC, and with these

unique data we describe connectivity changes between these structures that predict successful item encoding and that precede item retrieval. Oscillatory power during retrieval matched the pattern we observed during encoding, with low frequency desynchronization and a gamma band power increase. We discuss our findings in light of existing theories of episodic memory processing, including the information via de-synchronization hypothesis and retrieved context theory, and examine how our data fit with existing theories for the functional role of the PCC. These include a postulated role for the PCC in modulating internally directed attention and for representing or integrating contextual information for memory items.

Disclosures: **J.W. Germi:** None. **B. Lega:** None. **M. Rugg:** None.

Poster

840. Human Cognition and Memory VI

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 840.25/KKK12

Topic: H.02. Human Cognition and Behavior

Support: NIH Grant DA027001

NIH Grant DA024226

Title: ERP neural indices of nicotine withdrawal-related cognitive disruption during performance of N-back working memory task

Authors: *D. EVANS;
Population Sci., Moffitt Cancer Ctr., Tampa, FL

Abstract: *Introduction:* Cognitive disruption during nicotine withdrawal is believed to play a role in the nicotine dependence process. In particular, specific aspects of cognitive control (e.g., attention, working memory) that may be used to exercise self-control during quit attempts are compromised by nicotine deprivation. Previous findings examining working memory and its neural substrates during nicotine withdrawal have been inconsistent. The current larger scale study hypothesized that working memory would decline following overnight smoking/nicotine deprivation among heavy smokers. In addition to behavioral measures of working memory, event-related brain potentials (ERP) were used to assess neural substrates. *Method:* 117 smokers attended two laboratory sessions following overnight smoking/nicotine deprivation. Participants smoked 4 cigarettes containing moderate levels of nicotine (.60 mg nicotine yield) during one session (satiated), and 4 very low nicotine cigarettes (~ .05 mg nicotine yield) during the other session (deprived). Sessions were double-blind and counterbalanced. Participants completed the

0-, 1-, 2-, and 3-back versions of an N-back working memory task. *Results:* Nicotine deprivation was associated with significantly extended response times, but these effects did not vary as a function of memory load. Accuracy was unaffected by nicotine deprivation at all levels of working memory. However, N2 and P3 ERP component amplitudes evoked during performance of the N-back were affected by nicotine deprivation. Specifically, frontal P3 was reduced across all memory loads and trial types following nicotine deprivation. Frontal P3 amplitude to match (i.e., compared to non-match) trials was additionally reduced in the nicotine deprivation condition, with this effect being driven by the 0- and 3-back conditions, suggesting reduced cognitive control during target detection and the most difficult memory load condition. Occipital N2 amplitude was reduced (i.e., less negative) and central N2 amplitude enhanced across all levels of memory load and trial types in the deprivation condition. The frontal N2 amplitude was greater to match trials across memory load conditions in the deprivation condition. *Discussion:* Findings suggest that the N-back may not be behaviorally sensitive to withdrawal-related cognitive disruption. However, N2- and P3-related neural substrates of executive function during an attentional control and working memory task may provide valid markers of withdrawal-related cognitive disruption.

Disclosures: D. Evans: None.

Poster

840. Human Cognition and Memory VI

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 840.26/KKK13

Topic: H.02. Human Cognition and Behavior

Support: NRF-2014R1A1A2055116

Title: Altered neural substrates within cognitive networks of postpartum during working memory process

Authors: *Y. BAK[1], Y. NAH[2], N.-Y. SHIN[1];
[1]Dept. of Radiology, Ewha Womans Univ. Sch. of Med., Seoul, Korea, Republic of; [2]Dept. of Psychology, Yonsei Univ., Seoul, Korea, Republic of

Abstract: Large number of women in postpartum periods complain that cognitive decline after giving birth disrupts their daily business, supported by reliable evidence in several behavioral studies and neuropsychological tests. However, almost nothing is known about the neural correlates underlying impaired cognitive abilities in postpartum. As working memory is a fundamental component among other cognitive functions, here, we conducted fMRI study

employing simple working memory task (N-back) to explore altered neural process of postpartum compared to that of control. 24 women in postpartum periods and 27 controls performed N-back task varying cognitive load (0, 1, 2-back) during fMRI scanning. Behaviorally, Postpartum demonstrated slower response times for the working memory task relative to control, implying Postpartum struggled to achieve comparable performance. In Postpartum, bilateral dlPFC showed greater activation throughout the N-back task compared to control. We found significant group (Postpartum vs. Control) and cognitive load (0-back vs. 1-back vs. 2-back) interaction in ACC and Insula/Putamen, and these regions along with dlPFC are regarded as members of task positive network (TPN). Group comparisons during fixation periods, which were inserted between task blocks, revealed that Postpartum showed less activation in mPFC in Postpartum than control. Similar results were also found in resting-state fMRI analysis where Postpartum showed deactivation in dorsal area of mPFC, known as main node for default mode network (DMN). Since these fMRI results demonstrated that Postpartum have altered activation pattern within TPN and DMN, we conducted further network analysis to investigate interactivity between neural nodes within these networks by calculating pairwise correlation coefficients. As results, we found relatively elevated connectivity within TPN in Postpartum against control, showing that Postpartum demand hyper-connectivity among brain regions mainly involved in cognitive processing. Taken together, our results suggest that impaired cognitive process in Postpartum is reflected in neuronal network level.

Disclosures: **Y. Bak:** None. **Y. Nah:** None. **N. Shin:** None.

Poster

840. Human Cognition and Memory VI

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 840.27/KKK14

Topic: H.02. Human Cognition and Behavior

Support: NIH Grant R01MH100121

Title: Reinstatement of schemas in sensory neocortex is guided by medial prefrontal cortex and hippocampus

Authors: *R. J. MOLITOR[1], M. L. SCHLICHTING[1], M. L. MACK[1], K. F. GUARINO[1], S. MCKENZIE[2], H. EICHENBAUM[3], A. R. PRESTON[1];
[1]Univ. of Texas At Austin, Austin, TX; [2]New York Univ., New York, NY; [3]Boston Univ., Boston, MA

Abstract: One of the hallmarks of episodic memory is its flexibility; information learned in one episode can be used to guide behavior in new contexts. Leading memory theories suggest that such generalization of knowledge is supported by hippocampal-medial prefrontal interactions that promote reactivation of goal-relevant knowledge in sensory neocortex. Reactivation of associative knowledge frameworks, or schemas, is thought to facilitate performance by providing predictions for appropriate action during novel events. While there is extensive evidence that hippocampus drives reactivation of predictive information in sensory cortex during explicit acts of retrieval, there is little evidence linking hippocampus and medial prefrontal cortex (mPFC) to reinstatement of schematic knowledge during generalization behavior. Here, we used functional magnetic resonance imaging (fMRI) to investigate how neocortical schemas are reinstated to support new learning and generalization. Participants completed a contextual rule-learning task by studying context-dependent reward contingencies of objects (A, B, C, D) in a set of spatial contexts (C_1 and C_2). The spatial contexts had opposing reward patterns, such that objects that were rewarded in one context (e.g., C_1: A+/B-) were not rewarded in the other context (e.g., C_2: A-/B+). Initial rule learning was followed by a transfer task in novel spatial contexts (C_3 and C_4). Critically, the reward structure in the novel contexts overlapped with the reward structure in the initial contexts (e.g., C_3: A+/B-; C_4: A-/B+), which allowed participants to use their prior knowledge of the contextual rules and facilitated rule-learning in the novel contexts relative to the initial contexts. We measured knowledge organization for the learned contextual rule by using a representational similarity analysis to characterize the association between events (e.g., C_1:A+ and C_1:B-) as a function of shared spatial and/or reward valence information. Using a searchlight analysis, we found that visual cortical representations active during transfer corresponded to the rule schema formed in the initial contexts. Moreover, visual cortex activation patterns were more similar for initial and transfer contexts that shared the same rule structure versus those with opposing rule structures. Importantly, engagement of visual cortex during transfer was enhanced through interactions with mPFC and hippocampus, evincing the role of these regions in guiding reinstatement of rule schemas during new learning. Collectively, our findings provide a representational account linking generalization to hippocampal-mPFC mediated retrieval processes.

Disclosures: R.J. Molitor: None. **M.L. Schlichting:** None. **M.L. Mack:** None. **K.F. Guarino:** None. **S. McKenzie:** None. **H. Eichenbaum:** None. **A.R. Preston:** None.

Poster

840. Human Cognition and Memory VI

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 840.28/KKK15

Topic: H.02. Human Cognition and Behavior

Support: NIMH Grant R01MH080833 (EAK)

NSF-GRFP Fellowship DGE1258923 (SMK)

Title: Emotional memory enhancements related to intrinsic and recognition-related functional connectivity of the right lateral occipital cortex

Authors: *S. M. KARK, E. A. KENSINGER;
Psychology, Boston Col., Chestnut Hill, MA

Abstract: Previous work has shown greater retrieval-related reactivation of the right lateral occipital cortex (rLOC) for negative visual stimuli, compared to neutral visual stimuli, and that activity is correlated with emotional memory enhancement across participants (Emotional d' - Neutral d') (Kark & Kensinger, 2015). In the present functional magnetic resonance imaging study, we examined 1) how post-encoding resting state functional connectivity of the rLOC relates to subsequent memory performance and 2) rLOC functional connectivity during a recognition memory task. Seventeen participants studied line-drawings of 150 images (50 negative, 50 positive, and 50 neutral) followed by the complete colorful image. Resting state scans were acquired during a consolidation period (20 minutes) that immediately followed encoding. During a surprise recognition memory task, participants were presented with old and new line-drawings and asked to make a memory judgment and a confidence rating. Context-dependent psycho-physiological interaction effects (gPPI) analyses were implemented to examine functional connectivity of the rLOC region during the recognition task. RSFC analyses showed that enhanced emotional memory was associated with greater connectivity between the rLOC and amygdala during the consolidation delay, while enhanced memory for negative or positive stimuli specifically was related to greater connectivity of the rLOC with the left temporal pole or inferior frontal gyri, respectively. During retrieval, connectivity between the rLOC, left fusiform gyrus, and right hippocampus was greater for negative hits compared to positive hits, and that difference in functional connectivity was correlated with enhanced memory for negative items compared to positive items across participants (Negative d' - Positive d'). These findings suggest 1) connectivity of LOC during consolidation relates to subsequent memory performance in valence-specific ways (i.e., anterior ventral visual stream processing for negative items and frontal processing for positive items) and 2) greater functional connectivity of the rLOC and hippocampus during recognition is associated with enhanced emotional memory.

Disclosures: **S.M. Kark:** None. **E.A. Kensinger:** None.

Poster

840. Human Cognition and Memory VI

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 840.29/KKK16

Topic: H.02. Human Cognition and Behavior

Support: National Natural Science Foundation of China No. 81420108012

National Natural Science Foundation of China No. 91432000

National Natural Science Foundation of China No. 81171021

National Natural Science Foundation of China No. 91132727

Title: The impact of cognitive reserve on event-related potential changes during working memory activation in amnesia mild cognitive impairment

Authors: *L. GU;
Neuropsychiatric Inst., Jiangsu, China

Abstract: In order to investigate the effect of cognitive reserve (CR) on age-related cognitive decline and cognitive impairments in amnesia mild cognitive impairment (aMCI), a working memory related event-related potential (ERP) was applied to get task performance data and brain activation during different load tasks. Otherwise, the study examined the mediation effect of neural efficiency on association of CR and task performance in healthy elders. Whether APOE polymorphism moderated the correlation between CR and cognitive performance was also explored in healthy controls. It reported that higher CR could contribute to better task performance in healthy elders via partial mediation effect of higher neural efficiency, especially in APOE ε4 carriers in healthy elders. Notably, no correlation was observed between CR and neural efficiency in aMCI patients, but higher CR could improve the task performance. In summary, enhancing CR would be a meaningful target for prevention and treatment of aMCI.
Keywords: cognitive reserve, neural efficiency, event-related potential, aMCI, working memory, apolipoprotein E

Disclosures: L. Gu: None.

Poster

841. Human Cognition: Individual Differences II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 841.01/KKK17

Topic: H.02. Human Cognition and Behavior

Title: Hyperalignment increases reliability and consistency of individual differences in brain responses

Authors: *F. MA[1], J. S. GUNTUPALLI[1], J. V. HAXBY[1,2];
[1]Psychological and Brain Sci., Dartmouth Col., Hanover, NH; [2]Ctr. for Mind/Brain Sci., Univ. of Trento, Trento, Italy

Abstract: Hyperalignment is a method that aligns representational spaces from different subjects into a common space, which increases inter-subject similarities of neural response profiles and representational geometry, and facilitates between-subject multivariate pattern classification (Guntupalli et al., 2016; Haxby et al., 2011). However, it's still unknown whether individual differences still persist with such increase of inter-subject similarities. Here we try to answer this question using an fMRI data set obtained when 11 subjects were watching an audio-visual movie. For each movie half, we computed the multivariate dissimilarity between each pair of subjects to form an individual differences dissimilarity matrix (ID DSM). ID DSMs from two movie halves were further vectorized and compared to obtain the reliability of individual differences. We repeated this procedure three times using pairwise dissimilarities based on concatenated time-series (TS), functional connectivity (FC), and representational geometry (RG) respectively, and obtained reliable individual differences with each kind of dissimilarity measurement (TS: r = .89; FC: r = .77; RG: r = .79). Furthermore, the three kinds of ID DSMs also inter-correlate with each other for both movie halves (r ranging from .44 to .86 for the first half, and .70 to .87 for the second half), suggesting individual differences are consistent across dissimilarity measurements. We then applied searchlight hyperalignment (Guntupalli et al., 2016) on the data set and performed the same analysis on hyperaligned data. Interestingly, despite the increase in between-subject similarity, individual differences still persisted after hyperalignment, and were equally or more reliable after hyperalignment (TS: r = .91; FC: r = .92; RG: r = .84), and more consistent across dissimilarity measurements (r ranging from .57 to .87 for first half, and .78 to .95 for the second half). A further searchlight analysis yielded an overall increase in individual differences reliability with hyperalignment, similar to the whole-brain analysis results. These results demonstrate that hyperalignment does not eliminate individual differences in brain responses; on the contrary, by aligning brain responses into a common space, hyperalignment minimizes the effects of anatomical variability to afford a less confounded analysis of individual differences in functional architecture, which resulted in increased reliability and consistency of inter-subject dissimilarity geometry.

Disclosures: **F. Ma:** None. **J.S. Guntupalli:** None. **J.V. Haxby:** None.

Poster

841. Human Cognition: Individual Differences II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 841.02/KKK18

Topic: H.02. Human Cognition and Behavior

Support: NIH Grant R21MH99617

Title: Prenatal androgen effects on neural processing of reward

Authors: ***S. L. ZELLE**, A. M. BELTZ, K. L. KORMAN BRYK, S. J. WILSON, S. A. BERENBAUM;
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Abstract: Sex matters for psychopathology. Most research on sex-differentiated neural substrates of psychopathology concerns postnatal influences, but there is likely a role for early developmental factors, particularly prenatal androgens. Reward processing is an important domain relevant to psychopathology.
In this study, we examined the influence of prenatal androgens on reward-related functional systems within the brain by studying women exposed to high (sex-atypical) androgens during early development because of a genetic disorder, congenital adrenal hyperplasia (CAH; n=13) and compared them to their unaffected sisters (n=6). We expected that women with CAH would have masculinized neural processing of reward, including greater striatal activation but less connectivity among reward regions, consistent with their behavioral masculinization in other domains (e.g., interests, spatial ability).
We used functional MRI (fMRI) to examine neural activity during a monetary incentive task in which participants won or lost money in each trial of a card guessing game. Standard preprocessing was conducted using FSL and a general linear model (GLM) was used to examine brain activity in win versus loss trials (with p set at <.05). Individual-level connectivity analyses were conducted for an illustrative sibling pair, utilizing unified structural equation modeling (uSEM), a data-driven method that maps lagged and contemporaneous directed connections among brain regions of interest (ROIs). A priori ROIs were the bilateral striatum and insula, posterior cingulate cortex, and ventromedial prefrontal cortex.
GLM results were consistent with predictions. Compared to unaffected sisters, women with CAH demonstrated greater bilateral caudate (part of the striatum) activation during trials in which they won versus lost money. Connectivity analyses were also consistent with predictions. The woman with CAH had less connectivity (i.e., fewer connections among ROIs) than her sister;

particularly for connections with the ventromedial prefrontal cortex and left ventral striatum. Using a natural experiment, we provided preliminary evidence that prenatal androgens masculinize functional reward systems: women with CAH showed greater striatal activation but less connectivity than their sisters. This suggests that a "masculinized" reward system is modular, dominated by the activity of relatively isolated regions, while a "demasculinized" or "feminized" reward system is integrated, relying on communication among regions.

Disclosures: S.L. Zelle: None. **A.M. Beltz:** None. **K.L. Korman Bryk:** None. **S.J. Wilson:** None. **S.A. Berenbaum:** None.

Poster

841. Human Cognition: Individual Differences II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 841.03/KKK19

Topic: H.02. Human Cognition and Behavior

Support: Presidential Scholars in Society and Neuroscience Program

Title: LDA classification of EEG reveals differences between improvising and non-improvising musicians in a musical Stroop task.

Authors: *A. GOLDMAN[1], P. SAJDA[2];
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Abstract: Many recent studies have used EEG and fMRI to demonstrate acquired perception-action coupling in expert musicians. The present experiment uses similar methods to compare *types* of musicians, i.e., improvisers and non-improvisers. Improvisers are hypothesized to have stronger perception-action coupling owing to differences in their training regimens. Differences in the cognitive representation of musical structures, as evidenced by neurophysiological differences in the perception of auditory stimuli and motor planning, are theorized to underlie improvisers' ability to use their musical knowledge creatively. To examine this, EEG data was acquired in a shielded room using a BioSemi Active Two AD Box ADC-12 with 64 active scalp electrodes while groups of jazz pianists and classical pianists performed a musical Stroop task. Participants played chords on a MIDI keyboard in which auditory feedback from the instrument was either congruent with what they played, or artificially altered to be incongruent with their movements. Participants had to identify the type of chord they heard (not played) using a computer keyboard. Behavioral data confirmed the presence of a Stroop effect, with incongruent stimuli having significantly higher RTs and lower accuracy. LDA modeling was used to create discriminating scalp maps both between congruent and incongruent conditions, and between

groups of musicians. These models were used to classify both within-group and between-group variables. This study not only contributes further evidence of perception action coupling in trained musicians in a harmonic context (i.e., playing chords instead of single notes), but also, crucially, explores differences between groups of musicians. Thus it begins to explain musical improvisatory abilities in terms other than novelty and spontaneity as past neuroscientific studies on improvisation have done. It also shows that there is important variation among musical experts that should be considered in future studies. Finally, it contributes to a neuroscientific characterization of creativity.

Disclosures: A. Goldman: None. **P. Sajda:** None.

Poster

841. Human Cognition: Individual Differences II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 841.04/KKK20

Topic: H.02. Human Cognition and Behavior

Support: NIH grant R01-HL102119

NIH grant R01-MH107571

NIH grant R01-NR004281

NIH grant P30-NS045839

CTRC UL1RR024134,

ENN IOA Pilot Project

Title: Effects of sleep deprivation on white matter integrity in the human brain

Authors: *S. XU[1,2], Z. FANG[1,2], F. YANG[1], A. SPAETH[1,3], N. GOEL[3], M. BASNER[3], D. DINGES[3], S. WANG[4], J. DETRE[1,5], H. RAO[1,2,3];
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Abstract: Introduction: Sleep loss significantly impairs a range of neurocognitive performance and disrupts brain function. However, whether and how sleep loss affects brain white matter

integrity remain unknown. In this study, we used diffusion tensor imaging (DTI) to examine the effects of one night of acute total sleep deprivation (TSD) on fractional anisotropy (FA), an index reflecting the degree of anisotropic water diffusion in brain white matter.
Method: Fifty-one healthy adults (23 females, mean age = 33.2 ± 8.9 years) participated in a 5-day and 4-night in-laboratory controlled protocol. They were randomized to either a TSD condition (n=39) without sleep on night 2, or a control condition (n=12) with 8-9 hour normal sleep on every night. Using a Siemens 3T Trio scanner, DTI data were acquired on the morning (0700-1000) of days 2 and 3. Participants also completed a 10-minute psychomotor vigilance test (PVT) during each scan and the PVT performance was used to determine their cognitive vulnerability to sleep loss. Imaging data were analyzed using SPM8 and PANDA toolbox.
Results: The control group showed no differences in FA between the two DTI scans. However, in the TSD group, significant FA increases were found in the right superior longitudinal fasciculus (SLF, corrected $p < 0.05$), the axonal pathway connecting the frontal and parietal regions, after one night of sleep loss compared to baseline. When the TSD group was median split into individuals who were cognitive vulnerable (n=20) or resistant (n=19) to sleep loss based on the PVT performance changes after TSD, FA increases were only observed in the vulnerable subjects, while no changes were found in the resistant subjects. Moreover, vulnerable subjects showed significantly lower FA in the right SLF than resistant subjects at baseline before sleep loss.
Conclusions: Higher baseline FA in cognitive resistant individuals is consistent with previous studies and supporting the view that differential white matter microstructural properties may contribute to cognitive vulnerability to sleep deprivation. In this study, vulnerable subjects also exhibited increased FA after sleep loss, suggesting both trait- and state-dependent interactions between SLF microstructure and cognitive vulnerability to sleep deprivation.

Disclosures: **S. Xu:** None. **Z. Fang:** None. **F. Yang:** None. **A. Spaeth:** None. **N. Goel:** None. **M. Basner:** None. **D. Dinges:** None. **S. wang:** None. **J. Detre:** None. **H. rao:** None.

Poster

841. Human Cognition: Individual Differences II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 841.05/KKK21

Topic: H.02. Human Cognition and Behavior

Support: ARL W911NF-10-2-0022

Swartz Foundation

Title: Hierarchical clustering for neuroelectrophysiological data analysis

Authors: *C.-S. WEI[1], Y.-T. WANG[2], C.-T. LIN[3], T.-P. JUNG[2];
[1]Bioengineering, [2]INC, UCSD, LA Jolla, CA; [3]FEIT, Univ. Technol. Sydney, Sydney, Australia

Abstract: Cluster heat map has been widely used in current scientific research that leverages big data. In the field of bioinformatics, cluster heat map is often used in data visualization and exploration of gene expression. This study proposed to exploit the cluster heat map of neuroelectrophysiological measurements to extract neuroscientific information in large-scale database. In this study, a heat map was constructed by the measurements of human electroencephalographic (EEG) correlates of neurocognitive drowsiness (i.e. the correlations between EEG spectrum and task performance), and hierarchical clustering analysis was applied to the heat map to investigate the inter- and intra-subject variability of drowsiness-related human brain dynamics.The clustering across the dimension of 77 sessions from 36 subjects participating in a simulated driving task showed that different sessions from a single individual may or may not be grouped together, depending on the intra-subject variability in the EEG compared to inter-subject variability. As the relationship between drowsiness and EEG spectrum was commonly shared across different subjects, it is favorable to model and predict drowsiness level using large-scale EEG data from multiple subjects. Furthermore, the result of hierarchical clustering analysis also showed that the EEG correlates of drowsiness within each frequency band were tightly clustered together, revealing the redundancy in spatial domain of the drowsiness-related brain dynamics. The analysis of similarity and discrepancy among EEG correlates of human behavioral performance across scalp locations and frequency bands could inspire a new design of EEG feature selection and extraction that could improve the efficiency of big data usage. In sum, the insight into the EEG correlates of task performance obtained from the proposed hierarchical clustering analysis might open up a new direction of big data approaches to electrophysiological research.
Support: This work was supported in part by Army Research Laboratory (W911NF-10-2-0022) and a gift fund from Swartz Foundation.

Disclosures: **C. Wei:** None. **Y. Wang:** None. **C. Lin:** None. **T. Jung:** None.

Poster

841. Human Cognition: Individual Differences II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 841.06/KKK22

Topic: H.02. Human Cognition and Behavior

Support: NSF GSF DGE-1106400

Title: Connector and local hub connectivity predicts modularity and performance in multiple cognitive tasks

Authors: *M. A. BERTOLERO[1], B. T. T. YEO[2], M. D'ESPOSITO[1];
[1]Univ. of California, Berkeley, Berkeley, CA; [2]Natl. Univ. of Signapore, Singapore, Singapore

Abstract: Brain regions and their connectivity can be analyzed as a complex network. These analyses reveal a modular organization—autonomous communities of tightly interconnected nodes. They also reveal local hubs with many connections to their own communities (high within-community-degree (WCD)) and connector hubs with many connections to different communities (high participation coefficient (PC)). A recent analysis showed that only connector hubs exhibit increased activity if more communities are engaged in a task, which suggests that connector hubs are involved in processes that are more demanding as more communities are engaged. A parsimonious explanation of this finding is that connector hubs integrate information and coordinate connectivity across communities, which allows for modular local processing. However, it is not known how individual subject variations in the connectivity of connector hubs predict individual subject variations in the modularity (Newman's Q) of the subjects' networks or the subjects' task performance. We hypothesized that, across individual subjects, when connector hubs are connected to many communities (high PC), they are able to integrate information and coordinate connectivity optimally, which facilitates increased global Q and higher behavioral performance in any task. Similarly, processing is more modular when local hubs are predominantly connected to their own communities (high WCD). Utilizing the Human Connectome Project fMRI data (n=500), we analyzed how individual subject changes in the connectivity of connector and local hubs predicts the Q of individual subjects' networks. We discovered that, across all six tasks and resting-state, the increased PCs of connector hubs and the increased WCDs of local hubs predicts higher Q in the subjects' networks. Moreover, we were able to accurately predict individual subjects' task performance using the PCs of connector hubs and the WCDs of local hubs. The performance of the subjects in four of the tasks—working memory, a relational reasoning task, a mixed math and language task, and a social cognition task—was higher when connector hubs have high PCs and local hubs have high WCDs. Finally, a subject's higher Q during a task, relative to resting-state, predicted increased performance in all four tasks, and that higher Q value was predicted by the individual's connector hubs' PCs remaining high from rest to task. In summary, when an individual's network has connector hubs that are optimally connected to integrate information and coordinate connectivity across communities (i.e., high PCs), the individual's network modularity is maintained and their task performance is higher.

Disclosures: **M.A. Bertolero:** None. **B.T.T. Yeo:** None. **M. D'Esposito:** None.

Poster

841. Human Cognition: Individual Differences II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 841.07/KKK23

Topic: H.02. Human Cognition and Behavior

Support: NIDA022582

NSF GRFP DGE-1313911

Title: Males and females evaluate facial attractiveness using different cognitive and affective strategies

Authors: *K. M. RAPUANO, T. F. HEATHERTON, W. M. KELLEY;
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Abstract: Although males and females ascribe similar importance to mate-selection goals for reproductive success, sex differences in selection criteria have been widely explored. Previous studies have observed activity within putative reward regions of the brain (e.g., the nucleus accumbens [NAcc]; orbitofrontal cortex [OFC]) to increase with increasing facial attractiveness ratings, and further report a sex difference in the OFC (Cloutier et al., 2008). An open question is whether this sex difference in OFC reflects a fundamental difference across genders or whether this effect reflects different evaluation strategies by males (e.g., sexual interest) and females (e.g., physical aesthetics) while evaluating opposite-sex attractiveness. Sixty-six subjects (30 male) viewed opposite-sex faces during functional magnetic resonance imaging (fMRI). In order to equate cognitive strategies between sexes, subjects were instructed to make either attractiveness judgments or sexual desirability judgments on a 1 (“Very attractive”; “Very desirable”) to 3 (“Unattractive”; “Undesirable”) rating scale. Using FreeSurfer-defined probabilistic masks of the NAcc and OFC, we examined activity within these regions for sex differences during evaluations of attractiveness and sexual desirability. Across all participants, activity in both the OFC and NAcc were significantly correlated with attractiveness ratings. Consistent with our previous findings, OFC activity - but not NAcc activity - demonstrated a difference between males and females while evaluating facial attractiveness. Here we extend these findings to show that this sex difference is eliminated when females are explicitly instructed to judge sexual desirability. Further, voxelwise response patterns (MVPA) in the OFC were more similar between sexual interest and facial attractiveness tasks in males than in females, and this degree of similarity was associated with self-reported sexual desire. These results suggest that males and females draw upon different evaluative strategies while considering the attractiveness of the opposite sex, and that this distinction is minimized when explicitly judging sexual desirability. Finally, greater representational similarity in males between sexual interest and attractiveness tasks suggests that males may be engaged in implicit

sexual evaluations while judging attractiveness, while females are engaged in more explicit cognitive evaluations of physical aesthetics.

Disclosures: K.M. Rapuano: None. **T.F. Heatherton:** None. **W.M. Kelley:** None.

Poster

841. Human Cognition: Individual Differences II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 841.08/KKK24

Topic: H.02. Human Cognition and Behavior

Support: U.S Army Research Laboratory contract W911NF-10-2-0022

Title: How network topology drives individual differences in structure-function relationships

Authors: *H. E. BAIDOO-WILLIAMS[1,2], C. GREENE[3], S. T. GRAFTON[3], J. M. VETTEL[2,4,5], S. F. MULDOON[6];
[1]Univ. At Buffalo - The State Univ. of Ne, Buffalo, NY; [2]U.S Army Res. Lab., Aberdeen Proving Ground, MD; [3]Physiological and Brain Sci., [4]Dept. of Psychological and Brain Sci., Univ. of California, Santa Babara, Santa Babara, CA; [5]Bioengineering, Univ. of Pennsylvania, Philadelphia, PA; [6]Mathematics and CDSE Program, Univ. at Buffalo, SUNY, Buffalo, NY

Abstract: Understanding how individual variability in structure-function coupling contributes to focal versus global brain activation is important for developing individualized performance enhancement and control strategies. Here, we use a biologically motivated computational model of regional brain dynamics to investigate the role of network topology in driving differences in focal vs global activation of brain regions. Our computational model is applied to 440 tractography networks derived from diffusion weighted imaging (DWI) data from the Human Connectome Project (HCP), with regional brain activity modeled using biologically motivated Wilson-Cowan oscillators coupled through the observed tractography networks. Focal and global regional dynamics show a wide range of variability across models derived from different subjects' connectomes. In order to understand what features of the network topology give rise to such variability, we quantify differences in structural network connectivity across individuals and observe how these differences drive the dynamics of local versus global functional activation patterns.

Disclosures: H.E. Baidoo-Williams: None. **C. Greene:** None. **S.T. Grafton:** None. **J.M. Vettel:** None. **S.F. Muldoon:** None.

Poster

841. Human Cognition: Individual Differences II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 841.09/KKK25

Topic: H.02. Human Cognition and Behavior

Support: NIH Grant DE022746

Title: Whole-brain spatiotemporal dynamics in fMRI resting state activity is longitudinally distinct in individuals

Authors: *A. T. BARIA, A. V. APKARIAN;
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Abstract: It has been shown that networks of correlated brain activity are stable over time, between recording periods that are many days apart. This stability nonetheless occurs over shorter-term fluctuations in the brain state, elicited by both conscious and unconscious processes, ranging from seconds to minutes. However, it is unknown to what extent the temporal evolution of brain states is distinct to the individual, and how it change across time. We calculated the frequency of spatial pattern recurrence in each scan and compared this measure in the same individuals taken from scans weeks to months later, to determine the consistency of short-term, whole-brain spatiotemporal dynamics across long time spans.

We performed resting state fMRI on 7 healthy subjects in which participants rested quietly with their eyes open. We scanned each subject 3 times: baseline, 6 weeks, and 6 months later. We extracted the whole brain activity pattern from every voxel (N=6554 voxels, 6mm isotropic, covering the entire brain) at every time point, and pairwise correlated all spatial patterns in each scan. This resulted in a square time x time spatial similarity matrix for each scan. From this matrix we generated a spatial correlation time series and used a Welch's power spectrum to determine the overall distribution of frequency-power across the entire bandwidth of each signal. The log-linear transform of the average power spectrum was linearly fit, and the slope of the fit (α) indicated the balance between high and low frequency power. The measure, α, is then an arbitrary unit in which high values indicate relatively similar patterns recur slowly, while low values suggest they recur much more quickly.

A group-level repeated measures ANOVA on α, testing for differences across scans, was not significant, indicating that α was stable up to 6 months after the initial scan. Likewise, α covaried highly consistently across time. That is, for example, high levels of α at baseline remained relatively high at subsequent scans. Baseline vs. 6-week scans correlated at $r = 0.95$ ($p<0.01$), however the baseline vs. 6-month correlation was not significant at $r = 0.41$ ($p = 0.36$).

These results collectively suggest that the short-term evolution of spatial patterns in the brain, or brain states, is governed by mechanisms that are distinct within individuals, and highly

consistent across, at least, many weeks. Further analysis remains to be done on scans separated by days and years. The overall aim of this work is to build a bridge between emerging research in brain state trajectories at short time scales and stability of function across the lifespan of individuals.
Funded by NIH R01DE022746

Disclosures: **A.T. Baria:** None. **A.V. Apkarian:** None.

Poster

841. Human Cognition: Individual Differences II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 841.10/KKK26

Topic: H.02. Human Cognition and Behavior

Support: Department of Education Grant P120A140012 ($

Title: The association between the COMT Val158Met polymorphism and psychological and cognitive performance

Authors: S. M. LYLE[1], X. F. TATIN[3], L. D. HILL[1], M. S. LORENZETTI[1], A. TARTAR[2], *J. L. TARTAR[1];
[1]Psychology and Neurosci., [2]Biol. Sci., Nova Southeastern Univ., Fort Lauderdale, FL;
[3]AgroParisTech, Paris, France

Abstract: The Catechol-O-methyltransferase (COMT) enzyme is critical for the clearance of dopamine (DA) in the prefrontal cortex (PFC). For this reason, the COMT gene is thought to play a role in cognitive processing. Indeed, there is a functional single nucleotide polymorphism (SNP) in the COMT gene (Val158Met) where enzyme activity is 3-4 times greater in Val allele carries relative to the Met allele carriers. This greater COMT activity is associated with decreased DA activity and decreased cognitive performance. However, in spite of the increased cognitive performance abilities of MET allele carries, they are reported to be at a disadvantage under stressful conditions, possibly to due stress-related increase in dopaminergic transmission. Increased DA activity under non-stress condition in the MET allele carries is advantageous for cognitive (especially PFC-dependent) processing, while increased DA activity in this group (in the presence of stress) creates an inverted U-type pattern where greater DA release is associated with poor- cognitive performance. However, it is currently uncertain how different cognitive domains are related to the COMT genotype and also how mood might be related to COMT genotype under stress and non-stress conditions. In order to test these uncertainties, we carried out three experiments. First, we tested the role of the COMT genotype on various mood and

health measures under non-stress conditions. Second, we tested the role of the COMT genotype across a variety of cognitive domains. Third, we tested the role of the COMT genotype on mood and cognition in a social stress (the trier social stress test, TSST) and non-stress (control TSST) condition. Results from our first experiment showed that, relative to the GG (VAL) genotype (n=54), A allele carriers (n=24) have significantly less depressive symptomatology (CES-D), less mood disturbances (POMS), less perceived stress (PSS), and lower cortisol levels (all p's < 0.05). In agreement with the idea that COMT activity preferentially influences PFC-dependent cognitive processing, results from our second experiment show that A allele carriers (n=29) significantly outperform GG genotypes (n=18) on PFC-dependent cognitive tasks (p's < 0.05), but not other measures of cognitive functioning. We are currently analyzing data from our third experiment that examines the effect of TSST and control TSST on measures of psychological health and cognitive performance. Results show that, at least under non-stressful conditions, the COMT MET allele carriers have an advantage on PFC-dependent cognitive processing and clinical health measures.

Disclosures: **S.M. Lyle:** None. **X.F. Tatin:** None. **L.D. Hill:** None. **M.S. Lorenzetti:** None. **A. Tartar:** None. **J.L. Tartar:** None.

Poster

841. Human Cognition: Individual Differences II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 841.11/KKK27

Topic: H.02. Human Cognition and Behavior

Title: Perceptions of brain training: an Internet survey of 1946 adults

Authors: *C. SIMONE, S. MACLEOD, G. MORRISON;
Lumos Labs, Inc, San Francisco, CA

Abstract: "Brain training", or computerized cognitive training, is relatively new, and has received a great deal of attention in the media, both positive and negative. Though the academic community has yet to reach a consensus on how to conduct and interpret research on "brain training", it is important to understand the consumer perspective to promote more well-designed studies. To this end, we conducted a consumer survey on perceptions of brain training compared to other commonly referenced methods used to challenge cognitive abilities.
The survey was administered over the Internet in 2015, polling 1,026 adults in the US from ages 18 to 70+. These respondents were reached through a SurveyMonkey audience panel, where they are rewarded with a donation to charity for completing surveys.
Respondents rated complex activities, such as learning a language or musical instrument or

engaging in a challenge at work, as the most effective methods. Interestingly, respondents rated crossword puzzles as more effective than brain training products at challenging cognitive abilities. This belief was true across all levels of education, with PhDs preferring crosswords over brain training more than the other education levels. Males tended to prefer brain training less than females. Playing the math game Sudoku ranked slightly above brain training in one survey and slightly below brain training in the other. At the bottom of the list were action video games, casual mobile and web games, and board games or card games.
Respondents were generally aware of the concept of brain training and believed it to be relatively effective at challenging cognitive abilities. However, respondents rated brain training as less effective than crossword puzzles, and about on par with Sudoku. Video games were rated least effective of all. These perceptions should be considered in study designs evaluating brain training programs, as expectation bias should be controlled for as much as possible with an active control group. These results suggest that crossword puzzles or Sudoku would make better active control conditions than video games.

Disclosures: **C. Simone:** A. Employment/Salary (full or part-time): Lumos Labs. **S. MacLeod:** A. Employment/Salary (full or part-time): Lumos Labs. **G. Morrison:** Other; former employee of Lumos Labs.

Poster

841. Human Cognition: Individual Differences II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 841.12/KKK28

Topic: H.02. Human Cognition and Behavior

Support: NIH Grant T32AG000175

Title: The relationship between cortisol and cognitive functioning across the adult lifespan

Authors: *U. SAELZLER[1], S. RESNICK[2], S. D. MOFFAT[1];
[1]Georgia Inst. of Technol., Atlanta, GA; [2]Natl. Inst. on Aging, Blatimore, MD

Abstract: Age-related declines in cognitive functioning have been well documented, however, there are individual differences in the age of onset and magnitude of these changes. This observation has spurred the investigation of the potential risk factors for cognitive decline. Chronic elevations of the steroid hormone cortisol have been shown to compromise hippocampal- and frontal cortex- dependent cognitive tasks in rodents, non-human primates and in Cushing's disease patients. The present study investigated the relationship between basal cortisol levels, indexed by a single 24-hr urinary free cortisol, and performance on twelve

cognitive outcomes in a sample of 1,853 non-demented adults aged 18 to 93 years (M_{age} 58 ± 15). The results showed that elevated cortisol levels had small but significant negative effects on verbal learning and working memory performance across the lifespan and significant negative effects limited to older adults on a measure of speeded processing. These results will be discussed in the context of allostatic load and its influence on neural structure and subsequent functioning across the adult lifespan, with a focus on older adulthood.

Disclosures: U. Saelzler: None. **S. Resnick:** None. **S.D. Moffat:** None.

Poster

841. Human Cognition: Individual Differences II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 841.13/KKK29

Topic: H.02. Human Cognition and Behavior

Support: P60AA011605

KL2RR025746

T32DA007244

T32AA007573

UL1RR025747

F31AA020132

The Howard Hughes Medical Institute

Title: Genetic contributions to individual differences in functional neuroimaging measures of impulsive decision making

Authors: *A. ELTON[1], C. T. SMITH[3], M. H. PARRISH[2], S. H. OPPLER[4], T. H. MCKIM[4], C. A. BOETTIGER[5];
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Abstract: Background: Individuals at risk for alcohol or drug use problems based on a family history (FH) of these disorders show increased impulsive decision making behavior in delay discounting (DD) tasks. Similarly, the Val158Met polymorphism (rs4680) of the catechol-O-

methyltransferase (COMT) gene predicts impulsive choices and associated brain activity during a DD task. We hypothesized that heritable factors associated with differences in impulsive behavior would be associated with altered brain functional connectivity during decision making in a DD task.
Methods: We tested 95 healthy adults (50 females) in a DD task in which they chose between smaller, immediate and larger, delayed hypothetical monetary rewards during fMRI. Fifty-three subjects reported a FH of alcoholism and subjects provided saliva samples for COMT genotyping, yielding 20 Met/Met, 48 Met/Val and 25 Val/Val genotypes. We operationalized the tendency to select smaller, sooner rewards over larger, delayed rewards as the impulsive choice ratio (ICR). Following standard preprocessing of the fMRI data, we selected *a priori* six large-scale neural networks, then identified 35 regions-of-interest within these networks from which to extract representative time series; we also extracted time series from each gray matter voxel. We then used network-level and voxel-wise beta-series functional connectivity analyses to generate measures of DD task-evoked connectivity changes. The strength of changes in functional connectivity between subjective decision making trials and control choice trials was calculated for within- and between-network connections, as well as between each gray matter voxel.
Results: A FH of alcoholism was associated with greater ICR. COMT genotype independently predicted ICR, but differently for each sex: Val/Val males and Met/Met females, representing the extreme high and low ends of the COMT activity spectrum, respectively, were most impulsive. FH was associated with reduced strength of task-induced functional connectivity changes at both the network and voxel levels. COMT genotype also predicted functional connectivity strength, again dependent on sex. For the network-level analyses, Val/Val males demonstrated reduced changes in functional connectivity strength compared with male Met carriers. Conversely, Met/Met females demonstrated reduced changes in functional connectivity strength compared with female Val carriers. These results were replicated at the voxel level.
Conclusions: Heritable factors associated with greater DD behavior demonstrate corresponding deficits in the flexible reorganization of functional connections when making decisions.

Disclosures: **A. Elton:** None. **C.T. Smith:** None. **M.H. Parrish:** None. **S.H. Oppler:** None. **T.H. McKim:** None. **C.A. Boettiger:** F. Consulting Fees (e.g., advisory boards); BlackThorn Therapeutics, Inc..

Poster

841. Human Cognition: Individual Differences II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 841.14/KKK30

Topic: H.02. Human Cognition and Behavior

Support: Korea NRF Grant 2014R1A1A3051034

Title: The influence of handedness on space-magnitude association

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Abstract: Previous studies of number processing have not thoroughly investigated the effect of handedness in relation to space-magnitude association. The present study aimed to explore whether space-magnitude association is influenced by handedness. To this end, we used a magnitude comparison task which requires comparison between an Arabic number and a dot array. This task was carefully designed to effectively reduce the influence of continuous visual characteristics of the dot array (such as the cumulative spatial area and individual dot size, etc.). Sixty-six college students (28 left-handed, 33 females) participated in the present study. An extensive handedness questionnaire was administered which yielded each individual's handedness score on a 1 to 5 point scale (1 vs. 5 representing completely left- vs. right- handed, respectively.) In the "Dot-Number (DN)" condition, an array of dots (non-symbolic magnitude) and an Arabic number (symbolic magnitude) were presented in the left vs. right side of the screen, respectively. In the "Number-Dot (ND)" condition, an Arabic number and an array of dots were presented in the left vs. right side of the screen, respectively. Participants were asked to indicate the stimulus representing the larger magnitude with a key press.
The degree of handedness influenced performance depending on the left vs. right spatial location of stimuli. Both left-handed (LH) and right-handed (RH) participants showed the highest Inverse Efficiency Score (IES) (i.e., response time divided by accuracy) when the target stimulus was presented on the right side of the screen. That is, LH subjects responded most efficiently in the ND condition, if the set size of the dot array was larger than the magnitude of the Arabic number; and RH subjects responded most efficiently in the DN condition when the magnitude of the Arabic number was larger than the set size of the dot array.
The present result seems to reflect attentional bias in the direction of the dominant hand. Participants may benefit from attention being allocated first to the Arabic digit when it is presented on the side of space corresponding to their dominant hand. This may be understood by the fact that symbolic magnitude (i.e., the Arabic number), rather than non-symbolic magnitude (i.e., the dot array), is processed more efficiently in adults especially when it is given top-down attention in the side of space corresponding to their dominant hand.

Disclosures: H. Lee: None. **S. Cho:** None.

Poster

841. Human Cognition: Individual Differences II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 841.15/KKK31

Topic: H.02. Human Cognition and Behavior

Support: NIH Grant DA034685

Title: Dopaminergic modulation of intrinsic striatal functional connectivity varies with dopamine synthesis capacity

Authors: *D. FURMAN[1], R. WHITE[1,2], A. BERRY[1], W. JAGUST[1], M. D'ESPOSITO[1]; [1]Helen Wills Neurosci. Inst., Univ. of California Berkeley, Berkeley, CA; [2]Univ. of California - San Francisco, San Francisco, CA

Abstract: Despite a growing number of reports that dopamine (DA) impacts functional connectivity in human brain imaging data, the cumulative results of this work have been largely equivocal. A notable exception is the finding that both DA augmentation and DA system variability impact the activity of, and functional connectivity between, the caudate nuclei and posterior cingulate cortex, as well as other nodes of the putative "default mode network" (DMN). To better understand the nature of this effect, we examined changes in functional connectivity following administration of two mechanistically-distinct dopaminergic probes -- tolcapone, a catechol-O-methyltransferase (COMT) inhibitor thought to increase prefrontal extrasynaptic DA levels, and bromocriptine, a D2 receptor agonist. Importantly, research from our lab and others has demonstrated that the effects of dopaminergic agents on brain function can vary significantly with individual differences in baseline DA system function; thus, we examined drug effects on functional connectivity in relation to striatal DA synthesis capacity. Twenty-eight participants (age 18-30 years) underwent fMRI scanning once each after administration of placebo, tolcapone (200mg), and bromocriptine (1.25mg). During each session, eyes-open resting echo planar BOLD data were collected with a Siemens 3T Trio scanner (TR=2.0s, 180 volumes, voxel size = 3.0 x 3.0 x 3.5 mm). Subsequently, participants underwent [^{18}F]fluorometatyrosine (FMT) PET (Siemens Biograph scanner) to assay DA synthesis capacity, which was defined as the uptake of FMT (K_i) within anatomically-defined striatal regions-of-interest (including precommissural caudate) referenced to the cerebellum. BOLD correlation analyses were conducted between striatal seed regions and both the whole brain and previously-defined networks-of-interest. Subject-level correlation maps and network coefficients were analyzed at the group level with caudate FMT K_i as a predictor of interest. There was no main effect of drug on functional connectivity. However, whole brain and network-based analyses revealed an interaction of drug and right caudate FMT Ki on caudate-DMN functional connectivity. Specifically, lower caudate FMT Ki values predicted increased connectivity, whereas higher caudate FMT Ki values

predicted decreased connectivity, on tolcapone relative to placebo. Our pattern of results suggests an inverted-U-shaped relationship between caudate-DMN functional connectivity and striatal DA synthesis in the context of increased prefrontal DA.

Disclosures: D. Furman: None. **R. White:** None. **A. Berry:** None. **W. Jagust:** None. **M. D'Esposito:** None.

Poster

842. Perception and Imagery: Perception and Related Predictions Across Different Modalities

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 842.01/KKK32

Topic: H.02. Human Cognition and Behavior

Support: NSF Grant IOS-1150209

Title: Tactile texture invariance and its peripheral neural basis

Authors: *H. P. SAAL, J. D. LIEBER, Z. M. BOUNDY-SINGER, A. I. WEBER, S. J. BENSMAIA;
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Abstract: Our sense of touch endows us with an exquisite sensitivity to surface texture. We can distinguish surfaces whose elements differ in size on the order of tens of nanometers and in inter-element spacing on the order of hundreds or nanometers. The perception of texture not only allows us to make fine discriminations - like telling real silk from fake silk - but also guides object manipulation. Indeed, our perception of the surface properties of objects informs how much grip force we apply on them: more force is required for slippery objects. One of the remarkable aspects of tactile texture processing is that it operates over 6 orders of magnitude in element sizes, from the smallest discernible elements (on the order of 10s of nanometers) to the largest elements that can fit on a fingertip, measured in tens of millimeters.
This wide dynamic range of tangible textures is made possible by the recruitment of different fibers, which encode textural features using different neural codes. Coarse textural features, on the order of millimeters, are most faithfully encoded in the spatial pattern of activation across one population of afferents. Fine features, on the order of micrometers, are not resolved by this spatial mechanism because the fingertip skin filters them out and because tactile afferents innervate the skin too sparsely. Rather, to perceive fine features, movement between skin and surface is necessary. Scanning a surface elicits texture-specific vibrations in the skin that in turn produce a characteristic temporal pattern of spiking in another population of tactile afferents; our

ability to perceive these fine features is mediated by these precisely timed spiking patterns. Furthermore, the frequency composition of the elicited vibrations, and in turn the neural responses, shifts systematically along the frequency axis with changes in scanning speed. While afferent responses are highly dependent on exploratory parameters, such as contact force and scanning speed, the perception of texture is highly invariant with respect to these parameters. Indeed, our perception of textural features, such as their roughness, stickiness, or softness is constant, independent of how fast a texture is scanned across the skin. The dependence of the peripheral neural signal on scanning and the invariance of perception with respect to it invites a comparison with timbre processing in the auditory system: Our perception of timbre is invariant with respect to pitch, even though the peripheral representation shifts systematically along the frequency axis with changes in pitch. Thus, similar neural mechanisms might underlie the processing of tactile texture and auditory timbre.

Disclosures: H.P. Saal: None. **J.D. Lieber:** None. **Z.M. Boundy-Singer:** None. **A.I. Weber:** None. **S.J. Bensmaia:** None.

Poster

842. Perception and Imagery: Perception and Related Predictions Across Different Modalities

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 842.02/KKK33

Topic: H.02. Human Cognition and Behavior

Support: Human Frontier Science Program project RG0015/ 2013

European Research Council Advanced grant CONCEPT

Italian MIUR grant HANDBOT

Title: Accumulation of vibrissal and neuronal evidence leads to texture decisions in rats

Authors: *M. E. DIAMOND, Y. ZUO;
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Abstract: Models of evidence accumulation and bounded integration appear to explain many forms of passive (receptive) sensing and decision making, such as judgment of visual motion direction. To find out whether this form of model also applies to active (generative) sensing, we measured whisker kinematics together with neuronal activity from primary (S1) and secondary (S2) somatosensory cortex while rats palpated textures to identify them. Rats show marked trial-to-trial variability in the number of touches (from 1 to 6) onto the discriminanda prior to

expressing their decision; we take this variability as a key to understanding the nature of information integration. The motor system might generate a plan that includes inherent variability: the number of whisks could be controlled by internal state, independently of sensory feedback. Alternatively, the rat may execute successive whisks until obtaining some threshold quantity of evidence, at which time it commits to a decision. We constructed a linear model that combines 9 kinematic features of whisker motion with optimal weights to specify, on average, the contacted texture. This allowed us to calculate the evidence provided per touch, for each candidate texture, according to the kinematics of that touch. By what integration algorithm might evidence be accumulated? To answer this, we computed total evidence per trial after weighting and accumulating single-touch evidence according to different models. The results support a model of summation by exponentially-weighted primacy (SEWP), where the weight applied to the evidence of each touch declines non-linearly from the first touch onwards. When integrated by SEWP, the total quantity of evidence per trial is found to be equivalent, independently of the number of touches on that trial. Other models lead to highly variable quantities across trials. To explore the neuronal accumulation of evidence, we recorded activity in S1 and S2 cortex. As was the case for whisker signals, neuronal signals accumulate over successive touches until reaching a decision threshold that varies little from trial to trial. These results suggest that the sensorimotor tactile system generates evidence until the accumulated knowledge is sufficient to support a well-grounded choice.

Disclosures: **M.E. Diamond:** None. **Y. Zuo:** None.

Poster

842. Perception and Imagery: Perception and Related Predictions Across Different Modalities

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 842.03/KKK34

Topic: H.02. Human Cognition and Behavior

Support: DFG SCHW577/10-2

Title: Whisker-based texture discrimination using near-instantaneous versus intensive codes

Authors: ***C. SCHWARZ**, M. OLADAZIMI;
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Abstract: Classically, texture discrimination has been thought to be based on spatial or temporal intensive codes, i.e. frequency (signal analysis based on spectral decomposition) or intensity (signal analysis based on averaging). Both classical coding schemes rely on integration of the

vibrotactile signal across time and/or space. Recently, an alternative coding scheme - the slip hypothesis - has been suggested based on the insight that frictional relative movement of a whisker across a texture complexly transforms a continuous 3D surface into a vibrotactile signal that is composed of a series of discrete short lasting kinematic events (i.e. stick-slip movements called slips). We have revisited biomechanical measurements of relative movements of a rat vibrissa across textures (sandpapers) of different roughness. We confirm the findings of Hipp et al., (J. Neurophysiol. 95:1792, 2006) that intensive codes convey some texture discrimination. However, we find that slip-based near-instantaneous code far exceeds the intensive code. Further, the intensive code, was found to be almost independent on velocity and distance. In contrast, the near-instantaneous code was found to clearly reflect these parameters, which are normally set by the behavioral choice of the whisking animal. That is, using a slip-based code the animal can control the discriminability of a given set of textures by using a different strategy of active touch. These findings compare well to the ability of rats to passively discriminate pulsatile stimuli when constraining them to use intensive codes vs. allowing them to use also the near-instantaneous code.

Disclosures: **C. Schwarz:** None. **M. Oladazimi:** None.

Poster

842. Perception and Imagery: Perception and Related Predictions Across Different Modalities

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 842.04/KKK35

Topic: H.02. Human Cognition and Behavior

Support: NSF Career IOS-1150209

Title: The coding of natural textures in primate somatosensory cortex

Authors: ***J. D. LIEBER**[1], H. P. SAAL[1], Z. M. BOUNDY-SINGER[1], A. I. WEBER[2], S. J. BENSMAIA[1];
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Abstract: Our ability to perceive texture by touch operates over six orders of magnitude, endowing us with the ability to discern surfaces whose elements vary in size from nanometers to millimeters. In the nerve, texture information is encoded in the responses of three populations of mechanoreceptive afferents, each sensitive to surface elements at different spatial scales. Furthermore, textural features are encoded in different ways depending on their scale: Coarse features are represented in spatial patterns of activation whereas fine features are represented in

temporal spiking patterns. How these separate peripheral representations are integrated in the central nervous system to achieve a unitary sensory experience of texture is unknown. Furthermore, while afferent responses are highly dependent on exploratory parameters, such as contact force and scanning speed, the perception of texture is highly invariant with respect to these parameters. Nothing is known about how this invariance is achieved.
In the present study, we sought to address these outstanding questions in texture coding by investigating the representation of texture in primary somatosensory cortex (S1). To this end, we scanned a large set of natural and artificial surfaces across the fingertip of awake Rhesus macaques while recording the responses evoked in single units in S1 (including Brodmann's areas 3b, 1 and 2). First, we found that S1 neurons carry rich information about texture in both the strength and temporal patterning of their responses. A subset of neurons exhibit a receptive field structure that is well suited to extract information about coarse textural features from spatially patterned afferent inputs. Another subset of neurons exhibit highly-precise texture-specific temporal spiking patterns that follow the high-frequency skin vibrations elicited during scanning of finely textured surface and seem to mirror the responses evoked in vibration-sensitive afferents. Second, we found that, while texture-specific temporal spiking patterns scale dilate or contract with decreases or increases in scanning speed, as is the case for nerve fibers. However, the firing rates of texture-evoked responses were constant across speeds, in contrast to their peripheral counterparts. The texture representation in S1 seems to constitute an intermediate stage in the construction of speed invariant texture representations.

Disclosures: J.D. Lieber: None. **H.P. Saal:** None. **Z.M. Boundy-Singer:** None. **A.I. Weber:** None. **S.J. Bensmaia:** None.

Poster

842. Perception and Imagery: Perception and Related Predictions Across Different Modalities

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 842.05/KKK36

Topic: H.02. Human Cognition and Behavior

Support: Wellcome Trust - DBT India Alliance

DBT-IISc Partnership Programme

Title: What can texture representations in monkey IT neurons tell us about human texture perception?

Authors: *Z. A. KALATHUPIRIYAN[1], S. P. ARUN[2];
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Abstract: Texture is a salient material attribute of objects in our world, yet texture perception and its underlying neural basis is poorly understood. Here, we set out to characterize how a large library of 480 natural textures are represented in human perception and at the level of single neurons in monkey inferotemporal cortex. To assess texture perception in humans, we asked subjects to perform visual search for one texture embedded in a field of images of another texture. To characterize texture representations at the neuronal level, we recorded from IT neurons in monkeys engaged in a fixation task. Our main goal was to understand whether texture processing in humans can be understood by sampling neuronal representations in monkey IT cortex. A second goal was to survey the ability of popular computational models to explain the neuronal and behavioral data. Our results are as follows: First, texture discrimination in humans was significantly correlated with texture discriminability in IT neurons, for both discrete textures (average r = 0.69) and natural textures (average r = 0.41); Second, a model based on statistical properties of textures yielded the best account of neuronal responses to natural textures that generalized to discrete textures as well. While model features themselves predicted human texture discrimination to some degree, the performance improved dramatically upon fitting model parameters to neural data (average r = 0.61). The fitted model parameters across neurons reflected a variety of statistical properties of textures. Taken together, our results show that texture perception in humans can be understood using neuronal representations in monkey IT neurons.

Disclosures: Z.A. Kalathupiriyan: None. **S.P. Arun:** None.

Poster

842. Perception and Imagery: Perception and Related Predictions Across Different Modalities

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 842.06/KKK37

Topic: H.02. Human Cognition and Behavior

Title: Measuring tactile roughness perception using 3D-printed parametric textures

Authors: *C. TYMMS[1], E. P. GARDNER[2], D. ZORIN[1];
[1]New York Univ., New York, NY; [2]New York Univ. Sch. of Med., New York, NY

Abstract: Roughness is one of the most important aspects of haptic perception. Roughness perception is a major identifier for judging material composition and is tied closely to judgments of comfort and friction and to aspects of manual dexterity, such as required grip force. Some attention has been given to perception of surface roughness in the past, but it has typically focused on non-controllable natural materials or on a narrow range of artificial materials. The advent of high-resolution 3D printing technology provides the ability to fabricate arbitrary 3D shapes with textures of precise surface geometry to be used in tactile studies. Using stereolithography 3D printing, we manufactured a variety of square plates with surface textures at a resolution of 50 μm. Textures varied in multiple controllable parameters: texture element spacing (varying in 0.0625 mm intervals) shape (0.1-0.5 mm, flat or rounded), and arrangement. We recruited subjects for two-alternative forced choice experiments to investigate the contributions of these parameters to roughness perception. In each trial, subjects felt two textured squares using the fingertips of digits 2 and 3 and indicated the smoother texture. Results indicated that larger spatial periods produce higher estimations of roughness (Weber fraction 0.31), and smaller texture elements felt rougher than large texture elements. Square-oriented textures felt smoother than randomly oriented textures, which in turn felt smoother than diagonally-oriented textures. Comparisons of textures varying in both wavelengths and shape suggested that equivalencies exist among textures differing along both of these parameters. These stimuli and the manufacturing process may be used in further studies of tactile roughness perception and in related neurological applications.

Disclosures: **C. Tymms:** None. **E.P. Gardner:** None. **D. Zorin:** None.

Poster

842. Perception and Imagery: Perception and Related Predictions Across Different Modalities

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 842.07/KKK38

Topic: H.02. Human Cognition and Behavior

Title: Markov-chain roving-like paradigm reveals bayesian surprise in somatosensory mmn

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Abstract: According to the *Bayesian coding hypothesis*, our brains represent sensory information not in a deterministic way, but as probability distributions (Knill & Pouget, 2004). In

fact, our sensory apparatus is assumed to perform Bayesian inference (BI) when faced with sensory uncertainty. Similarly, *predictive coding* proposes BI to be the core principle at work when the brain is making predictions about the world and reducing prediction errors (Friston & Kiebel, 2009). The mismatch negativity (MMN), a negative deflection of the EEG elicited by a deviant event following standard events studied mostly in the auditory domain, connects these hypotheses to sequential observations on a low sensory level in the absence of attention. Ostwald et al. (2012) found evidence for a somatosensory MMN (sMMN) expressing Bayesian surprise (BS) as calculated by the Kullback-Leibler divergence between prior and posterior distributions of stimulus probabilities. However, it remains unclear under what circumstances higher order statistical properties of sequences are processed in the somatosensory system, and if BS is a better proxy for the MMN than predictive surprise (PS; negative log prediction error). In our Markov-chain roving-like paradigm, 11 participants received continuous median nerve stimulation with 650 ms ISI using two stimulation intensities (2x and 3.5x sensory threshold) in four different transitional probability (TP) conditions while recording EEG. Condition A had a fixed TP of 0.5 for all transitions, while conditions B, C, and D switched with 1% probability between high (0.625, 0.75, 0.875) and low (1 - high) stimulus change probabilities. TP condition order was randomized across 8 stimulation blocks of 12 min duration. We instructed participants to ignore the stimulation and fixate on a cross in the middle of a screen while watching muted TV clips. For the ERP analysis, deviant stimuli are an intensity change after 3 identical stimuli, standards are the stimuli preceding the deviants. In accordance with other sMMN studies, we found a sMMN peaking 119 ms after stimulus presentation over right somatosensory cortex (FC2). Additionally, sMMN amplitude increased with larger TP differences over FC6 peaking at 134 ms. In a single-trial analysis using parametric empirical Bayes, we tested BS regressors on 0^{th} and 1^{st} order statistical properties of the sequences against PS. The BS model family explains trial-by-trial fluctuations in the MMN period better than PS. Since no properties of the sequence were task-relevant, BS is the simpler and more efficient model for the brain to process incoming information. Thus, we provide initial evidence for the sMMN as BS rather than PS.

Disclosures: **K. Tertel:** None. **D. Ostwald:** None. **F. Blankenburg:** None.

Poster

842. Perception and Imagery: Perception and Related Predictions Across Different Modalities

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 842.08/KKK39

Topic: H.02. Human Cognition and Behavior

Support: ERC-2013-StG-336050

Title: Prototype effects on the retrieval of location information in touch

Authors: *E. AZAÑÓN, R. D. FINZI, M. R. LONGO;
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Abstract: When remembering the location of a visual stimulus, accuracy is improved by averaging the metric estimate of the instance with a central prototypical value. Estimates made in this fashion are less variable, but will be biased toward the prototype. For instance, memories of the location of visual stimuli on a circle are biased towards the centroids of each quadrant (Huttenlocher, Hedges & Duncan, 1991, Psychological Review, 98, 352-76). It is unknown, however, whether spatial judgements of tactile events that occur on the skin are also influenced by prototypical information and whether this information reflects the distribution of exemplars within a set of items. To test this, participants had to remember the location of a touch on the dorsum of their hand, and reproduce this location on a lifesize silhouette of a hand. Each touch was presented for one second either with a light or an intense pressure, using a grid of landmarks approximately centred on the dorsum. To study the existence of biases towards prototypical information we had to cancel out any pre-existing distal bias, i.e., the fact that participants tend to perceive touch as being located substantially more distally than it actually is (Mancini, Longo, Iannetti, & Haggard, 2011, Neuropsychologia, 49, 1194-1201). To do so, we analysed the pattern of errors from the strong to the weak stimuli, under the assumption that the amount of bias would increase when the quality of the metric memory decreases, in accord with Bayesian principles (Huttenlocher et al., 1991, Psychological Review, 98, 352-76). Analyses of cosine similarity between localization errors from the strong to the weak stimuli and predicted errors towards prototypes confirmed a systematic pattern of bias towards the centre of the hand. In a second experiment, we changed the distribution of the targets on the hand, by using a triangle grid of landmarks centred either on the bottom left of the hand dorsum or on the top right of the hand dorsum. We found that location estimation was biased relative to the spatial distribution of target locations, showing a bias towards the centre of mass of the participant's responses. The results of this study reveal the use of prototypes in the location of tactile information from memory. It further reveals a key role of experience in location estimation by showing that prototypes are generated in real-time as opposed to be stored in memory.

Disclosures: E. Azañón: None. **R.D. Finzi:** None. **M.R. Longo:** None.

Poster

842. Perception and Imagery: Perception and Related Predictions Across Different Modalities

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 842.09/KKK40

Topic: H.02. Human Cognition and Behavior

Support: The Development of Medical Devices and Systems for Advanced Medical Services from Japan Agency for Medical Research and development, AMED

Title: Kinesthetic perception resulting from integration of kinesthetic illusion induced by tendon vibration and visual stimulus

Authors: *E. SHIBATA, F. KANEKO, R. TAKAHASHI, Y. ITAGUCHI;
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Abstract: Tendon vibrations mainly activate Ia-type afferents from muscle spindle primary endings and can cause a vivid kinesthetic illusion of limb movement. Visual stimuli can also induce a kinesthetic illusion. We investigated kinesthetic perception induced by perceptual integration. The purpose of this study was to investigate the velocity and direction of kinesthetic perception resulting from the integration of the kinesthetic illusion induced by afferent inputs from different types of sensory receptors. Twelve healthy young subjects participated in this study. Tendon vibration was applied to the right wrist extensor at 40, 60, or 80 Hz. Since the velocity of the illusory movement induced by tendon vibration depends on the vibration frequency, subjects perceived fast wrist flexion in accordance with a gradual increase in the vibration frequency. As visual stimulus, we produced a video imitating perceptual movement when the wrist extensor muscle was vibrated at 60 Hz, i.e., the velocity of perceived movements induced by the visual stimulus and tendon vibration at 60 Hz were equal, and not during vibration at other frequencies. The movie was displayed in an appropriate position on the subject's forearm (illusion) or in front of the subjects (non-illusion position). This study included the following three combined vibration-visual stimulus conditions with three vibration frequencies: visual stimulus at illusion position with vibration (V+IL), non-illusion position with vibration (V+nIL), and vibration alone (V). During each trial, the perceived movement sensations were quantified by measuring the velocity and direction of hand movement on the contralateral side. Furthermore, the ratio of the velocity in the V+IL and V+nIL conditions relative to the velocity in the V condition was calculated to evaluate degree of the perception to change by combination with the tendon vibration and visual stimulus. The average velocities of the perceived movement increased with increasing vibration frequency in all conditions. The ratio of the velocity in the V+IL condition to the V condition significantly changed depending on vibration frequency, while no significant change was observed in the ratio between the velocities in the V+nIL and V conditions. The present results show that the velocity of perceived movement resulting from the integration of a kinesthetic illusion induced by tendon vibration and visual stimulus differed with the magnitude of afferent inputs from the muscle spindle. Furthermore, even if it used the same visual stimulus, the change ratio of the velocity was different depending on whether the kinesthetic illusion was induced by a visual stimulus.

Disclosures: **E. Shibata:** None. **F. Kaneko:** None. **R. Takahashi:** None. **Y. Itaguchi:** None.

Poster

842. Perception and Imagery: Perception and Related Predictions Across Different Modalities

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 842.10/KKK41

Topic: H.02. Human Cognition and Behavior

Support: NIH Grant EY22428

Howard Hughes Medical Institute

Title: Opposing effects of summary statistics on peripheral discrimination

Authors: *C. M. ZIEMBA[1,2], E. P. SIMONCELLI[1,2];
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Abstract: A converging view of peripheral vision holds that the brain represents statistical summaries of visual content in local portions of the visual field, resulting in a loss of information that can explain the phenomenon of "crowding." Here, we show that such statistical representation can either help or hinder visual discrimination performance depending on the observer's task. We created synthetic texture stimuli by matching a set of higher-order statistics measured from natural photographs (Portilla & Simoncelli, 2000). Observers were asked to discriminate these stimuli windowed by apertures of different sizes and at increasing eccentricities. When observers compared images with different statistics, performance increased with increasing patch diameter. This is expected, since the parameters of the model converge to different values as the patch size increases. Interestingly, when observers compared different images with identical statistics, performance decreased as patch diameter increased. Specifically, as the statistics converge to their target values with increasing patch diameter, subjects were no longer able to utilize the local cues that enable high performance with small patch sizes. We found these opposing effects of patch size regardless of whether subjects discriminated simultaneously presented stimuli across space or sequentially presented stimuli across temporal intervals. These results are consistent with analogous effects observed for discrimination of auditory textures as a function of temporal window duration (McDermott & Simoncelli, 2013), and suggest a general processing strategy for sensory systems. Curiously, there was little effect of eccentricity on the pattern of discrimination performance, in contrast to the well known eccentricity-dependence of crowding. We show that both the opposing effects of stimulus size, and the relatively minor effect of eccentricity, are predicted by a model for the visual periphery in which higher-order statistics are computed within pooling regions that grow with eccentricity at the scale of V2 receptive fields (Freeman & Simoncelli, 2011). At increasing eccentricities, the decrease in the number of pooling regions responding to the stimulus is partially counteracted

by the stability of statistical summaries averaged over larger regions, resulting in a relatively modest effect of eccentricity on performance. Thus, we extend previous observations on peripheral vision by demonstrating that a simple model computing local statistical summaries can capture a complex pattern of human discrimination performance across different image sizes and eccentricities.

Disclosures: C.M. Ziemba: None. **E.P. Simoncelli:** None.

Poster

842. Perception and Imagery: Perception and Related Predictions Across Different Modalities

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 842.11/KKK42

Topic: H.02. Human Cognition and Behavior

Support: NIH Grant EY07977

Title: Simple combination rules for sensitivities to image statistics.

Authors: *J. D. VICTOR, S. M. RIZVI, M. M. CONTE;
Feil Family Brain and Mind Res. Inst., Weill Cornell Med. Col., New York, NY

Abstract: Natural scenes are typically complex and cluttered. Segmenting such images into components and characterizing their surface properties therefore depends on visual processing of image statistics. However, analyzing the underlying computations is hindered by the interdependencies of these statistics, and their extremely high dimensionality. To address these issues, we previously developed a dimensionally-reduced stimulus domain: a 10-dimensional space of binary (black-and-white) images in which contrast, edge, and corner could be varied independently. We found that first-, second-, third- and fourth-order image statistics were visually salient, and that a simple combination rule governed how pairs of image statistics combine. Here we take the first steps in extending these results to images with multiple gray levels and determine to what extent these findings generalize.
The stimulus domain is a set of synthetic images, parameterized by the probabilities of all configurations of black, gray, and white checks in 2x2 neighborhoods. The gray luminance value is halfway between black and white, as rendered on a calibrated monitor. As in the binary case, this stimulus domain probes image statistics of orders 1 through 4, but here in the ternary case there are 66 dimensions (2 first-order, 16 second-order, 32 third-order, and 16 fourth-order). Each of these dimensions corresponds to an image statistic, whose value ranges from -1 to 1; the origin of the space is the fully random texture. All first- and second-order statistics are visually

salient, but in contrast to the binary case, only some third- and fourth-order ternary statistics are visually salient. To quantify sensitivity to these statistics, we measured discrimination thresholds in a 4-alternative forced-choice segmentation task. Stimuli consisted of a 64x64 array of 14-min checks, with a 16x64 target in one of four possible locations. Thresholds were determined in N=2 subjects from Weibull fits to their psychometric functions. We examined sensitivities on 16 independent coordinate axes and in 8 selected planes, covering image statistics of orders 1 through 3. We found that (a) sensitivities to positive and negative values of an image statistic are very nearly equal, and (b) pairs of image statistics combine in an approximately quadratic fashion, yielding elliptical isodiscrimination contours. These simplifying features extend previous findings from the study of binary image statistics, and their applicability to ternary textures suggests that they will generalize to the complexity of natural scenes.

Disclosures: **J.D. Victor:** None. **S.M. Rizvi:** None. **M.M. Conte:** None.

Poster

842. Perception and Imagery: Perception and Related Predictions Across Different Modalities

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 842.12/KKK43

Topic: H.02. Human Cognition and Behavior

Support: NWO Rubicon grant 446-15-004

NWO VIDI grant 452-13-016

James S. McDonnell Foundation, Understanding Human Cognition, 220020373

Title: Prior expectations induce pre-stimulus sensory templates

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Abstract: Perception is heavily influenced by prior expectations. Accordingly, many theories cast perception as a process of inference, integrating bottom-up sensory inputs and top-down expectations (Lee & Mumford 2001, Friston 2005). However, it is unclear how this integration is neurally implemented. It has been proposed that expectations lead to baseline increases in sensory neurons tuned to the expected stimulus, which in turn leads to improved processing of matching stimuli (Wyart et al. 2012). In order words, expectations may induce stimulus templates in sensory cortex, prior to the actual presentation of the stimulus. Alternatively, top-

down influences in sensory cortex may exert their influence only after the bottom-up stimulus has been initially processed, and the integration of the two sources of information may become apparent only during later stages of sensory processing (Nienborg & Cumming 2009). The evidence necessary to distinguish between these hypotheses has been lacking. fMRI studies have revealed stimulus-specific patterns of activation in sensory cortex as a result of expectation (Kok et al. 2014), but this method lacks the temporal resolution necessary to distinguish pre- from post-stimulus periods. Here, we combined MEG with multivariate decoding techniques to probe the representational content of neural signals in a time-resolved manner (King & Dehaene 2014). We trained a forward model to decode the orientation of passively observed gratings from the MEG signal, and applied this decoder to trials in which participants expected a grating of a particular orientation to be presented. This analysis revealed a representation of the expected grating in the neural signal already before it was presented, demonstrating that expectations can indeed induce the pre-activation of stimulus templates. The fact that expectations could be detected by a decoder trained on physically presented gratings suggests that these expectation signals resemble activity patterns induced by actual stimuli. The expectation signal remained present throughout the trial, extending into the post-stimulus period, suggesting the tonic activation of a stimulus template. Recent theories of sensory processing state that perception reflects the integration of bottom-up inputs and top-down expectations, but ideas diverge on whether the brain continuously generates stimulus templates in sensory cortex to pre-empt expected inputs (Berkes et al. 2010), or rather engages in perceptual inference only after receiving sensory inputs (Bar et al. 2006). Current results are in line with the brain being proactive, constantly forming predictions about future sensory inputs.

Disclosures: **P. Kok:** None. **P. Mostert:** None. **F.P. De Lange:** None.

Poster

842. Perception and Imagery: Perception and Related Predictions Across Different Modalities

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 842.13/KKK44

Topic: H.02. Human Cognition and Behavior

Support: NIH Grant EY07977

NSF Grant PHY-1058202

Ann M Hermundstad, Ph.D., holds a Career Award at the Scientific Interface from BWF

Title: Local multipoint correlations support categorical classification of objects and backgrounds

Authors: ***A. M. HERMUNDSTAD**[1,2], T. TESILEANU[3], J. J. BRIGUGLIO[1], K. SLAVKOVA[1], S. M. RIZVI[4], M. M. CONTE[4], J. D. VICTOR[4], V. BALASUBRAMANIAN[1]; [1]Dept. of Physics and Astronomy, Univ. of Pennsylvania, Philadelphia, PA; [2]Janelia Res. Campus, Ashburn, VA; [3]Initiative for the Theoretical Sci., Grad. Center, City Univ. of New York, New York, NY; [4]Feil Family Brain and Mind Res. Inst., Weill Cornell Med. Col., New York, NY

Abstract: Parsing a visual scene relies on identifying and distinguishing between visual features that capture texture and shape. In recent work, we showed that a low-dimensional space of local image statistics can be used to capture visually-salient information about natural scenes. To demonstrate this, we identified a set of ten independent coordinates that capture local multipoint correlations between binarized pixels in an image. We found that these coordinates are informative about the ensemble of natural scenes, and the visual system is tuned to represent these coordinates in an efficient manner. In the present study, we ask whether, and to what extent, this low-dimensional space of image statistics is informative about segmentation and categorization. To this end, we analyze local image statistics that occur within different categories of natural and manmade objects and backgrounds. Images are taken from a database that has undergone automated and hand-curated segmentation. Each segmented image is divided into patches that lie fully within or fully outside an object boundary. We assign categorical classes to each image patch using a hierarchical class structure with three levels: (i) foreground/background, (ii) within-foreground: animate/manmade, and (iii) within-animate: mammals/birds/fish. At each level of the hierarchy, we analyze the statistics within each class by projecting the corresponding set of patches onto the ten-dimensional coordinate space. This projection assigns a specific set of coordinate values to each image patch in the ensemble. We then use linear discriminant analysis (LDA) to determine the hyperplanes that best separate classes. Using LDA, we find that classification error is significantly below chance within each level of the hierarchy, confirming that local image statistics can be used to discriminate between classes of objects and background. The direction of maximal discriminability (e.g. between foreground/background) differs from the direction of maximal informativeness about the ensemble of images, suggesting that the combinations of image features that are useful for categorization differ from those that are useful for segmentation. Together, these results show that local image statistics are informative about specific aspects of scene content, and they suggest that local processing could play an adaptable role in segmentation and categorization. If the visual system exploits this local information, then our results make specific, testable predictions about the perceptual spaces that are used for different visual tasks.

Disclosures: A.M. Hermundstad: None. **T. Tesileanu:** None. **J.J. Briguglio:** None. **K. Slavkova:** None. **S.M. Rizvi:** None. **M.M. Conte:** None. **J.D. Victor:** None. **V. Balasubramanian:** None.

Poster

842. Perception and Imagery: Perception and Related Predictions Across Different Modalities

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 842.14/KKK45

Topic: H.02. Human Cognition and Behavior

Support: BBSRC BB/H016813/1

Wellcome Trust / Royal Society WT098418MA

Royal Society RG2010R2

Title: The neural representation of timbre in auditory cortex

Authors: *J. K. BIZLEY, K. C. WOOD, T. ETHERINGTON, G. P. JONES, H. ATILGAN, S. M. TOWN;
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Abstract: Auditory timbre is the perceptual attribute that allows us to distinguish two musical instruments playing the same note, or two vowel sounds spoken by the same voice. Perceived timbre is influenced by both temporal features, in particular the onset dynamics of a sound, and spectral features, notably the spectral envelope. The identity of spoken vowels is determined by the position of energy peaks (formants) in the spectral envelope. Formants must be extracted independently of the underlying spectral details such as pitch or voicing which lead to variation in the way that the spectral envelope is sampled. In order to identify timbre-specific representations we have explored both neural and behavioural discrimination of spectral timbre across orthogonal sound dimensions. While previous work in naïve anesthetized animals demonstrated that spiking responses were frequently sensitive to spatial, pitch and timbral sound features (Bizley et al., 2009) in some neurons this information was temporally multiplexed potentially providing an unambiguous representation of any single feature (Walker et al., 2011). We hypothesized that (i) the neural representation of spectral timbre might show a greater tolerance across task-irrelevant acoustic features in animals engaged in a task than when animals that are not actively processing such sounds and (ii) neural decoding of timbre would mirror animals' behavioral performance.
We trained ferrets in a two-alternative forced choice vowel identification task and determined that, like human listeners, they were able to identify vowels across variation in sound level, pitch, spatial location, background noise and voicing. Neural activity was recorded from tonotopic auditory cortex in freely moving animals while they were actively discriminating such sounds. To determine how information about sound timbre was represented, we decoded neural activity while systematically varying the duration and onset time of the analysis window in order

to ascertain the timecourse of maximal information about both the task relevant feature (vowel identity) and task irrelevant features (level, pitch, location, background noise, voicing). Supporting our hypothesis, individual units were capable of encoding vowel identity across orthogonal stimulus dimensions. We compared the decoder parameters that best decoded each stimulus feature and observed that across the population of recorded units timbre information was decoded earlier than pitch information. Varying signal-to-noise ratio and noise structure provided evidence for our second hypothesis with neural and behavioral decoding ability showing similar performance impairments.

Disclosures: **J.K. Bizley:** None. **K.C. Wood:** None. **T. Etherington:** None. **G.P. Jones:** None. **H. Atilgan:** None. **S.M. Town:** None.

Poster

842. Perception and Imagery: Perception and Related Predictions Across Different Modalities

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 842.15/KKK46

Topic: H.02. Human Cognition and Behavior

Support: NSF STC award CCF-1231216 to the CBMM

Title: Lossy compression of sound texture by the human auditory system

Authors: ***W. F. MLYNARSKI**, J. H. MCDERMOTT;
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Abstract: Recent work has found that human sensitivity to the temporal detail of sound textures (as generated by rain, fire, swarms of insects etc.) decreases with the stimulus duration. This observation implies that after the first few hundred milliseconds following stimulus onset, the detailed structure of texture sounds is not retained by the auditory system. Instead, it seems to retain a lossy, compressed representation consisting of a set of time-averaged statistics. This result might be considered surprising given the known temporal precision of the auditory system and its ability to encode fine temporal variation of sound. The teleological question of why certain sounds have such a coarse perceptual representation remains open. One possible explanation is that the auditory system compresses stimuli when they exceed its informational bandwidth. Insensitivity to the temporal detail of sound could thus reflect a physical limit of the auditory system to transmit sensory information above a certain rate. Here we consider an alternative explanation motivated by a normative perspective. We assume that the goal of the auditory system is to maximize information about the environment while minimizing energy

expenditure. To achieve this goal the system should decrease encoding accuracy of stimuli which carry little information about the state of the environment. Stimuli originating from a known and predictable distribution would therefore be compressed, losing information about the waveform detail because it conveys no new information about the distribution parameters. Auditory textures are a prime candidate for such compression because their statistical properties are typically stationary over time. In order to distinguish between the two hypotheses we dissociated waveform coding cost (entropy, i.e. "density") from stationarity, introducing practical measures of these properties in order to quantify them in natural sounds. In a psychophysical study we found that sound source stationarity, rather than entropy rate, was predictive of human performance in an exemplar discrimination task. Sounds generated by a homogenous source seem to be compressed by the auditory system (impairing exemplar discrimination) regardless of their entropy rate, indicating that compression is not primarily due to coding capacity limits. In a second experiment we found that human listeners are sensitive to the temporal detail of unexpected sounds even if they are high-entropy. Taken together, the results suggest that perceptual compression of auditory textures reflects an adaptive coding strategy that minimizes neural resources when representing uninformative stimuli.

Disclosures: W.F. Mlynarski: None. **J.H. McDermott:** None.

Poster

842. Perception and Imagery: Perception and Related Predictions Across Different Modalities

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 842.16/KKK47

Topic: H.02. Human Cognition and Behavior

Support: the Max Planck Society

Title: The effect of music on resting-state fMRI

Authors: *Z. LIN[1], E. WENGER[2], S. KÜHN[2,3];
[1]Psychology, Univ. of Michigan, Ann Arbor, MI; [2]Max Planck Inst. for Human Develop., Berlin, Germany; [3]Univ. Clin. Hamburg-Eppendorf, Hamburg, Germany

Abstract: Previous studies have shown that different mental states may produce differences in signal changes in fMRI resting state. We investigated the effects of listening to different types of music on 5 min resting state fMRI. We tested 29 adults (18-28 years old), each measured with MRI over two consecutive time points, approximately 12 weeks apart. Participants were musicians recruited in Berlin, Germany. At each time point, all participants underwent 3 resting

state conditions: no music, listening to a piece by Johann Sebastian Bach (classical), and listening to a piece by Anton Webern (atonal). The fMRI images were preprocessed and analyzed by using the DPARSF toolbox v3.1, focusing on regional homogeneity (ReHo). The patterns of ReHo were consistent for the two time points, that is, there was no change over time in how participants listened to the musical pieces. We observed similar patterns of ReHo in Bach conditions compared to the no music condition. Interestingly, participants showed significantly higher ReHo in bilateral temporal regions when listening to the atonal compared to the classical piece (left superior temporal gyrus, peak MNI coordinate -45 30 9, 516 voxels in this cluster; right superior temporal gyrus, peak 54 -15 3, 696 voxels; $p < 0.05$, with FDR correction). One may suspect that, compared to the "more typical" or culturally well-known music of Bach, the very unusual, atonal music of Webern elicits a stronger, or more intense listening response indicated by more coherence in auditory cortex.

Disclosures: **Z. Lin:** None. **E. Wenger:** None. **S. Kühn:** None.

Poster

842. Perception and Imagery: Perception and Related Predictions Across Different Modalities

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 842.17/KKK48

Topic: H.02. Human Cognition and Behavior

Title: The dissociation of global and local auditory regularity perception with fluctuations in conscious vigilance

Authors: *R. M. GIBSON[1], A. M. OWEN[2], D. CRUSE[3], T. A. BEKINSCHTEIN[4]; [2]Psychology, [1]Univ. of Western Ontario, London, ON, Canada; [3]Sch. of Psychology, Univ. of Birmingham, Birmingham, United Kingdom; [4]Psychology, Univ. of Cambridge, Cambridge, United Kingdom

Abstract: The beat of a musical rhythm refers to a regularly recurring pulse that is perceived by the listener. Finding the beat in a musical rhythm is a psychological process that most humans perform naturally. In fact, humans often generate spontaneous movements in time with the beat, such as foot tapping or head nodding. To perceive and respond to the beat of a musical rhythm, one must identify the temporal structure based on auditory input and then synchronize motor responses with that structure. The auditory predictive coding framework postulates that neocortex generates predictions about upcoming sounds using the transitive probabilities of past sounds. While fluctuations in conscious vigilance disrupt predictive coding for some sound patterns, beat perception can occur pre-attentively for other sound patterns. We examined

cortical prediction error signals at the time of the beat in simple auditory rhythms from a sample of 20 healthy volunteers. Using event-related potential markers of global prediction errors, it was observed that beat perception was abolished by a stream of competing visual stimuli and fluctuations in vigilance immediately prior to sleep onset. However, event-related potential markers of early auditory processing, sensory response adaption, and local prediction errors were relatively preserved regardless of vigilance. These findings suggest that the perception of higher-order sound patterns requires conscious vigilance, but that local auditory regularity detection continues even when vigilance is disrupted.

Disclosures: **R.M. Gibson:** None. **A.M. Owen:** None. **D. Cruse:** None. **T.A. Bekinschtein:** None.

Poster

842. Perception and Imagery: Perception and Related Predictions Across Different Modalities

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 842.18/KKK49

Topic: H.02. Human Cognition and Behavior

Support: Marie Curie International Outgoing Fellowship within the 7th European Community Framework Programme

Human Frontier Science Program Long-term Fellowship (LT001118/2012-L)

MH103814

Title: Tracking "what" predictions across the auditory processing hierarchy

Authors: ***L. MELLONI**[1,2], C. M. SCHWIEDRZIK[3], T. THESEN[1], W. DOYLE[1], O. DEVINSKY[1], W. SINGER[2], C. E. SCHROEDER[4,5];
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Abstract: The brain relies on predictions based on internal models derived from past experience to decode and rapidly respond to the noisy sensory input that it receives. Despite the critical role of predictions in perception and action, their implementation in the human brain remains poorly understood. A likely mechanism for the implementation of predictions about the content of upcoming inputs (“what” predictions) is the modulation of prestimulus activity. This could operate across brain areas/processing levels, selectively synchronizing the pool of neurons

coding for the predicted stimuli, amplifying and sharpening evoked responses to predicted stimuli. In addition, such "priming" of evoked responses may improve information transmission to higher order areas such that predicted stimuli are transmitted faster. Thus, across the processing hierarchy, predictions could have several different effects on stimulus processing and representation. We tested how "what" predictions are instantiated in the auditory processing hierarchy in ten epilepsy patients undergoing intracranial ECoG monitoring. "What" predictions were provided to the subjects through cross-modal associative learning. A sequence of visual stimuli predicted the occurrence of auditory syllables; this was contrasted with a condition in which visual stimuli did not predict the syllables. We observed significantly faster reaction times when subjects could anticipate the auditory stimuli, as well as higher error rates and slower reaction times when predictions were violated. We also found increased prestimulus activity in the high gamma (HG) band in the superior temporal gyrus (STG) when subjects could anticipate which syllable would be presented, accompanied by increased HG stimulus-evoked activity in the pSTG. In higher order areas, e.g., the supramarginal gyrus (SMG), we observed a shift in response latencies, with shorter latencies for predicted than for unpredicted stimuli. Together, these findings suggest that "what" predictions take effect by organizing the temporal structure of neural activity during the pre-stimulus period, which in turns amplifies stimulus-evoked activity, thereby improving transmission and extraction of information.

Disclosures: **L. Melloni:** None. **C.M. Schwiedrzik:** None. **T. Thesen:** None. **W. Doyle:** None. **O. Devinsky:** None. **W. Singer:** None. **C.E. Schroeder:** None.

Poster

842. Perception and Imagery: Perception and Related Predictions Across Different Modalities

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 842.19/KKK50

Topic: H.02. Human Cognition and Behavior

Title: Music-induced attentional enhancement during visual perceptual tasks

Authors: *A. HEWETT[1], B. MORILLON[2];
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Abstract: Music is a potent phenomenon, likely to impact cognition in various ways (Salimpoor et al., 2013). Why some types of music tend to induce a relaxing state while some other helps us focus remains an open question. In this study we investigated attentional enhancement induced by music listening. We first tested whether music listening could enhance attentional focus during basic visual tasks, and second whether this enhancement depended on the presence of

amplitude modulations in melodies. This hypothesis is based on multiple assumptions: First, large-scale neuronal networks composing the human brain are characterized by frequency-specific neuronal oscillations (Siegel et al., 2012). Second, neuronal oscillations can be entrained by auditory stimuli, and frequency-specific entrainment is observed when manipulating the temporal dimension of the acoustic signal (i.e. amplitude-modulation; (Schroeder and Lakatos, 2009)). The resulting idea is that amplitude modulations present in melodies are key parameters to entrain a specific neuronal network, hence induce a specific cognitive state. We estimated attentional focus on three behavioral reaction time tasks performed by 17 participants: A simple detection task, a go/no-go task, and a pattern recognition task. For each task we tested three conditions: silence; listening to a melody with amplitude modulations; and to a placebo melody. These were computer generated by Brain.fm, software that can generate music with or without modulations. Tasks and conditions were counter-balanced across participants. For each experiment we observed significant differences across the three conditions. These results indicate that music, and especially music with amplitude modulations, has a positive impact on attentional focus. We conclude that neuronal entrainment by music is a good strategy to induce specific cognitive states, and propose that the manipulation of amplitude modulations in melodies is a key factor to obtain optimal results. **References** Henry MJ, Herrmann B, Obleser J (2014) Entrained neural oscillations in multiple frequency bands comodulate behavior. Proc Natl Acad Sci USA. Salimpoor VN, van den Bosch I, Kovacevic N, McIntosh AR, Dagher A, Zatorre RJ (2013) Interactions between the nucleus accumbens and auditory cortices predict music reward value. Science 340:216-219. Schroeder CE, Lakatos P (2009) Low-frequency neuronal oscillations as instruments of sensory selection. Trends in Neurosciences 32:9-18. Siegel M, Donner TH, Engel AK (2012) Spectral fingerprints of large-scale neuronal interactions. Nat Rev Neurosci.

Disclosures: **A. Hewett:** None. **B. Morillon:** F. Consulting Fees (e.g., advisory boards); Research Contractor.

Poster

842. Perception and Imagery: Perception and Related Predictions Across Different Modalities

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 842.20/KKK51

Topic: H.02. Human Cognition and Behavior

Support: R01NS065395

Title: Simultaneous measurements of BOLD fMRI activity in the Superior Temporal Sulcus and behavior during perception of the McGurk effect

Authors: *J. RENNIG, M. S. BEAUCHAMP;
Neurosurg., Baylor Col. of Med., Houston, TX

Abstract: Speech is the most common form of human communication and is fundamentally multisensory: observing the mouth of the talker allows us to identify otherwise ambiguous auditory information. A powerful demonstration of the multisensory nature of speech is the illusion discovered by McGurk and MacDonald (1976) in which the combination of incongruent different auditory and visual syllables evokes the percept of a completely different syllable. Recent evidence suggests that there are large interindividual differences in the McGurk effect, with some low-susceptibility subjects who never perceive the illusion and some high-susceptibility subjects who always perceive it (Basu Mallick et al., 2015). BOLD fMRI studies have demonstrated a correlation between the amplitude of responses in the superior temporal sulcus (STS) and McGurk susceptibility in both adults (Nath & Beauchamp, 2012) and children (Nath, et al., 2011). However, these studies did not require subjects to report their perception in the MR scanner and instead measured McGurk susceptibility in a separate behavioral session. In the present study, we addressed this deficiency by simultaneously measuring brain activity and behavior. Subjects viewed McGurk and control stimuli from two talkers and reported their percept with a button press. This allowed us to sort trials in which subjects perceived the illusion from trials in which they did not.
Across individuals (N = 8), there was a positive correlation between each subject's degree of McGurk susceptibility and the amplitude of the response in that subject's STS. However, this relationship was observed only for trials on which the McGurk effect was perceived ($r = 0.35$). In trials on which the effect was not perceived, there was no cross-subject correlation between susceptibility and amplitude of STS response ($r = -0.01$). A possible explanation for this finding is eye movements. Previous studies have demonstrated that subjects who are susceptible to the McGurk effect are more likely to fixate the mouth of the talker (Gurler et al., 2015). The talker's mouth movements would then be expected to evoke large responses in the STS. In contrast, subjects who are less susceptible to the effect are more likely to fixate the eyes of the talker (which do not make obligatory movements during speech production) resulting in smaller evoked responses in the STS; a similar process could occur in trials in which the illusion is or is not perceived. To test this idea, it will be necessary to record the eye movements made in response to McGurk stimuli while measuring BOLD fMRI activity.

Disclosures: J. Rennig: None. **M.S. Beauchamp:** None.

Poster

842. Perception and Imagery: Perception and Related Predictions Across Different Modalities

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 842.21/KKK52

Topic: H.02. Human Cognition and Behavior

Support: DFG GL 342/3-1

BMBF 01EO0901

Title: Angular distance reproduction using multimodal sensory information

Authors: *S. GLASAUER[1], J. BAYER[1], J. YUDICE[1], C. J. BOCKISCH[2];
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Abstract: When we turn around, multimodal sensory input from vestibular, visual, or other self-motion cues is used unconsciously to estimate our turning distance. We have previously shown for unimodal input that prior knowledge dynamically acquired during the course of an experiment is used to improve estimation in magnitude reproduction (Petzschner & Glasauer, J Neurosci 31, 2011; Petzschner et al., TICS 19, 2015). This dynamic estimation process causes systematic error patterns known as regression effect. However, from unimodal experiments it cannot be decided whether prior knowledge is modality-dependent or amodal. We therefore conducted a distance reproduction experiment in 12 human participants on a rotating chair (Tönnies, Acutronic) with three different production conditions: visual-only, vestibular-only, and matching visual-vestibular (5 distances 50-130 deg, max. angular velocity 25 deg/s, 180 trials per condition). Reproduction was always performed with matching visual-vestibular input, i.e., under the putatively best possible condition. Depending on whether participants are able to fuse multimodal inputs, we expected different patterns of regression effects in the three conditions. Predictions were done using normative Bayesian modeling. We found that only about half of the participants successfully fused visual and vestibular cues so that the overall variability was reduced when compared to the unimodal conditions. The remaining participants were either only able to use and reproduce one sensory input, or averaged between the two inputs, as if both inputs were caused by different sources of information. Our results show that visual-vestibular fusion is not a must, not even for stimuli in a natural range of distances and durations.

Disclosures: **S. Glasauer:** None. **J. Bayer:** None. **J. Yudice:** None. **C.J. Bockisch:** None.

Poster

842. Perception and Imagery: Perception and Related Predictions Across Different Modalities

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 842.22/KKK53

Topic: H.02. Human Cognition and Behavior

Support: NSFC 91232725

NSFC 81330032

Title: Motor systems are involved during imaging composition of music

Authors: *J. LU, H. YANG, C. LUO, D. YAO;
UESTC, Sichuan, China

Abstract: Introduction. Until now, several studies have focused on the neural effects of creating music as a model to discover the relationship between creativity and the human brain, however, they only focus on pianists in previous studies (Bengtsson et al. 2007, Limb et al. 2008, Donnay et al. 2014). As we know, performance and composition are two different stages in the creation of music. Pianists are performers, who usually create music through experiences of playing piano. As a result, motor systems in their brains were always reported to be activated. In order to test whether motor systems are involved during a purely form of music composition, we recruited 28 musical composition majors and subjected them to fMRI scan. **Subjects.** 28 composers (15 females, the average age is 20 years old), from the Department of Composition, Sichuan Conservatory of Music participated in this experiment. They were all right-handed according to the Edinburgh Inventory with normal hearing, normal vision, and no history of neurological disorders. **Tasks.** All the subjects were asked to imagine composing several pieces of music according to the cues under different instructions, which were programmed by E-prime 2.0 (Psychology Software Tools, Inc., USA). The tasks included composing 10 pieces of music with a familiar cue and composing 20 pieces of music with an unfamiliar cue. **Image data acquisition.** The musical composition task scan were conducted on a 3T magnetic resonance imaging (MRI) scanner (GE Discovery MR750, USA) at the MRI Research Center of University of Electronic Science and Technology of China (UESTC). All the subjects participating in the experiment gave informed consent before the experiment was conducted according to the established guidelines of the Ethics Committee of School of Life Science and Technology at UESTC. **Results.** The generalized linear model was used to calculate the activated brain areas during the imaging composing task. We find that composing with both familiar and unfamiliar cues can activate the left supplementary motor area. Additionally, compared to the condition of composing with familiar cues, bilateral precentral cortex and cerebellum are activated during composing with unfamiliar cues. **Conclusions.** These findings indicate that the motor systems

are involved during imaging composition by composers, which can help us to unravel the creative activity of music.

Disclosures: **J. Lu:** None. **H. Yang:** None. **C. Luo:** None. **D. Yao:** None.

Poster

842. Perception and Imagery: Perception and Related Predictions Across Different Modalities

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 842.23/KKK54

Topic: H.02. Human Cognition and Behavior

Support: SNSF project no 105314_124572/1

NCCR 51NF40-104897—D.G

Title: Functional connectivity of human voice-sensitive brain areas

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Abstract: The organization of the human cortex evolved toward a functional specialization of distributed brain regions, and the superior temporal cortex was found to preferentially respond to human voice stimuli. In the present work, we investigated functional connectivity between/within temporal voice areas in order to better understand the role of the voice-sensitive brain network as a whole in the perception of human voices. A total of 98 participants underwent a block-design (8sec blocks) fMRI procedure during which they listened to vocal (47 speakers; speech or non-speech) and non-vocal (natural sounds, human environment, musical instruments) auditory stimuli at a constant sound pressure level of 70dB. Regarding whole-brain data analysis, vocal > non-vocal events revealed expected clusters of activation within the bilateral inferior/mid/superior parts of the temporal cortex (TC), as well as bilaterally in the amygdalae, putamen, medial geniculate body, medial dorsal nucleus, dorso-lateral prefrontal cortex and inferior/superior frontal cortex. Non-vocal > vocal events revealed strong activations bilaterally in the parahippocampal gyrus and the dorso-lateral prefrontal (DLPFC) and anterior cingulate cortex (ACC). Whole-brain regions (N=26) were then used as regions of interest (ROI) for functional connectivity analyses revealing high positive functional connectivity between bilateral

TC regions and inferior frontal cortices as well as negative connectivity with the parahippocampal gyrus (seed-to-voxel analyses). Left/right parahippocampal gyrus activity interestingly led to negative connections with posterior TC, inferior frontal cortex and amygdala (Seed-to-voxel analyses) besides strong negative connections with the left DLPFC and positive connectivity with the right DLPFC and ACC (Seed-to-seed analyses; N(ROIs)=26). While the existence of human temporal voice areas is already well known, our specific connectivity analyses revealed crucial ties between the bilateral temporal and inferior/dorsolateral frontal cortex and the amygdalae. Moreover, our specific analyses using input-ROIs from both vocal and non-vocal events highlighted a crucial yet poorly known player in voice perception, namely the parahippocampal gyrus. In fact, while recent voice-related studies focused on temporal voice areas, the parahippocampal gyrus seems to contribute to voice perception in a fundamental way by having feed-forward and/or feedback functional connectivity with dorsal/inferior frontal (positive and negative connections) and mid/posterior temporal brain areas (negative connections).

Disclosures: **L. Ceravolo:** None. **E. Scariati Jaussi:** None. **S. Frühholz:** None. **D. Van De Ville:** None. **D. Grandjean:** None.

Poster

842. Perception and Imagery: Perception and Related Predictions Across Different Modalities

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 842.24/KKK55

Topic: H.02. Human Cognition and Behavior

Title: Cognitive processes of familiar and novel tastes.

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Abstract: In various sensory modalities, subjects are unable to process all the information available, leading to a situation where sensory input overflows the cognitive processing (Block 2011, Lau and Rosenthal 2011). Language, which is an integral part of human cognition, cannot represent all the information available in sensory input. It is known that the performance of recognition in subjects generating a detailed memory-based description of nonverbal stimuli is worse than controls participating in the recognition task without verbal description (verbal overshadowing, Schooler and Schooler 1990, Melcher and Schooler 1996). Perceptual discrimination is fundamental in forming adaptive patterns of behavior in the presence of sensory inputs. It is interesting to study how the human brain conducts efficient cognitive processes in

the presence of an overflow of sensory input.
In human vision, where the visual field is massively parallel in nature, it is well established that the cognitive processes fail to register salient changes in the visual environment (e.g. inattentional blindness, Mack and Rock 1992; change blindness, Simons and Levin 1997). It is of interest to study the nature of cognition in more "compact" sensory modalities such as taste, where the sensory input occurs in the topologically compact space of the mouth.
In order to study the nature of cognitive processes of taste, depending on and independent of verbal description, it is significant to compare the effects of familiar and novel stimuli. Anecdotal evidence suggests that the first experience of beer is just bitter and unfavorable for most people. Repetition is known to induce accelerated change of hedonic response to a taste (Rozin & Vollmecke 1986), where the direction of the change (i.e. positive or negative) has been shown to be unpredictable (Kahneman & Snell 1992). Repetition can be the source of false memory (Loftus & Pickerell 1995).
Here we study the cognitive process of preference, verbal description, and memory in the taste of drinks. The subjects were instructed to taste several commercially available popular drinks, as well as "cocktails" of those drinks designed to make novel flavors,
conducting recognition tasks with or without verbal description. We analyzed how the cognitive system establishes the uniqueness of a taste through repetitive experience and comparison, with possible distortion introduced by verbal description. We analyzed any possible effects of shared experience (e.g. Boothby et al. 2014), where the subjects tasted the drinks (familiar and/or novel) in the presence of other subjects.

Disclosures: A. Onzo: None. **K. Mogi:** None.

Poster

842. Perception and Imagery: Perception and Related Predictions Across Different Modalities

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 842.25/KKK56

Topic: H.02. Human Cognition and Behavior

Support: Kobayashi International Scholarship Foundation

Title: Molecular complexity influences olfaction to mixed odorants compared to component odorants

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Abstract: What makes the change of the olfactory note of an odorant if it mixed by another odorant? Some pairs of odorants are perceived by maintaining the original odors of their components, whereas others are perceived as new odors. However, the determinants of this change in perception from individual odorants to novel mixture-based odorants have not been elucidated. Odorants bind to olfactory receptors based on the structure of odorant molecules. Therefore, we hypothesized that the molecular complexity of odorants is critical to determining perception as either original or new odors. In order to test this hypothesis, we performed a psychophysical experiment investigating the relationship between complexity and perception. Fourteen participants (8 women) with normal olfaction completed our experiment. The molecular complexities of odorants were obtained from an open database of chemicals, Pubchem. We categorized odorants into 3 groups, based on complexity scores: low (<50), moderate (~100), and high (>150). Each group included 4 odorants. Four odorants were selected for each group, resulting in 6 combinations of 2 odorants. The intensity of each odor component was equivalent. Olfactory perceptions evoked by the odorants were listed based on reference to the Sigma Aldrich database. Participants were asked to select more than 4 odors from the list for each mixture. In order to examine alterations in the perceived odors, we counted the number of participant matches to the Sigma Aldrich database. We defined olfactory validity as the ratio of the number of odors that were congruent with the database, divided by the number of notes listed by participants. For further confirmation of the reproducibility of olfaction, we also examined whether participants indicated the same odors after 24 h.
We found that olfactory validity significantly decreased for mixtures composed of the moderate group compared to the other groups. However, we found no significant differences between groups for olfactory reproducibility. Therefore, our findings support the hypothesis that the molecular complexity of odorants is critical to determining whether an odor is perceived as original or new.
Grant: Kobayashi International Scholarship Foundation

Disclosures: **M. Hamakawa:** None. **T. Okamoto:** None.

Poster

843. Language in Normal and Damaged Brains

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 843.01/KKK57

Topic: H.02. Human Cognition and Behavior

Support: Agence Nationale de la Recherche (France)

Fondation Roger de Spoelberch (France)

Fondation Bettencour Schueller (France)

Title: Neurophysiological dynamics of phrase structure building operations during sentence reading

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Abstract: Although sentences unfold one word at a time, most linguistic theories agree that the proper description of language structures is not a linear sequence of words, but a tree structure of nested phrases. Yet this description remains a theoretical construct with neurophysiological underpinnings that have never been directly observed. Here we demonstrate intracranial neurophysiological evidence for the construction of such structures in the left hemisphere language network. Epileptic patients implanted with electrodes volunteered to perform a meaning-matching task of sentence pairs presented word-by-word using Rapid Serial Visual Presentation. Sentences of 3 to 10 words in length were automatically generated with a range of varied syntactic structures across sentences. Patients were asked to compare the meaning of the sentence to a second sentence presented after a 2-second delay. We analyzed the time-dependent broadband high gamma power (70 to 150 Hz), which is considered to be a reliable marker of the overall activation rate of the local neuronal population near the recording site. For electrodes located in key parts of the left hemisphere language network, particularly the left temporal pole (TP) and anterior superior temporal sulcus (aSTS), broadband high gamma power gradually builds-up with each successive word in the sentence. This built-up activity then collapses following moments when these words can be unified into a constituent phrase, and then builds-up again with the presentation of additional words in the next phrase of the sentence. This activity corresponds to the number of open nodes of a syntactic tree that could be built to represent the sentence, which we propose is reflected in this activity. Simultaneously, when these constituent unification events occur, electrodes in the left inferior frontal gyrus (IFG) and posterior superior temporal sulcus (pSTS) show a transient activation separate from the effect of tracking of open nodes, with a magnitude that increases with the number of nodes being closed. This may reflect constituent structure building operations associated with the closing of the open nodes in the tree structure. We compare the data to precise computational linguistic models and find that the data most closely matches the operations of models of bottom-up parsing that can be implemented using push-down automata to parse incoming language into syntactic trees. We suggest that neural activity in the left-hemisphere language network reflects the sequence of steps leading to the formation of phrasal structures in this manner.

Disclosures: **M.J. Nelson:** None. **I. El Karoui:** None. **K. Giber:** None. **L. Cohen:** None. **S. Cash:** None. **J. Parvizi:** None. **L. Naccache:** None. **J. Hale:** None. **C. Pallier:** None. **S. Dehaene:** None.

Poster

843. Language in Normal and Damaged Brains

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 843.02/KKK58

Topic: H.02. Human Cognition and Behavior

Support: Simons Collaboration on the Global Brain Award from the Simons Foundation

R01DC05660

Title: Multimodal sensory-motor transformations for speech

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Abstract: Linking sensory and motor processes is one of the core computations of the brain. Sensory-motor transformations link incoming sensory information to outgoing motor actions and can also enable unified access to higher order cognition. This type of interactive neural computation is particularly important for speech as it exists in the sensory domain as auditory (listening) or visual (reading) perception, and in the motor domain as speech production (speaking). Despite the importance of this linkage, it is unclear how these two distinct speech sensory perceptual processes are integrated with speech motor production. Here, using magnetoencephalography (MEG) we investigate multimodal sensory-motor speech transformations while participants performed a delayed word repetition task. The words were presented either auditorily or visually to assess the integration of different sensory modalities. We find that motor cortex activation was present during speech production, auditory cortex during auditory-sensory processing, and visual cortex for reading-sensory processing. Interestingly, we find that the superior temporal gyrus (STG) and the inferior frontal gyrus (IFG) were active for auditory input, visual input, as well as motor output. These results further establish the role of the speech sensory-motor system for speech integration and supports a privileged role of the STG and IFG in integrating multimodal speech input with speech motor output. These results also suggest that the sensory-motor speech system can be divided into

sensory specific and abstract processing streams. Taken together, the speech sensory-motor system may help form the basis for different levels of speech representation.

Disclosures: **G.B. Cogan:** None. **J. Viventi:** None. **D. Poeppel:** None. **B. Pesaran:** None.

Poster

843. Language in Normal and Damaged Brains

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 843.03/KKK59

Topic: H.02. Human Cognition and Behavior

Support: DFG Grant, SFB 673

DFG Grant, EXC 277

Title: Response-related readiness potential to speech preparation

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Abstract: In a spoken dialogue, speaker change (turn-taking) is mostly adjusted very efficiently avoiding both, long gaps or overlapping speech. We investigated the process of spoken response-utterance preparation and its temporal aspects in turn-taking by measuring the EEG readiness potential (RP) of speech articulation. We manipulated two variables: 1) the cognitive load of the question-answer-dialogue for response preparation and 2) the number of syntactic completions points of the stimulus questions leading to an earlier or delayed response preparation. The question was whether the RP-onset is more related to the actual motoric speech preparation process or the pure intention to speak after turn-anticipation. We conducted an EEG experiment with 30 right-handed healthy participants (17 f, 20-35 y) listening to 25 interrogative clauses that varied from 1300 ms to 6643 ms in length (O = 3989 ms). Our finding indicates that 1) participants did not already intend to respond at an early syntactic completion point within the stimulus-question, and 2) undelayed answers (simple questions) and delayed answers (more difficult questions) are accompanied by the same RP-onset time to response-onset interval. This indicates that the RP-onset is more related to the actual speech preparation process than the pure intention to speak.

Disclosures: **H.M. Mueller:** None. **H. Wesselmeier:** None.

Poster

843. Language in Normal and Damaged Brains

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 843.04/KKK60

Topic: H.02. Human Cognition and Behavior

Support: UK Medical Research Council Grant G0300117/65439

Title: Emergence of cognitive, language and motor deficits associated with structural brain abnormalities in an infant with the FOXP2 mutation

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Abstract: Introduction *FOXP2* is the first gene to be identified as critical for speech and language development. The KE family is a large pedigree in which half the members are affected with a point mutation in the *FOXP2* gene and suffer from a pronounced verbal and orofacial dyspraxia. The birth of a fourth generation affected KE infant provided the unique opportunity to explore the ontogeny of verbal and orofacial dyspraxia. Our aim is to determine (a) whether the reported abnormalities of the caudate nucleus resulting from the *FOXP2* mutation can be detected in early infancy, and (b) to chart the trajectory of cognitive, language, and motor development in the first year of life. Methods Voxel-based morphometry (VBM) was conducted on T1- and T2-weighted structural MRIs of the affected infant (aKE-I) versus a group of healthy controls (NC, N = 7; X age at scan = 11 weeks; aKE-I age at scan = 16 weeks) to detect differences in grey matter density. The Bayley Scales of Infant and Toddler Development was administered at 6 months and 12 months to provide standardised scores in the domains of cognition, expressive language, receptive language, gross motor, and fine motor skills. Results Morphometric analyses revealed a significant reduction in grey matter density in the right caudate nucleus of aKE-I compared to the NC group. This reduction was the only non-spurious cluster revealed by the VBM (k_E = 42 voxels, p<0.005 unc.) The aKE-I obtained significantly lower standard scores compared to the NC group in the domains of cognition, receptive and expressive language, and gross and fine motor function, at both 6 and 12 months (all p<0.001). ConclusionThese results provide insights into the ontogeny of language and motor-related deficits that emerge during development in individuals with the mutation of the *FOXP2* gene. The deficits may be associated with structural abnormalities in brain circuits that become recruited to serve speech articulation and execution of oromotor sequences.

Disclosures: **M.K. Saini:** None. **R. Elward:** None. **G. Argyropoulos:** None. **M. Mishkin:** None. **F. Vargha-Khadem:** None.

Poster

843. Language in Normal and Damaged Brains

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 843.05/KKK61

Topic: H.02. Human Cognition and Behavior

Support: JSPS Fellows 25-40252

KAKENHI 15K02745

KAKENHI 25580121

Title: Brain mechanisms of speech modification following feedback in second language communication

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Abstract: Receiving feedback on ill-formed utterances and modifying such utterances during conversational interaction play a major role in promoting language acquisition and development. Although potential processing mechanisms (e.g., awareness and error monitoring) are discussed, few linguists have examined the neural mechanisms. Previous neuroimaging studies have reported that the anterior cingulate cortex (ACC) and superior temporal gyrus are involved in monitoring the outcome of speech (e.g., Christoffels & Formisano, 2007, Human Brain Mapping). However, these studies are limited in that they focus on the first language. The current study thus contributes to the neuroimaging literature, by investigating these neural mechanisms associated with second language (L2) communication. The participants were 30 healthy, right-handed Japanese native speakers (14 females, mean age 21.5) who had acquired an intermediate proficiency level in English as L2. fMRI data were collected on 3T in the following two conditions: self and others. In the self-condition, participants were asked to describe, within 10 seconds, various pictures in English to a native listener. In the others-condition, they were required to listen to what others describe. Immediately after describing or listening to the utterances, participants received a feedback instruction (either 'Pardon' or 'Repeat') from the native listener, and then modified or repeated original utterances, respectively. Neural responses during speech modification and repetition following feedback were modeled to examine the effect of speech modification. The Repeat condition was used as a control condition. As a result, four conditions (Self-Pardon, Self-Repeat, Others-Pardon, and Others-Repeat) were presented with an event-related design paradigm. In the statistical analyses, we included only correct trials in which the participants successfully performed their respective tasks (two-way repeated ANOVA with SPM12, a random effects model, corrected to $p<0.05$ by cluster level). A

significant effect of Pardon, compared to Repeat, was observed in the supplementary motor area, ACC, left inferior frontal gyrus, left parietal lobe, and right cerebellum. These areas play a role in monitoring and modifying speech, regardless of whether speech is generated by self or others. Second, as an interaction effect, the Self-Pardon condition produced greater activation in the left premotor area and cerebellum along with the left inferior temporal gyrus. Therefore, the motor-adaptation and sematic memory systems have an important role in modifying self-generated speech following feedback during L2 communication.

Disclosures: **H. Jeong:** None. **B. Thyreau:** None. **R. Saito:** None. **C.S. Kikuchi:** None. **T. Nozawa:** None. **W. Suzuki:** None. **M. Sugiura:** None. **R. Kawashima:** None.

Poster

843. Language in Normal and Damaged Brains

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 843.06/KKK62

Topic: H.02. Human Cognition and Behavior

Support: VA CSR&D Merit Review Award, PI Turken

VA CSR&D Merit Review Award, PI Dronkers

Title: Role of network disruption in chronic post-stroke aphasia

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Abstract: How long-distance white matter pathways contribute to language processing and language deficits in aphasia relate to white matter disconnection are not fully understood. Traditional models have focused exclusively on the importance of the arcuate fasciculus in interlinking Wernicke's and Broca's areas. However, there is a growing appreciation that language is supported by an extensive network of brain regions integrated by multiple pathways, and that white matter disconnection can result in severe aphasic symptoms (Dronkers, 2000; Turken and Dronkers, 2011). Here, we examined the effects of white matter disconnection and gray matter loss on language abilities in a large group of aphasic patients. Behavioral and structural brain imaging data were acquired from 210 left hemisphere chronic stroke patients. Thirty-eight patients and 44 age-matched healthy controls also completed HARDI diffusion MRI for white matter tractography analysis (Siemens Verio 3T MRI scanner, 64 directions, b = 2000

s2/mm). The Western Aphasia Battery (WAB, Kertesz, 1982) provided a comprehensive assessment of speech and language abilities. Brain lesions were digitally reconstructed and transformed to standard MNI space. High-resolution T1w anatomical images were processed with SPM8's unified segmentation/normalization algorithm. The Harvard-Oxford Atlas was used to quantify gray matter loss in atlas-defined regions of interest (ROIs). Probabilistic constrained spherical deconvolution tractography (MRTrix v3, Tournier et al. 2012) was used to identify 1) major white matter association pathways, and 2) corti-cortical interhemispheric connections. Healthy control tractography datasets were used to derive probabilistic maps of white matter tracts and structural connectivity matrices. which are applied to quantify white matter tract loss and cortico-cortical disconnection in patients for whom only lesion reconstructions were available. WAB performance measures were correlated with gray matter loss in each atlas ROI, connectivity loss in each major tract, and cortico-cortical disconnection inferred from structural connectome analysis. PLS regression related patterns of gray matter loss and white matter disconnection with WAB performance profiles. We found that 1) each white matter tract supports more than domain, so that there is not a one-to-one relationship between specific language functions and individual tracts; 2) how disconnected cortical networks have become is a better predictor of chronic aphasia severity than damage to individual cortical regions or white matter tracts.

Disclosures: A.U. Turken: None. **T.J. Herron:** None. **K. Parker:** None. **B. Curran:** None. **N.F. Dronkers:** None.

Poster

843. Language in Normal and Damaged Brains

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 843.07/KKK63

Topic: H.02. Human Cognition and Behavior

Title: Embodied information processing for action-related words the effect of constrained arm posture

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Abstract: Several studies have shown that brain areas which are responsible for action planning and execution are activated during information processing of action-related words (e.g., pick, or kick). A plausible explanation for these findings is that information processing of action-related words is embodied; that is, the brain areas which are involved into representing body (i.e., body

schema) are also involved into processing words expressing body and action. To address whether this explanation would be the case, we conducted three experiments to see if constraining arm posture, which could disturb motor planning and imagery of that arm, would lead to delayed judgment of words referring to arm actions. Young participants were asked to judge as quickly as possible whether the presented object and the verb would be compatible (e.g., ball-throw) or not (e.g., ball-pour). They reacted either manually (Exp.1), vocally (Exp.2), or with feet (Exp.3). We expected that the effect of constrained arm would be observed particularly when reacting manually. Two types of verbs were used: manipulation (transitive verbs related to the manual manipulation of an object) and non-manipulation. The results showed that, when reacting manually or vocally, the judgment of the manipulation verbs was delayed when arm posture was constrained (i.e., kept in an unusual posture with behind the back). Such an effect was not found when reacting with the foot. Constrained arm posture has led to delayed judgments both for the manipulation words and the non-manipulation words. These findings suggest that body schema may be used for processing of both action-related and no action-related words.

Disclosures: M. Yasuda: None. **T. Higuchi:** None.

Poster

843. Language in Normal and Damaged Brains

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 843.08/KKK64

Topic: H.02. Human Cognition and Behavior

Title: Non-invasive brain stimulation improves lexical retrieval of action words in post-stroke aphasia

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Abstract: One-third of stroke survivors worldwide suffer from aphasia. While speech and language therapy (SLT) is the gold-standard treatment for aphasia, some patients show only limited improvement. Non-invasive brain stimulation is a promising adjuvant strategy to improve outcomes with SLT. However, depending on lesion size and location, stroke might render "classical" language regions ineffective as an optimal stimulation site.
A recent randomized, controlled trial showed the effectiveness of motor cortex stimulation in combination with high intensive naming therapy to improve outcomes in chronic aphasia (Meinzer et al. 2016). Although this study highlights the involvement of the motor cortex, the

functional aspects by which it influences language are yet unclear.
Here, we tested the effect of anodal tDCS to the left motor cortex on lexical retrieval in 16 patients suffering from post-stroke aphasia in a sham-controlled, double blind study. Subjects had to classify between object- and action-related real words or pseudowords (for study design the figure 1). Anodal tDCS did not influence reaction times, but improved accuracy in lexical decision, in particular, for words with action-related content and for pseudowords with a "verb-like" ending ($p = 0.036$), not for words with object-related content and pseudowords with "noun-like" characteristics ($p = 0.438$). We here show as a proof-of-principle that the motor cortex may play a specific role in lexico-semantic access in aphasia. Lexical access is often disturbed in aphasic patients and impedes re-learning of lost vocabulary. Thus, motor cortex stimulation may strengthen word-to-semantic concept association for action-related words during language treatment in post-stroke aphasia.

Disclosures: M. Branscheidt: None. **J. Hoppe:** None. **P. Zwitserlood:** None. **G. Liuzzi:** None.

Poster

843. Language in Normal and Damaged Brains

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 843.09/KKK65

Topic: H.02. Human Cognition and Behavior

Support: Medical Research Council UK (grants Nos. G0300117-65439 and G1002276-98624)

The Intramural Research Program of the National Institute of Mental Health, NIH/DHHS

The National Institute for Health Research Biomedical Research Centre , UK

Title: Disruption of laughter and sneezing in individuals with a mutation of the FOXP2 gene

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Abstract: Based on speech and language assessments, and examination of sequential orofacial movements, we characterized the phenotype of the disorder in the affected members of the KE family as a "verbal and orofacial dyspraxia" (Vargha-Khadem, et al., 1995; 2005). However, the birth of a 4th generation infant in the KE pedigree diagnosed with a point mutation in the

forkhead-domain, provided the opportunity to deep phenotype FOXP2 before the emergence of speech dyspraxia. Our investigations of the affected infant, relative to his unaffected twin, and to unaffected members of the pedigree, revealed two features that highlight abnormalities in the mechanism and structure of airway passages involved in speech articulation.
First, like his affected relatives, the affected infant is unable to sneeze. The sneeze reflex involves two phases, a nasal sensitive phase whereby afferent olfactory pathways converge on the medulla, and a second phase involving the dilatation of the glottis giving rise to an explosive exit of air through the mouth and nose. One or both of these phases appear to be compromised as a consequence of the genetic mutation resulting in an inability to sneeze and to clear debris and irritants from the nasal passages. Second, again as with other affected family members, the affected infant is unable to laugh with characteristic human laughter, which involves regular stable voicing, and sustained egressive airflow resulting from the rhythmic contraction of the diaphragm.
Implications:
1. Identification of these phenotypic features can lead to an early diagnosis of verbal and orofacial dyspraxia *before* the emergence of speech to implement appropriate support and therapeutic interventions.
2. Both aspects of the phenotype are consistent with the expression pattern of *foxp2* in the lungs and the airway passages
3. There is a potential impact of these phenotypes on the development of speech and language inasmuch as human speech is marked by consistently regular vocal-fold vibration and sustained egressive airflow.
References
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Vargha-Khadem, F., Gadian, D. G., Copp, A., & Mishkin, M. (2005). *Nat.Rev.Neurosci*., 6, 131-138.

Disclosures: F. Vargha-Khadem: None. **M. Mishkin:** None.

Poster

843. Language in Normal and Damaged Brains

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 843.10/KKK66

Topic: H.02. Human Cognition and Behavior

Support: NIH Grant AG038490

NIH Grant AG017586

NIH Grant DC013063

Title: The role of the frontal lobes in abstract word production

Authors: *K. A. COUSINS, S. ASH, M. GROSSMAN;
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Abstract: While canonical semantic memory regions are located in the temporal lobe and perisylvian areas, frontal regions have been shown to selectively support semantic processing. Specifically, imaging studies in controls have implicated the inferior frontal gyrus in tasks that require semantic selection and control. These executive functions are theorized to be important to abstract word processing; compared to concrete words, abstract words tend to more polysemous and contextually diverse, and so require selection processes during their processing. In this study, we examine how disease to the frontal lobes in behavioral variant frontotemporal dementia patients (bvFTD) affects the production of abstract nouns. To collect speech samples, 42 bvFTD patients participated in a Cookie Theft picture description task, and performance was compared to 32 age- and education- matched controls. Performance was then related to grey matter probability (GMP) in bvFTD patients. Behavioral results showed that bvFTD patients and controls produced a statistically equivalent number of nouns per 100 words. However, the nouns produced by bvFTD patients were significantly less abstract and less semantically diverse than those produced by controls. A pairwise t-test between GMP in bvFTD patients and controls indicated that bvFTD patients have extensive frontal lobe atrophy, and regression analyses revealed that the decreased production of abstract nouns in bvFTD related to reduced GMP in the left inferior frontal gyrus and bilateral caudate. Our results indicate that the frontal lobes support abstract noun processing, and that atrophy to the frontal lobes in bvFTD can result in poor production of abstract nouns.

Disclosures: **K.A. Cousins:** None. **S. Ash:** None. **M. Grossman:** None.

Poster

843. Language in Normal and Damaged Brains

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 843.11/KKK67

Topic: H.02. Human Cognition and Behavior

Support: Parkinson's QLD, Inc grant

Title: Lexical ambiguity processing in Parkinson's disease: A neurophysiological study

Authors: *A. ANGWIN[1], N. DISSANAYAKA[2,1], K. MCMAHON[1], P. SILBURN[2,1], D. COPLAND[1];
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Abstract: *Objective:* Previous behavioural research has shown deficits in the attention based selection of ambiguous word meanings in people with Parkinson's disease (PD). This study utilised event related potentials (ERPs) to explore lexical ambiguity resolution during sentence processing in PD.
Methods: Sixteen mild to moderate PD patients and 16 healthy adults completed cognitive tests and an ERP task. The ERPs were recorded while participants read sentences on a computer screen and judged (via button press) whether a target word was related to the meaning of each sentence. Sentence stimuli were divided into 3 conditions; 'related' - the target word was related to sentence meaning (She went to lunch; Target = MEAL); 'unrelated' - the target word was unrelated to sentence meaning (He wanted to smile; Target = BRACELET); 'ambiguous' - the final word of the sentence was ambiguous, and the target word represented the meaning of the ambiguous word that was not captured by the sentence (He dug with the spade; Target = ACE).
Results: Accuracy for the ambiguous condition was lower in the PD group (85.7%) relative to the control group (93.2%) ($t=2.08$, $p=.045$), however no between group differences in accuracy were evident for the related or unrelated condition. The mean ERP amplitude from 300-500ms was calculated from 3 clusters of electrodes in each hemisphere around the F3/4, C3/4 and P3/4 positions. Analyses indicated a prominent N400 for the unrelated and ambiguous conditions in the right hemisphere for both groups (condition x hemisphere interaction, $F=66.10$, $p<.001$). Difference waves (DW) for the unrelated and ambiguous conditions were calculated (relative to the related condition) in the central and parietal clusters in the right hemisphere. For the PD group, a measure of Stroop interference correlated positively with the ambiguous DW in the central ($R=.518$, $p=.040$) and parietal region ($R=.524$, $p=.037$), and with the unrelated DW in the central region only ($R=.588$, $p=.017$). No correlations were significant for controls.
Conclusions: The behavioural results suggest that PD patients experience mild difficulties selecting the appropriate meaning of lexical ambiguities on the basis of context. The ERP results suggest that sentence processing, and particularly ambiguity resolution, may be altered for PD patients with increased response inhibition deficits.

Disclosures: A. Angwin: None. **N. Dissanayaka:** None. **K. McMahon:** None. **P. Silburn:** None. **D. Copland:** None.

Poster

843. Language in Normal and Damaged Brains

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 843.12/KKK68

Topic: H.02. Human Cognition and Behavior

Title: Heritability of comprehension of narrative speech in a large normal population

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Abstract: INTRODUCTION: Comprehension of narratives constitutes a fundamental part of our everyday life experience. Although the neural mechanism of auditory narrative comprehension has been investigated in some studies, heritability of the neural correlates underlying this mechanism remain poorly understood. The current study, to the best of our knowledge, is the first to investigate heritability of auditory narrative comprehension in a large normal population.
METHODS: 429 (176/253 M/F; 98/94/237 Monozygotic/Dizygotic/Non-twin; 29.1±3.5 yr) participants of the Human Connectome Project were included in this study. Subjects listened to short narratives during the language task. After preprocessing of functional MRI (fMRI) data, contrast images corresponding to narrative *vs*. baseline were calculated, and significance level of results was set to the threshold of $p < 0.001$ (uncorrected). Then significant active voxels were classified to 116 automated anatomical atlas (AAL) areas. in We used the variance components method, implemented in the SOLAR-Eclipse software package, for the heritability estimation. The extent of activation of cortical areas was quantified by the numbers of significant voxels within the AAL areas. The calculated numbers of significant voxels in the AAL areas and also the behavioral measures in 429 subjects were used in the heritability analysis.
RESULTS: The neuropsychological language evaluation measures, i.e. oral reading recognition and picture vocabulary comprehension, were significantly heritable ($p < 1.1\text{x}10^{-23}$). The accuracy and average difficulty level of the story task were also significantly heritable ($p < 4.5\text{x}10^{-6}$). The extent of activation of 5 areas in the left hemisphere, i.e. superior temporal gyrus, pars opercularis of the inferior frontal gyrus (IFGop), medial superior frontal gyrus (SFGmed), supplementary motor area (SMA), and precuneus, as well as right middle frontal gyrus (MFG), were significantly heritable ($p < 0.001$). Additive genetic factors explained at least 33% of the residual phenotypic variance in the extent of activations of these six areas (h^2 0.33). The most significant heritability was observed in the left IFGop ($p = 0.00001$, $h^2 = 0.36$) followed by the left SMA ($p = 0.00011$, $h^2 = 0.35$). The least significant heritability was observed in the left SFGmed ($p = 0.00035$, $h^2 = 0.35$).
CONCLUSIONS: The extent of activation within five areas in the left hemisphere and one area in the right hemisphere during narrative comprehension were significantly heritable. Our results

can clarify heritability and functional contributions of linguistic and extra-linguistic cortices during narrative comprehension.

Disclosures: A. Babajani-Feremi: None.

Poster

843. Language in Normal and Damaged Brains

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 843.13/KKK69

Topic: H.02. Human Cognition and Behavior

Support: KAKENHI 26282218,

KAKENHI 15H01664,

KAKENHI 15H05874

Title: Kanji word processing in the ventral anterior temporal lobe: a postoperative neuropsychological study in patients with temporal lobe epilepsy

Authors: *M. OTA[1], R. MATSUMOTO[3], A. SHIMOTAKE[1], M. SAKAMOTO[1], M. DAIFU[1], T. NAKAE[2], T. KIKUCHI[2], K. YOSHIDA[2], T. KUNIEDA[2], S. MIYAMOTO[2], R. TAKAHASHI[1], M. A. LAMBON- RALPH[4], A. IKEDA[3];
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Abstract: Introduction: Importance of the ventral anterior temporal lobe (vATL) in semantic cognition has been recently highlighted by electrical cortical stimulation and functional neuroimaging. It has been also implicated by surface dyslexia and other semantic impairments in patients with semantic dementia. However, the progressive pathology underlying semantic dementia precludes precise localization of the area responsible for surface dyslexia. Different from the kana script, kanji is a semi-opaque orthography that consequently requires a greater contribution from the semantic system for accurate reading and writing. We aimed to clarify the role of the vATL in kanji word processing through a neuropsychological examination of patients with temporal lobe epilepsy (TLE) who underwent resection of the vATL. **Methods:** We studied eight patients with intractable TLE on the language-dominant side, who underwent resection of the vATL. Language dominance was defined by Wada test (Left:7, Right:1). We examined kanji/kana word reading and writing abilities using tasks from the Sophia Analysis of Language

in Aphasia (SALA) battery and an additional assessment of kanji reading which varies the typicality of the spelling-sound relationship (Fushimi, et al.1999). These assessments were performed pre-operatively in six patients, and 1 week - 6 months after surgery in all eight patients. The accuracy rate and the type of errors were evaluated. **Results:** Among the six patients who had preoperative assessment, three showed impairment in kanji writing and reading (accuracy rate writing 71 - 83%, reading 63 - 68%). In the post-operative assessment, six of eight patients showed impairment in kanji word writing, especially for words with lower frequency and imageability (accuracy rate 25 - 90%). The error types included spelling errors in which targets were replaced by either a homophone (6 patients) or a visually-similar kanji or pseudo-kanji form (6 patients). Four of the eight patients showed impaired kanji word reading. The majority of errors were observed for kanji words with an atypical spelling-sound relationship and were occasionally surface dyslexia. In contrast, all the patients showed excellent performance on kana word tasks. **Conclusion:** The majority of intractable TLE patients showed impairment of kanji word reading and writing, corresponding to surface dyslexia and dysgraphia. This impairment was induced by the resection itself and/or epileptic pathology. These results show that the language-dominant vATL is not only a crucial areas for semantic processing but also for the contribution of semantics to language processing.

Disclosures: **M. Ota:** None. **R. Matsumoto:** Other; Endowed department by UCB, GSK, NihonKoden, Otsuka. **A. Shimotake:** None. **M. Sakamoto:** None. **M. Daifu:** None. **T. Nakae:** None. **T. Kikuchi:** None. **K. Yoshida:** None. **T. Kunieda:** F. Consulting Fees (e.g., advisory boards); endowed by Otsuka. **S. Miyamoto:** F. Consulting Fees (e.g., advisory boards); endowed by Otsuka. **R. Takahashi:** B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution; DAINIPPON SUMITOMO PHARMA, Boehringer Ingelheim, NOVARTIS, Pfizer Co. Ltd., Takeda Pharmaceutical Company, Mitsubishi Tanabe Pharma, Kyowa Hakko Kirin Co., Otsuka Pharmaceutical Co., Nihon Medi-Physi. D. Fees for Non-CME Services Received Directly from Commercial Interest or their Agents (e.g., speakers' bureaus); Glaxo Smith Kline, FP PHARMACEUTICAL CORP, NOVARTIS, Boehringer Ingelheim Co., Kyowa Hakko Kirin Co., Dainippon Sumitomo Pharma Co., Mitsubishi Tanabe Pharma Co., Glaxo Smith Kline., Otsuka Pharmaceut. F. Consulting Fees (e.g., advisory boards); KAN Research Institute INC., DAINIPPON SUMITOMO PHARMA, AbbVie Inc., Takeda Pharmaceutical Company. **M.A. Lambon- Ralph:** None. **A. Ikeda:** Other; Endowed department by UCB, GSK, NihonKoden, Otsuka.

Poster

843. Language in Normal and Damaged Brains

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 843.14/KKK70

Topic: H.02. Human Cognition and Behavior

Support: JSPS Grant-in-Aid for Young Scientists (B) 25870325

Title: Evaluating the effects of melodic intonation therapy by functional and anatomical connectivity

Authors: *K. TABEI[1], M. SATOH[1], C. NAKANO[2], N. KATO[3], A. ITO[1], Y. SHIMOJI[4], H. KIDA[1], H. SAKUMA[1], H. TOMIMOTO[1];
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Abstract: Melodic intonation therapy (MIT) is a treatment program for the rehabilitation of aphasic patients with speech production disorders. In the present study, we reported four cases of severe non-fluent aphasia who received intensive training of Japanese version of MIT (MIT-J) for nine days after three to seventeen years of onset. The purpose of this study was to verify efficacy of MIT-J via the assessment of linguistic functionality, and further elucidate alterations in the neural processes participating in MIT-J by resting-state fMRI and diffusion tensor MRI. As a result, the output of the language, that is spontaneous speech, repetition, and naming, was improved in the Japanese version of Western Aphasia Battery. The improvement of Aphasia Quotient (AQ) was significant trend ($p = 0.06$). As for the naming of 90 words, the response time was significantly improved ($p = 0.042$). For functional connectivity changes, although we found small networks (e.g., right auditory area only or visual area only) before, we found higher connectivity between left angular gyrus and the visual cortex networks, as well as between insula, auditory cortex, and angular gyrus networks in the right hemisphere after MIT-J. We found increase of global fractional anisotropy (FA) after MIT-J compared to before MIT, especially in two patients whose AQ was significantly improved at ten or more points. The areas of increased FA in all patients included left superior longitudinal fasciculus and left superior corticospinal tract. Our results showed higher connectivity between each different functional area in patients that may be related to MIT-J, with decrease of cognitive load through the intensive training of MIT-J.

Disclosures: **K. Tabei:** None. **M. Satoh:** None. **C. Nakano:** None. **N. Kato:** None. **A. Ito:** None. **Y. Shimoji:** None. **H. Kida:** None. **H. Sakuma:** None. **H. Tomimoto:** None.

Poster

843. Language in Normal and Damaged Brains

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 843.15/LLL1

Topic: H.02. Human Cognition and Behavior

Support: Canadian Institutes of Health Research Grant #112359

Title: Abnormal self-schema in semantic memory in major depressive disorder: evidence from event-related brain potentials

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Abstract: Introduction: An overly negative self-schema is a proposed cognitive mechanism of major depressive disorder (MDD). Self-schema is a person's core conception of self, including how strongly one believes that one possesses various characteristics. Self-schema is thus presumably part of long-term semantic memory, our knowledge about concepts and their relationships. The degree of association between different concepts in semantic memory can be probed via the N400 event-related brain potential (ERP), which occurs in response to any meaningful stimulus, and is reduced in amplitude by greater association of the stimulus with preceding context. We aimed to use the N400 to measure association of self-concept with different characteristics in semantic memory in MDD patients. We hypothesized that MDD patients would exhibit greater than normal associations between self-concept and negative characteristics, as reflected in smaller (less negative in voltage) than normal N400 amplitudes for negative, relative to positive or neutral, adjectives in a self-referent context.
Methods: ERPs were recorded from patients with MDD (n=16) and healthy control participants (n=16) while they viewed the phrase "I am..." followed by target person-referent adjectives that were either positive (e.g., "loyal"), negative ("stupid"), or neutral ("skeptical"). Participants' task was to indicate via button-press whether or not they felt the target described themselves.
Results: The N400 difference wave formed by subtracting ERPs for negative adjectives from ERPs for positive adjectives was larger (more negative in voltage) than normal in MDD patients (p=0.03). In other words, N400 amplitudes were smaller than normal for negative relative to positive adjectives in patients.
Conclusions: The results suggest MDD is associated with stronger than normal functional neural

links between self-concept and negative, relative to positive, characteristics in long-term semantic memory.

Disclosures: **M. Kiang:** None. **F. Farzan:** None. **D.M. Blumberger:** None. **M. Kutas:** None. **M.C. McKinnon:** None. **V. Kansal:** None. **T. Rajji:** None. **Z.J. Daskalakis:** None.

Poster

843. Language in Normal and Damaged Brains

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 843.16/LLL2

Topic: H.02. Human Cognition and Behavior

Title: Method to study if Wernicke's aphasia patients understand that they do not understand language or speak it understandably

Authors: *E. L. ALTSCHULER[1], I. CHELLQUIST[4], S. SHADANI[4], S. WEPRIN[2], H. FAROOQI[4], A. SEIWELL[4], S. AZIZ[2], A. PRICE[3];
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Abstract: In 1874 Carl Wernicke described a new form of aphasia. Wernicke's patient, unlike those Broca described, was able to speak fluently but the speech was (i) incomprehensible gibberish, and (ii) the patient did not understand things said to him. Further, (iii) in a mystery enduring to this day, the patient seems oblivious to and not upset by (i, ii). But other than lacking phonology Wernicke's aphasia patients (WAPs) are apparently otherwise completely normal in perception and cognition (ELA et al. Med. Hypoth. 2006; 67:713-6.). Four questions seem crucial to answer (1a) do WAPs know or understand that they do not understand what is said to them (by a physician, for example)? (1b) if so is this upsetting? (2a) Do WAPs know/understand that no one understands them when they speak? (2b) if so is this upsetting? Also, to begin with we note that typical WAPs do not understand what is said to them: indeed, WAPs cannot follow a simple spoken command such as "raise your left hand," and similarly most speech of WAPs is not comprehensible. So the issue, as crystallized by the questions above is whether or not despite this lack of understanding of speech, or written language, WAPs think they understand language. The following method can be used to answer the preceding questions: (1a) The patient is first shown a series of pictures—questions—of a physician (recognizable by white coat, stethoscope) speaking via cartoon mouth bubble a picture of, for example, a hose, and then given a choice of three pictures as answers—as cartoon thought bubbles from a picture of their head—e.g., a firefighter, a baseball player and ????. The prediction is that the patient will give the normal target answer in (statistically) all cases. (Note that prior a series of examples, e.g., a very difficult

math or symbol questions, a person looking out a window for with weather choices, needs to be given to the WAP to insure/teach they will correctly respond ????.) Now the patient is shown the same questions and answers but with either (or both) expressed as the *word* "hose," "firefighter" etc. The key question is now will the patient simply give random guesses of the three answers implying that the WAP does not know that they do not understand language, or consistently answer ???? that would be consistent with an appreciation for lack of understanding language. (1b) After prior training with pictures of obviously happy or sad things WAPs would be asked after answers to (1a) to choose a happy or sad face. (2a) Roles are reversed from (1a) with the WAP shown speaking and the doctor list listening. (2b) Similarly as for (1b).

Disclosures: E.L. Altschuler: None. **I. Chellquist:** None. **S. Shadani:** None. **S. Weprin:** None. **H. Farooqi:** None. **A. Seiwell:** None. **S. Aziz:** None. **A. Price:** None.

Poster

843. Language in Normal and Damaged Brains

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 843.17/LLL3

Topic: H.02. Human Cognition and Behavior

Support: NIH Grant F32-DC013486

NIH Grant R00-NS065120

NIH Grant DP2-OD00862

NIH Grant R01-DC012379

NIH Grant R01-DC011538

NIH Grant R01-DC014767

Title: Cortical encoding of sensorimotor and linguistic features in American Sign Language

Authors: *M. K. LEONARD[1], B. LUCAS[1], S. BLAU[2], D. P. CORINA[2], E. F. CHANG[1]; [1]Neurolog. Surgery, UCSF, San Francisco, CA; [2]Ctr. for Mind and Brain, Univ. of California, Davis, Davis, CA

Abstract: Fluent production of sign language requires the tight coordination of motor and sensory representations of the hands and body, and higher-order linguistic representations. Previous studies have identified pre- and post- central gyri, supplementary motor areas, and inferior and superior parietal regions as being involved in sensorimotor, phonological, and

lexical sign processing. However, the fine-scale coordinated dynamics of these regions have not been explored. Here, we present a rare case study of a profoundly deaf signer who was implanted with high-density electrocorticography (ECoG) arrays during surgical resection of a tumor. The patient viewed videos of single signs and pseudosigns, and produced a variety of responses, including repetitions, fingerspellings, and non-linguistic gestures. His manual behaviors were recorded and annotated frame-by-frame to provide nearly 8000 events that could be time-locked to the neural data. We examined two aspects of sign language production: 1) How are sensorimotor and phonological (e.g., location and handshape) features encoded? 2) How do higher-order linguistic (e.g., lexical) representations modulate neural responses in real-time? We identified electrodes throughout sensorimotor and parietal cortex that responded selectively to signs produced at specific locations (e.g., 'face' vs. 'hand') and with specific handshapes (e.g., 'O' vs. 'S'). Population neural activity was examined using unsupervised hierarchical clustering, which revealed highly structured neural representations of sensorimotor-based phonological features. Supervised classification analyses demonstrated that location, handshape, and movement features could be decoded from neural activity with significantly above-chance accuracy for several hundred milliseconds around sign onset. Neural activity differentiated linguistic and non-linguistic movements with clear spatiotemporal patterns. Generally, there was greater activity on ventral and dorsal pre-central gyrus and supramarginal gyrus for linguistic movements. These patterns overlapped with greater responses to real signs compared to pseudosigns. Finally, dorsolateral prefrontal cortex was significantly modulated by the lexical factors of frequency and age of acquisition throughout the timecourse of sign production. Together, these results provide unprecedented detail of the cortical basis of sign language production. In addition to demonstrating striking similarity with the dynamics of speech production, this study indicates that population neural activity in supra-Sylvian cortex is sufficiently discrete to allow behavioral decoding.

Disclosures: **M.K. Leonard:** None. **B. Lucas:** None. **S. Blau:** None. **D.P. Corina:** None. **E.F. Chang:** None.

Poster

843. Language in Normal and Damaged Brains

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 843.18/LLL4

Topic: H.02. Human Cognition and Behavior

Support: JSPS KAKENHI Grant Number 26580076

Title: Linguistic P600 is dependent on syntactic prediction: Integration and syntactic violation

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Abstract: Recent studies have demonstrated that various linguistic phenomena can elicit a similar event-related potential (ERP). The positivity around the latency of 600 ms (P600), one of the most frequently discussed linguistic ERPs, is reported to be elicited by integration, syntactic violation, or reanalysis. However, it is difficult to differentiate between these P600s because they are different in their experimental settings and linguistic phenomena. We thus structurally manipulated a single linguistic phenomenon in Japanese to strictly differentiate between the neural activity of integration and that of syntactic violation.
A Japanese quantifier modifying a grammatical object can be displaced before or after its head noun without changing the propositional meaning. For example, "I read two books in the library" can be expressed in various orders in Japanese, namely, 'I two in the library books read' or 'I books in the library two read.' We recorded the electroencephalogram in processing these discontinuous words to examine the neural activity of integration and that of syntactic violation by the ERP elicited at the discontinuous words for the former and by the ERP by processing them with one of the discontinuous words in a syntactic island for the latter. Further, we manipulated their order to examine the effect of syntactic prediction. As a result, we observed a parietal P600 for both the integration and the syntactic island violation, but the P600 for integration was accompanied by (left) negativity and that for island violation was mainly observed in left hemisphere. The neural bases of the two thus can be different. Further, the effect of integration was significant only when a quantifier preceded the head noun, and that of island violation was significant only when a head noun preceded the quantifier. This indicated that the effect of integration occurred when the syntactic prediction was fulfilled, and that the effect of island violation occurred when the comprehender encountered an unexpected input. An English filler-gap dependency is often reported to elicit P600, but we should note that a discontinuous dependency in English can be predicted at the input of a filler. Our results thus suggest that the integration of discontinuous dependency does not always elicit P600. Further, a wh-phrase is preposed at the beginning of a clause in a sentence with island violation in English, and therefore its corresponding gap can be predicted at the wh-phrase. P600 for syntactic island violation in English thus can be confounded with the effect of syntactic prediction.

Disclosures: S. Tokimoto: None. **N. Tokimoto:** None. **Y. Miyaoka:** None.

Poster

843. Language in Normal and Damaged Brains

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 843.19/LLL5

Topic: H.02. Human Cognition and Behavior

Support: NIH Grant DC011538

Title: Conduction aphasia in American Sign Language

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Abstract: Conduction aphasia has received renewed interest in the neurobiology of language as the proposed impairment highlights unique architectural properties of the language system. Patients with spoken language conduction aphasia have fluent speech production with good auditory comprehension, but show a disproportionate inability to repeat, with frequent phonemic errors in production. This pattern is typically explained as resulting from damage to the interface between separate auditory and motor systems. We present a case study of a deaf user of American Sign Language who exhibits symptoms of conduction aphasia following bilateral strokes affecting the right temporal and left parietal lobes. The subject's sign language comprehension and spontaneous language abilities are near normal; however she shows a marked inability to repeat signed sentences, signed triplets and pseudo-sign sequences. She evidences limb apraxia and exhibits significant somatosensory loss of the arm, hand and fingers. To account for this unusual pattern of sparing and deficits we propose a model of sign language processing in which proprioceptive sensory signals define targets for sign actions. Here the disruption of internal proprioception limits the activation of lexical sign forms. This case study is important as it Illuminates components of lexical processing in a signed language and has implication for integrated state feedback control models of language which argue for motor and sensory based phonological systems.

Disclosures: **D.P. Corina:** None. **S. Pedersen:** None. **U. Bellugi:** None. **G. Hickok:** None.

Poster

843. Language in Normal and Damaged Brains

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 843.20/LLL6

Topic: H.02. Human Cognition and Behavior

Support: DARPA RP2009

Title: Phase analysis of network dynamics in human simple language production: formation and temporal evolution of reciprocal networks between primary language areas

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Abstract: Feedforward and feedback networks drive many aspects of cognition. Anatomical studies have shown that there are reciprocal feedforward/feedback connections between particular areas of cortex (Felleman and Van Essen, 1991). Later studies have found functional correlates of these anatomical feedforward and feedback connections in non-human primate V1 (Bastos and Fries, 2014). Functional connectivity is a way to study these networks in awake and behaving human patients and can grant new insights into the mechanisms of information exchange during behavior and disease. We hypothesize that there will be fluctuations in functional connections between primary language areas during simple language production in humans. Given a signal x(t) and its Hilbert transform y(t), the instantaneous phase φ of the signal may be calculated by: $\varphi(t) = \arctan(y(t)/x(t))$. Two signals are phase-locked if their instantaneous phase difference $\Delta\varphi(t) = \varphi1(t) - \varphi2(t)$ is concentrated around a specific value φ_{Lock}. The phase lag index (PLI) is a measure of coupling between two electrodes that are separated in space. The PLI is calculated from differences in the instantaneous phase of each signal (Stam et al. 2007). An asymmetry in the distribution of instantaneous phase difference between two signals requires that one signal consistently lags in time behind the other. PLI is calculated as: $PLI = |\langle sign(\Delta\varphi(t))\rangle|$. When PLI = 1, the signals are perfectly phase locked at $\varphi_{Lock} = \langle\Delta\varphi(t)\rangle$. When PLI = 0, the signals are non-coupled. PLI can be used to characterize the nature of the phase relationship between two signals, and evaluate functional connectivity and network dynamics. Data was collected from epicortical micro-electrode arrays implanted in a patient undergoing clinical monitoring for medically refractory epilepsy. Grids consisted of 40 μm diameter electrodes with 1 mm inter-electrode spacing. 16-channel grids were placed over face motor and Wernicke's areas. Following analysis of the micro-electrode data from the patient, we observed that reciprocally connected functional networks emerged between language areas during simple language production.

Disclosures: K.J. O'Neill: None. **P.A. House:** None. **B. Greger:** None.

Poster

843. Language in Normal and Damaged Brains

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 843.21/LLL7

Topic: H.02. Human Cognition and Behavior

Support: BCS-1533688

Title: An evaluation of different connectivity metrics for the mapping of human language networks

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Abstract: We humans have a remarkable ability to communicate through language by learning its underlying structure and grammar. We can spontaneously produce words from a vast mental lexicon, comprehend language through our auditory senses, read and write, and these are just a few of the functions our highly complex language system performs. Unfortunately, millions of people suffer from language disorders due to strokes and other brain injuries. The goal of this project is to develop fine-grained connectivity maps of the human language system in the brain, which will drastically improve our understanding of organization of language in the brain, paving way for one day remediating these language disorders. For generating these maps, we use human ECoG data obtained from cortical recording electrodes from patients undergoing epileptic surgeries, at University of Texas Health Science Center, who undergo a multitude of language tests. Specifically, we are evaluating human language networks in a picture-naming task, performed by the patients. This data is used to find effective brain connectivity networks - which give us direct causal connections between brain regions. We are developing a platform for modelling language systems using effective connectivity metrics like Directed Information (DI). DI has been shown to be particularly effective in modeling nonlinear relations underlying the data. Comparison with commonly used metrics like Partial Directed Coherence and Directed Transfer Function are done. The results describe the main components of the human language system involved in object naming.

Disclosures: **S. Yellapantula:** None. **B. Aazhang:** None. **N. Tandon:** None.

Poster

843. Language in Normal and Damaged Brains

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 843.22/LLL8

Topic: H.02. Human Cognition and Behavior

Support: NIH Grant EB00856

NIH Grant EB006356

NIH Grant EB018783

U.S. Army Research Office W911NF-08-1-0216

U.S. Army Research Office W911NF-12-1-0109

U.S. Army Research Office W911NF-14-1-0440

Fondazione Neurone

Title: Passive functional mapping of language areas using electrocorticographic signals in humans

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Abstract: Our ability to understand and produce verbal language relies on the activation of specific functional regions of the brain. During invasive brain surgeries, such as those required for tumor resection or the treatment of epilepsy, it is critical to localize and preserve these regions to prevent post-surgical deficits in language function. Current methods to localize language activity, such as electrical cortical stimulation (ECS), have multiple limitations. ECS is time-consuming, potentially seizure provoking, and may not be technically feasible in pediatric populations due to immature myelination. Moreover, the interpretation of ECS is subjective, not standardized, and historically based on qualitative level 4 observational evidence. A rapid real-time passive method to map language areas using electrocorticographic (ECoG) signals as a surrogate of neuronal functional activation has the potential to supplement or replace current modalities and simplify clinical mapping procedurally, while maintaining the primary necessity of protecting eloquent cortex and improving post-surgical outcome.
Several studies have described the use of passive functional mapping using ECoG signals in the broadband gamma band (70 - 110 Hz) to map expressive language function (Cervenka et al., 2013; Wang et al., 2016). To date, reports of ECoG-based mapping of receptive language function have been scarce (Korostenskaja et al., 2014). We here describe the first large-scale study that used ECoG for mapping receptive language areas. In this study, 23 patients listened to a part of the Boston Aphasia Battery while we recorded ECoG and identified receptive language areas in the temporal lobe using previously described methods (Brunner et al., 2009; Kapeller et al., 2015). These methods were effective in producing a map of receptive language in 22 of the 23 patients. We then compared these maps with those derived using ECS mapping in those 11 of the 23 subjects for whom ECS data was available. Using a nearest-neighbor approach, sensitivity reached 95% while specificity reached 64%, indicating accurate identification of ECS+ electrodes.
These results show that passive functional mapping reliably localizes receptive language areas, and that there is a substantial concordance between the ECoG- and ECS-based methods. They also point to a more refined understanding of the differences between ECoG- and ECS-based mapping, which may clarify the instances in which the two methods disagree. In summary,

passive functional mapping provides a fast, robust, and reliable method for identifying receptive language areas without many of the risks and limitations associated with ECS.

Disclosures: **J.R. Swift:** None. **W.G. Coon:** None. **C. Guger:** None. **P. Brunner:** None. **M. Bunch:** None. **T. Lynch:** None. **B. Frawley:** None. **A.L. Ritaccio:** None. **G. Schalk:** None.

Poster

843. Language in Normal and Damaged Brains

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 843.23/LLL9

Topic: H.02. Human Cognition and Behavior

Title: The effects of late bilingualism on the white matter of the brain, connectometry approach

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Abstract: Bilingualism, active using of two or more languages in daily life, has been founded to improve cognitive functions. Neuroimaging studies have revealed that these cognitive benefits are due to brain structural changes especially more specifically affecting integrity of the white matter.
But there remains an unresolved question whether beneficial cognitive effect of learning a new language can be achieved by simply learning a new language at any stage of life or there exists critical periods to achieve such goal with learning new languages?
The effects of early and simultaneous language learning on white matter integrity has been demonstrated; IFOF has significantly higher FA in simultaneous bilingual children.
Herein we investigated whether these effects are seen in late bilinguals.
Participants
19 healthy individuals who all spoke English as their second language and had lived in the United Kingdom for a minimum of 13 months with various first languages formed our “bilingual group”. The control group consisted of 25 age, sex and education matched native speakers of English.
Image data acquisition and analysis
A 3.0-Tesla Siemens MAGNETOM Trio MRI scanner was used with Syngo software to acquire DTI data.
A DTI diffusion scheme was used in DSI Studio, and a total of 60 diffusion sampling directions

were acquired. The b-value was 1000 s/mm2. The in-plane resolution was 2 mm. The slice thickness was 2 mm. The diffusion data were reconstructed in the MNI space using q-space diffeomorphic reconstruction to obtain the spin distribution function. A diffusion sampling length ratio of 1.25 was used, and the output resolution was 1 mm.
Diffusion MRI connectometry was conducted to compare group differences in a total of 44 subjects.

Results

The connectometry analysis results showed tracks with increased FA in group bilingual with an FDR of 0.0431034. These tracks include Corpus Callosum (CC) and cingulum bilaterally and left IFOF.

Discussion

We found CC bilaterally and left IFOF tract to have higher anisotropy in bilinguals which was in consistent with previous reports. IFOF takes part in semantic processing and its higher anisotropy in bilinguals signifies more efficient semantic processing in bilinguals.
We report for the first time a higher anisotropy in cingulum of bilinguals. We suggest that cingulum's role in language switching (which has been reported in previous works) is the reason for this increase in Anisotropy. If this shall be the case, we could emphasis on increasing importance of the immersion and active usage of a second language as the main factors of the bilingualism effects on the white matter structure comparing with just early learning of the second language.

Disclosures: A. Anjomshoa: None. **M. Dolatshahi:** None. **A. Kamalian:** None. **F. Rahmani:** None. **N. Hosseini:** None. **M.H. Aarabi:** None.

Poster

843. Language in Normal and Damaged Brains

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 843.24/LLL10

Topic: H.02. Human Cognition and Behavior

Support: NIH Grant 1DP5OD021352

Title: Network controllability underlies the role of the inferior frontal gyrus in word selection processes

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Abstract: In natural language production, humans are confronted with considerable selection demands. Often, we must select a word from among similar (or acceptable or competing) alternative words in order to construct a sentence that conveys an intended meaning. In recent years, the left inferior frontal gyrus (IFG) has been identified as critical to this ability. However, the mechanism by which the left IFG interacts with other nodes (brain regions) in the language network remains poorly understood despite an increasing emphasis on "network-based" approaches to understanding the neurobiology of language. Here, we take a novel approach to understand the basis of selection demands as a network control process in the brain. We posit that inter-individual variability in performance during word selection (measured by response times (RTs) to generate a task-appropriate word when there are many vs. few acceptable alternatives) may be attributable to the variable role of the left IFG in controlling dynamics across the brain. To test this hypothesis, we collected high resolution diffusion spectrum imaging data from 10 healthy adult subjects and computed diffusion tractography to build a structural network for each individual's brain. Then, we computed network controllability statistics in these networks. Out of the scanner, subjects performed a verb generation task including items of variable selection demands prior to and immediately following administration of theta-burst stimulation, a form of transcranial magnetic stimulation (TMS) that is assumed to suppress neural activity, to the left IFG. Using mixed effects models, we associated network controllability measures RTs during the verb generation task. We found that boundary controllability, a statistic that measures a region's role in integrating and segregating dynamics in the network, predicts selection RTs across individuals. In addition, the effect of TMS interacted with boundary controllability, indicating that individuals with high boundary controllability are more greatly slowed during selection than individuals with low boundary controllability. These results indicate that the ability to reconcile selection demands rely on the left IFG's ability to control dynamics across the human connectome, and that TMS effects in controlled language processing may depend on the specialization of IFG to drive the brain into integrated or segregated states. Future studies should examine the control role of other language regions in dynamic information processing and examine network control-based translational opportunities that utilize neuromodulatory techniques, including TMS.

Disclosures: J.D. Medaglia: None. **D. Harvey:** None. **N. White:** None. **D.S. Bassett:** None. **R.H. Hamilton:** None.

Poster

843. Language in Normal and Damaged Brains

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 843.25/LLL11

Topic: H.02. Human Cognition and Behavior

Support: the National Natural Science Foundation of China (31170970)

the National Key Basic Research Program of China (2014CB846102)

the Fundamental Research Funds for the Central Universities to Taomei Guo

Title: The plasticity of lexical selection mechanism in word production: event-related potential evidence from short-term language switching training in unbalanced Chinese-English bilinguals

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Abstract: The present study examined the plasticity of lexical selection mechanism in bilingual word production by training a group of unbalanced Chinese-English bilinguals with a language switching task. The experimental group received an 8-day language switching training, while the control group received no training. Before and after training, the behavioral and event-related potential (ERP) data of both groups in a cued picture naming task were collected. ERP results revealed a training effect such that after training, the N2 peak latency in cue-locked ERPs was shortened only in the experimental group. These results suggest that short-term language switching experience could improve the efficiency to establish the target language task schema to inhibit activation of the non-target language, and that inhibitory control acting as the lexical selection mechanism of word production in unbalanced bilinguals could be modulated by language switching experience.

Disclosures: **C. Kang:** None. **F. Ma:** None. **T. Guo:** None.

Poster

844. Schizophrenia Circuits and Systems

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 844.01/LLL12

Topic: H.03. Schizophrenia

Support: Z01 ES100221 to S.M.D.

Title: Chemo-genetic silencing of hippocampal area CA2 decreases hippocampal low gamma oscillations

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Abstract: Gamma oscillations (30-120Hz) found in local field potential recordings occur widely throughout the hippocampus and are believed to contribute to memory processes by coordinating the activity of dispersed neuronal populations into transient cell assemblies. These oscillations are subdivided into low (~25-55 Hz) and high (~65-120 Hz) gamma. Low gamma oscillations recorded in CA1 are thought to be driven by CA3 inputs and underlie memory retrieval, whereas high gamma oscillations are thought to be driven by layer 3 medial entorhinal cortical inputs and underlie memory formation. We previously demonstrated that chemo-genetic activation of area CA2 results in increased hippocampal low gamma oscillations, which are transmitted to prefrontal cortex. To determine whether CA2 neuronal activity plays an active role in hippocampal gamma oscillations under physiological conditions, we asked whether gamma oscillations are reduced when CA2 activity is inhibited. We infused adeno-associated viruses encoding a cre-dependent inhibitory DREADD (Designer Receptors Exclusively Activated by Designer Drugs) coupled to G_i into hippocampi of mice that express cre recombinase selectively in CA2 pyramidal cells. We then implanted electrode arrays to monitor activity of CA2 and CA1 neurons following administration of either vehicle or the DREADD ligand Clozapine-N-oxide (CNO; 5 mg/kg, subcutaneous) while animals ran in an open field. We found that power of gamma oscillations recorded in CA1 was lower following CNO administration than following vehicle administration, indicating that CA2 neuronal activity contributes to hippocampal gamma oscillations under physiological conditions. Further, we compared gamma oscillations recorded from areas CA2 and CA1. Whereas CA1 recordings displayed both low and high gamma oscillations, CA2 recordings were dominated by low gamma oscillations.
The involvement of CA2 in propagating hippocampal gamma oscillations is particularly interesting considering that patients with schizophrenia demonstrate reduced gamma oscillations during working memory tasks as well as selective loss of parvalbumin-positive interneurons, which interact with excitatory neurons to generate gamma oscillations, from CA2. Given these findings, impaired CA2 network activity may underlie at least some of the abnormalities in oscillatory activity and socio-cognitive function in patients with schizophrenia. Ongoing work is aimed at measuring gamma oscillations in the prefrontal cortex after silencing CA2 neuronal activity and correlating these changes in oscillatory activity with behaviors typically measured in animal models of schizophrenia.

Disclosures: G.M. Alexander: None. **L. Brown:** None. **S. Farris:** None. **D. Lustberg:** None. **B. Gloss:** None. **N. Plummer:** None. **P. Jensen:** None. **S.M. Dudek:** None.

Poster

844. Schizophrenia Circuits and Systems

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 844.02/LLL13

Topic: H.03. Schizophrenia

Title: A thalamo-cortical genetic co-expression network is associated with thalamic functional connectivity linked with familiar risk for schizophrenia

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Abstract: AIM:
The genetic architecture of schizophrenia is based on complex polygenic risk. Indeed, genes converge on molecular co-expression pathways, which may modulate crucial heritable traits of schizophrenia, the so-called intermediate phenotypes. In this regard, a recent study (Antonucci et al., 2016) has suggested thalamic functional dysconnectivity with prefrontal cortex and other cortical areas during attention as a viable intermediate phenotype for schizophrenia, even if there are no data linking it with genetic mechanisms of relevance for this disorder.
Here, we investigated in healthy humans the association of thalamic functional connectivity during attention with molecular correlates of relevance to schizophrenia. With this aim, we first characterized a co-expression network including genes with coordinated thalamo-prefrontal (THA-PFC) expression. Then, we assessed association of this co-expression pathway with genetic risk for schizophrenia. Finally, we investigated the relationship between a polygenic score indexing such co-expression with thalamic functional connectivity during attention.
METHODS: First, we used Braincloud and Brainspan datasets of *post-mortem* tissue to identify co-expression gene sets with THA-PFC coordinated expression (Pearson's and hypergeometric tests, Bonferroni corrected $p<.05$). Then, we assessed the enrichment of such gene sets (hypergeometric test) for loci identified in the largest genome wide association study on schizophrenia to date (Ripke et al., 2014). Thus, we detected genetic polymorphisms associated with the first principal component of the resulting gene set (module eigengene, ME) and combined their effects into a polygenic score (PGS), which was computed also for 265 healthy participants performing an attentional task during fMRI. Such PGS was used in a multiple regression on a component of interest obtained with an Independent Component Analysis (ICA) and including a thalamic cluster (Antonucci et al., 2016), which was our a priori region of interest (ROI) ($p<.05$, FWE corrected).
RESULTS: One gene set was enriched for coordinated THA-PFC expression and for

schizophrenia (Bonferroni-corrected p=.013). 14 SNPs were associated with its whole expression (ME). The resulting PGS predicted gene set co-expression ($p=7.64\times10^{-23}$), and was positively correlated with fMRI thalamic connectivity in our ROI (Bonferroni-corrected p=.001).
DISCUSSION: These results suggest a co-regulated molecular pathway relevant to schizophrenia and associated with thalamo-cortical connectivity during attention, which may implicate this imaging correlate as a crucial phenotype for this brain disorder.

Disclosures: L.A. Antonucci: None. **G. Pergola:** None. **P. Di Carlo:** None. **P. Taurisano:** None. **M. Papalino:** None. **R. Passiatore:** None. **A. Bertolino:** None. **G. Blasi:** None.

Poster

844. Schizophrenia Circuits and Systems

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 844.03/LLL14

Topic: H.03. Schizophrenia

Support: NIH Protocol 89-M-0006

NIH Intramural Research Program

Title: 7-Tesla MRI reveals regional hippocampal volume deficits of dentate gyrus in childhood-onset schizophrenia

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Abstract: Background
Childhood-onset schizophrenia (COS) is a rare and severe form of the disorder occurring before age 13. Previous work has established decreased hippocampal volume in both COS and adult-onset schizophrenia (AOS) patients. However, studies using 1.5- and 3-Tesla MRI have limited regional sensitivity due to lower image resolution, and reliable segmentation tools often classify individual hippocampal regions into diluted subfields. We use 7-Tesla imaging and new segmenting techniques to investigate regional alterations within the hippocampus in COS. We hypothesized that COS patients would show decreased volume in the dentate gyrus and in CA3, in accordance with the proposed glutamate-mediated plasticity deficit model of schizophrenia. In this model, abnormal glutamate signaling in the dentate and CA3 may relate to deficits in

plasticity, contributing to psychotic symptoms and impaired cognition.[1]

Methods

We acquired 0.7 mm isotropic MPRAGE scans and 0.5 mm T2*-weighted scans using a Siemens 7-Tesla Magnetom MRI scanner. Hippocampal subfields were automatically segmented using FreeSurfer v6.0 in COS patients (n=12, mean age= 20.4, 6 male), their unaffected siblings (n=9, age= 19.3, 2 male), and healthy controls (n=12, age = 20.5, 6 male). Analysis of covariance was used to compare volume differences between groups with covariates including age, sex, and intracranial or total cortical grey matter volume. Cohen's d was calculated using adjusted means and pooled standard deviation.

Results

We found that patients with COS had significant differences in subfield volumes localized to the dentate gyrus. Specifically, COS patients had smaller volume of the granular cell layer of the dentate compared to both controls (left hemisphere: $p = 0.0089$, Cohen's $d = 0.69$) and compared to siblings (right: $p = 0.031$, $d = 0.56$). Patients also exhibited reduced volumes in the molecular layer of the dentate compared to controls (left: $p = 0.037$, $d = 0.54$) but not siblings.

Conclusions

Volume loss within the dentate in COS may relate to previous abnormalities in this region, in keeping with the glutamate-mediated plasticity deficit model of schizophrenia. These results intersect with those of larger imaging consortia of AOS but exhibit higher effect sizes, underlining the benefits of new segmentation methods on 7T images and possibly more striking abnormalities for very early onset disorders.[2] Ongoing analyses are examining hippocampal shape differences using deformation morphometry, and investigating potential clinical correlates of these anatomical measures.

1. Tamminga, et al. (2010). *American Journal of Psychiatry*.
2. Mathew, I., et al. (2014). *JAMA Psychiatry.*

Disclosures: D. Zhou: None. **S. Liu:** None. **R.A. Berman:** None. **D.D. Broadnax:** None. **J.L. Rapoport:** None. **A.G. Thomas:** None.

Poster

844. Schizophrenia Circuits and Systems

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 844.04/LLL15

Topic: H.03. Schizophrenia

Support: Howard Hughes Medical Institute

Office of Naval Research

Swartz Foundation

NIH R01-MH065571

NIH MH042228

NIH MH079777

NIH MH087889

Title: Delay differential analysis for nonlinear dynamical clustering of mismatch negativity EEG data in large cohorts of schizophrenia patients and healthy participants

Authors: *R. KIM[1], C. LAINSCSEK[5,2], M. L. THOMAS[3], T. COGS INVESTIGATORS[4], T. J. SEJNOWSKI[5,2], G. A. LIGHT[3];
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Abstract: Background
Schizophrenia (SZ) patients suffering from psychosis display abnormal brain activity whose underlying nonlinear properties differ from those of healthy people. Due to the complex nature of the brain, traditional linear methods cannot fully characterize the variety of intrinsic states in EEG. In this study, delay differential analysis (DDA), a method based on embedding theory in nonlinear dynamics, was used to dynamically cluster control subjects as well as SZ patients. An embedding maps time series data (e.g. EEG) onto a sparse (low-dimensional) basis that gives insight into the nonlinear invariant properties of the underlying dynamical system (e.g. the brain) without having access to all the systems variables. We have previously shown that such analysis can extract ERP-like features from a small subset of raw EEG data without the use of amplitude information. Such features can then be used for dynamical clustering of EEG data.
Methods
SZ patients (n=877) and non-psychiatric comparison subjects (NCS; n=753) underwent EEG testing to measure mismatch negativity (MMN) as part of their participation in the Consortium on the Genetics of Schizophrenia (COGS-2) study. A novel dynamical clustering algorithm was developed using synthetic data generated from the Rössler system, one of the simplest nonlinear systems. The algorithm was then applied to all MMN recordings in COGS-2.
Results
Our dynamical clustering revealed six dissociable subgroups that differed on important demographic, clinical, cognitive, and functional characteristics. Interestingly, subgroups of misclassified NCS (n=224) and SZ patients (n=279) were also detected. For example, the subgroup of misclassified NCS had relatively lower global cognition compared to well-classified NCS; misclassified SZ patients had relatively higher global cognition compared to well-classified SZ. Characterization of DDA defined subgroups will be presented.
Conclusions
Delay differential analysis combined with dynamical clustering of EEG data is a promising novel approach for identifying subgroups that could help define meaningful clinical subgroups for a mental disorder.

Disclosures: **R. Kim:** None. **C. Lainscsek:** None. **M.L. Thomas:** None. **T. COGS investigators:** None. **T.J. Sejnowski:** None. **G.A. Light:** None.

Poster

844. Schizophrenia Circuits and Systems

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 844.05/LLL16

Topic: H.03. Schizophrenia

Support: NIH Grant 5P20RR021938/P20GM103472

NIH Grant R01EB020407

National Science Foundation Grant 1539067

NIMH Grant RO1MH076989

Max Kade Scholarship (EM)

Title: Dynamic functional connectivity in individuals at clinical high risk for psychosis, early illness schizophrenia patients, and healthy controls

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Abstract: Introduction:
The prodromal syndrome preceding schizophrenia consists of attenuated psychotic symptoms and deficits in social and cognitive functioning. While individuals prospectively diagnosed with this syndrome are at clinical high risk for psychosis (CHR), only 35% transition to psychosis within 3 years of initial diagnosis. This clinical outcome heterogeneity among CHR individuals underscores the need to develop biomarkers to improve the accuracy of psychosis risk prediction relative to the accuracy provided by clinical criteria alone. Toward this goal, we examined dynamic functional network connectivity (dFNC) from resting state functional magnetic resonance imaging (rsfMRI) data in CHR (n=44), early illness schizophrenia (SCZ; n=51), and healthy control (HC; n=76) participants.
Methods:

After initial standard preprocessing, rsfMRI data were decomposed into functionally homogeneous cortical and subcortical components using group-level spatial independent component analysis. Out of the 100 components obtained, we selected 50 components as intrinsic connectivity networks (ICNs) and assigned them to 8 functional domains. dFNC was computed as the correlations between ICN time courses using a sliding temporal window approach. Groups were compared with 2-sample t-tests. Clinical correlations with dFNC were assessed using PANSS (Positive and Negative Symptom Scale for SCZ) and SOPS (Scale of Prodromal Symptoms for CHR) symptom severity ratings.
Results:
We identified 5 discrete dFNC states. State 5, depicting the resting state with high intra-network connectivity and anti-correlation between default mode network and other functional domains, was abnormal in SCZ, with CHR showing milder abnormalities intermediate between SCZ and HC. In state 3, an intermediate connected state, CHR exhibited more divergent alterations than SCZ, both compared to HC. Further, in CHR subjects, functional connectivity between cognitive control and visual domains was correlated with symptom severity (SOPS disorganization symptoms) in a state showing high dysconnectivity (state 1).
Discussion:
dFNC alterations differ between psychosis risk states and early SCZ: State 5 shows gradual alterations with CHR subjects showing slight but well defined differences to HC that are more pronounced in SCZ. State 3, with a similar pattern to state 5, shows most pronounced abnormalities for CHR subjects compared to both HC and SCZ. This connectivity pattern as well as the correlation between symptom severity and FNC in state 1 is evident in CHR individuals; future studies will examine whether these patterns predict transition to psychosis in CHR individuals.

Disclosures: **E. Mennigen:** None. **D.H. Mathalon:** None. **B. Rashid:** None. **E. Damaraju:** None. **Y. Du:** None. **S.L. Fryer:** None. **R.L. Loewy:** None. **V.D. Calhoun:** None.

Poster

844. Schizophrenia Circuits and Systems

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 844.06/LLL17

Topic: H.03. Schizophrenia

Support: brain mapping by integrated neurotechnologies for disease studies (BRAIN/MINDS)

Title: Altered relationships between functional connectivity networks during the resting-state and auditory processing in schizophrenia

Authors: *R.-I. HASHIMOTO[1,2], R. OKADA[2], T. ITAHASHI[2], S. HASEGAWA[3], M. TANI[3], N. KATO[2], M. MIMURA[4];
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Abstract: Schizophrenia is characterized by a set of symptoms that stem from altered senses of self and reality such as auditory verbal hallucinations (AVH). Neural correlates of AVH in schizophrenia have been studied using fMRI under various experimental paradigms such as auditory oddball (AO) and auditory verbal working memory (aVWM) tasks as well as analysis of the resting-state brain activity. Although these studies were largely consistent in finding abnormalities in functional connections (FCs) in networks involving the auditory cortex, few studies have examined relationships between multiple abnormal patterns of FCs revealed by different approaches.
In order to address this issue, we collected fMRI data of multiple experimental conditions from the same participants and performed multivariate analysis to investigate the relationship between FC patterns under multiple conditions. Twenty five patients with chronic schizophrenia (SZ) and 25 normal controls (NC) underwent the three fMRI sessions of (i) AO, (ii) aVWM, and (iii) the resting-state. The AO and aVWM tasks were used as probes for sensory and cognitive aspects of neural abnormalities, while the resting-state fMRI was used as the baseline for the first two tasks. Under these three conditions, we first generated FC maps using a seed region in the left superior temporal gyrus (STG) as determined by a meta-analysis of previous studies of AVH. After generating FC maps separately for the three conditions in each individual, these maps were subjected into a multivariate analysis to find pairs of component maps of FCs that are associated between two different conditions. We then performed between-group comparisons regarding the loadings of the component maps and examined correlations between loadings and the severities of AVH in SZ.
In analysis of the relationship between FC maps of the resting-state and AO, we found that a component map involving positive FCs in the bilateral STG during the resting-state is significantly associated with a component map involving positive FCs in the bilateral STG and insular cortex during the AO. The group comparison revealed that loadings of that component were significantly reduced in SZ than in NC ($p<0.01$). We also found a significant group difference in loadings of component maps showing positive FCs in the bilateral STG during the resting-state and aVWM.
These findings revealed altered relationships between functional networks during the resting-state and auditory processing in individuals with schizophrenia, and further raised a possibility that the degree of such alteration may be associated with the severity of AVH in schizophrenia.

Disclosures: R. Hashimoto: None. **R. Okada:** None. **T. Itahashi:** None. **S. Hasegawa:** None. **M. Tani:** None. **N. Kato:** None. **M. Mimura:** None.

Poster

844. Schizophrenia Circuits and Systems

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 844.07/LLL18

Topic: H.03. Schizophrenia

Support: AMED-SRPBS

Title: Transdiagnostic mapping from intrinsic functional network onto working memory ability

Authors: *M. YAMASHITA[1], Y. YOSHIHARA[2], R. HASHIMOTO[3], N. YAHATA[4,5], N. ICHIKAWA[6], Y. SAKAI[1,7], T. YAMADA[1,3], N. MATSUKAWA[2], G. OKADA[6], S. C. TANAKA[1], K. KASAI[4], N. KATO[3], Y. OKAMOTO[6], B. SEYMOUR[1,8,9], H. TAKAHASHI[2], M. KAWATO[1], H. IMAMIZU[1,4];
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Abstract: Psychiatric diagnoses are generally categorical and distinctly classify patients based on their symptoms. However, recent transdiagnostic studies have identified common neurobiological substrates across a range of psychiatric disorders. An important next step is to establish bridges between abnormal behaviors and neurobiological dysfunctions. Here, we tested two alternative hypotheses: the mapping from neurobiology (functional connectivity; FC) onto behavior (cognitive performance) is (i) specific to each diagnostic category or (ii) common to healthy/typically developed individuals and patients of any psychiatric diagnoses. We focused on working memory ability (WMA), which is behaviorally impaired in descending order of severity in schizophrenia (SZ), major depressive disorder (MDD), obsessive compulsive disorder (OCD), and autism spectrum disorder (ASD).
We adopted a data-driven prediction model that has been shown to map an individual FC pattern onto WMA: the 'Working Memory Prediction Model' which is based only on Healthy Young Japanese participants (WMPM-HYJ). We found that the WMPM-HYJ predicted the WMA of individuals in an external validation dataset, which consists of much larger (N = 474) and more diversified USA healthy individuals than the discovery cohort. We used an independent dataset of SZ patients (N = 58), which consists of resting state-fMRI and the performance score of a working memory task. Moreover, we used independent datasets of patients with SZ, MDD, OCD, and ASD (N = 58, 77, 46, and 69, respectively) as well as their age- and gender-matched healthy/typically developed controls (N = 60, 63, 51, and 71).
We found that the WMPM-HYJ predicted (i) individual WMA in the independent USA validation cohort of a healthy population (partial Spearman’s rank correlation while factoring out

individual fluid intelligence, $\rho = 0.12$, $P = 0.0094$), (ii) individual WMA among patients with SZ (partial correlation while factoring out individual general cognitive performance, $\rho = 0.26$, $P = 0.049$), and (iii) the order and extents of WMA alterations for the four diagnoses (Hedge's g: [SZ, MDD, OCD, ASD] = [-0.68, -0.29, -0.15, 0.09]).
The present study provides the first evidence for a common transdiagnostic mapping from FC patterns onto cognitive performance. Diagnosis-specific WMA deficits were explained through the common mapping WMPM-HYJ by differential pathological changes in FC patterns characteristic to each diagnosis. This commonality in the computational mechanism for large-scale FC leaves open the possibility of exploring common mappings from FC to diverse cognitive functions and symptoms of a wider range of diagnoses.

Disclosures: **M. Yamashita:** None. **Y. Yoshihara:** None. **R. Hashimoto:** None. **N. Yahata:** None. **N. Ichikawa:** None. **Y. Sakai:** None. **T. Yamada:** None. **N. Matsukawa:** None. **G. Okada:** None. **S.C. Tanaka:** None. **K. Kasai:** None. **N. Kato:** None. **Y. Okamoto:** None. **B. Seymour:** None. **H. Takahashi:** None. **M. Kawato:** None. **H. Imamizu:** None.

Poster

844. Schizophrenia Circuits and Systems

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 844.08/LLL19

Topic: H.03. Schizophrenia

Title: Piriform functional connectivity in schizophrenia

Authors: S. KIPARIZOSKA[1], *T. IKUTA[2];
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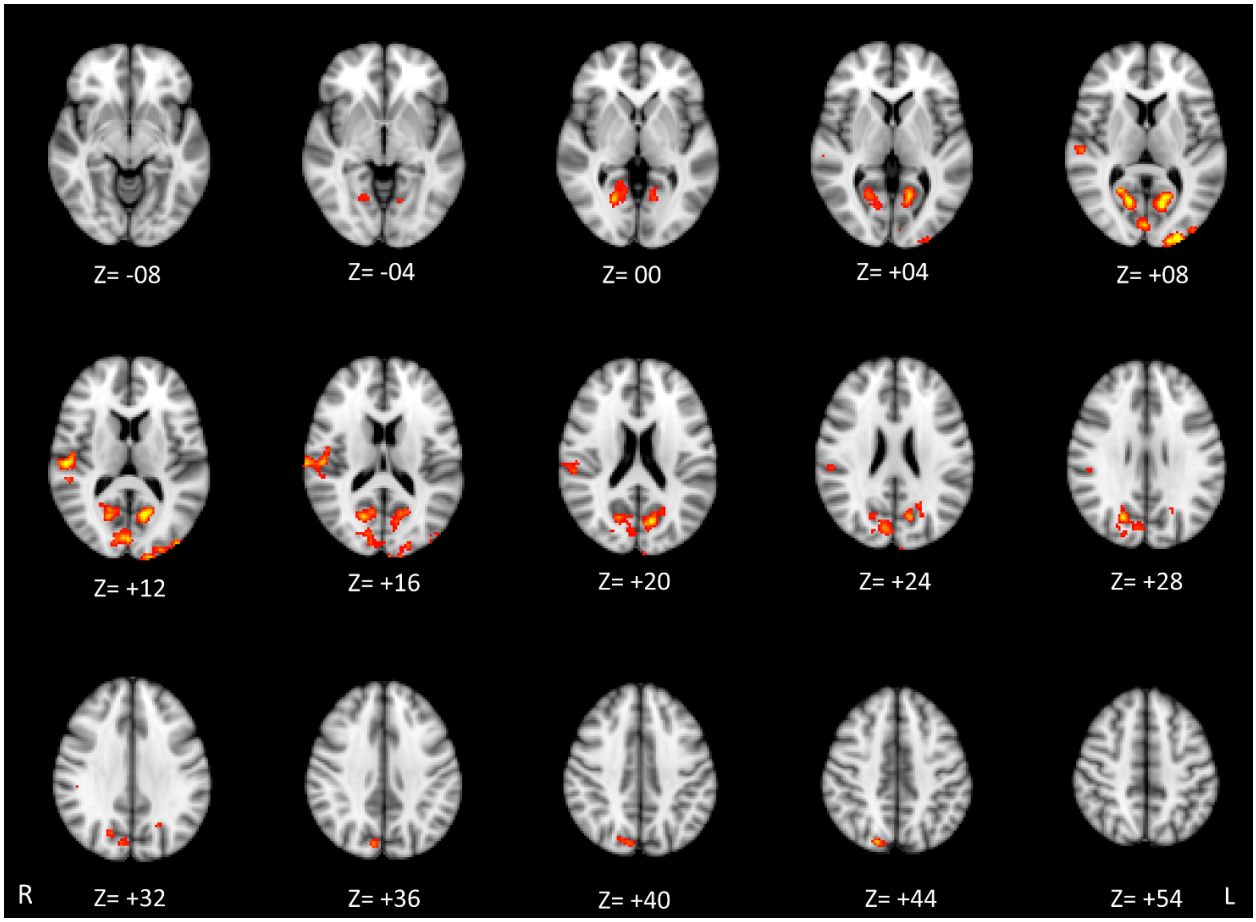
Abstract: While studies have shown that schizophrenia influences olfaction, the olfactory system in schizophrenia is not commonly studied. Different smell sensation and smaller odor sensitivity have been reported in schizophrenia compared to control cohorts. It has also been suggested that odor identification tests may be useful in diagnostic purposes. In the current typical understanding of schizophrenia, however, olfaction is not understood to contribute to the illness since altered olfaction would be not accounted for by dopaminergic or glutaminergic alternation. Therefore, it remains largely unclear why olfaction would be affected in schizophrenia, in the absence of logical relation to other symptoms. Here, we aimed to examine functional connectivity of the piriform cortex in order to isolate the olfactory network that would account for the altered olfaction. Functional connectivities were tested from the bilateral piriform cortex to the rest of the brain in the voxel-wise fashion. Using the resting state functional MRI data from Center for Biomedical Research Excellence, 71 patients of schizophrenia (SZ group)

and 74 individuals without schizophrenia (control group) were compared. The SZ group showed lesser piriform connectivity with primary auditory and primary visual cortices. The current results suggest that primary sensory regions are disconnected in schizophrenia. It may be possible to interpret that schizophrenia affects synchrony and integration of multiple sensory modalities.



Disclosures: **S. Kiparizoska:** None. **T. Ikuta:** None.

Poster

844. Schizophrenia Circuits and Systems

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 844.09/LLL20

Topic: H.03. Schizophrenia

Support: NIH MH104320

Title: Differential Impact of withdrawal from prior D2 antagonist vs aripiprazole treatment on dopamine system activity in MAM model of schizophrenia

Authors: *S. SONNENSCHEIN, K. M. GILL, S. A. MILLER, A. A. GRACE;
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Abstract: Novel target compounds for the treatment of schizophrenia have shown promise in preclinical research, but failed to show efficacy in clinical trials. However, preclinical research is typically performed on drug-naïve rats, whereas clinical trials are performed on patients that have received only brief withdrawal from years of prior antipsychotic drug (APD) treatment despite potential pervasive changes to the DA system. We previously found in the methylazoxymethanol acetate (MAM) model of schizophrenia that withdrawal from repeated haloperidol (HAL) treatment produces persistent changes, interfering with the ability of a novel target compound that is effective in non haloperidol-treated rats to reverse the hyperresponsive state of the DA system. In the current study, we examined the effects of withdrawal from mechanistically distinct APDs, with a focus on the D2 partial agonist aripiprazole (ARI). Saline (SAL) and MAM-treated offspring received repeated HAL (0.6 mg/kg), clozapine (CLO; 10 mg/kg or 20 mg/kg), ARI (10 mg/kg), or vehicle (0.23% glacial acetic acid) for 21 d, p.o. followed by 7d withdrawal. The number of spontaneously active DA neurons in the VTA was measured using in vivo extracellular recordings from anesthetized rats. After electrophysiological sampling, a subset of rats received a low dose of apomorphine (40 ug/kg, i.v.) to test for removal of depolarization block, followed by resampling the VTA in the opposite hemisphere. Recordings were also conducted in SAL and MAM rats 3 h following acute treatment with ARI (10 mg/kg, p.o). Finally, additional MAM and SAL rats withdrawn from repeated treatments were administered the DA agonist quinpirole (8mg/kg, i.p.) prior to measuring locomotion in an open field to test for DA supersensitivity. In contrast to D2 antagonists, withdrawal from ARI treatment did not reduce the number of spontaneously active DA neurons in normal rats. In contrast, MAM rats demonstrated reduced DA neuron activity following both repeated and acute treatment with ARI, which was maintained following administration of apomorphine, suggesting that it is unlikely the result of depolarization block. Preliminary data suggests that rats withdrawn from ARI treatment do not show increased locomotor response to quinpirole, indicating absence of APD-induced DA supersensitivity. Lack of evidence for depolarization block and preliminary findings showing lack of DA supersensitivity in ARI-treated rats suggests that brief withdrawal from ARI treatment may not interfere with the antipsychotic efficacy of novel target compounds.

Disclosures: S. Sonnenschein: None. **K.M. Gill:** None. **S.A. Miller:** None. **A.A. Grace:** None.

Poster

844. Schizophrenia Circuits and Systems

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 844.10/LLL21

Topic: H.03. Schizophrenia

Support: NIH Grant 1RO1 MH077851

Title: Hippocampal CA3 hyperactivity may contribute to a psychosis-like phenotype in mice.

Authors: *D. SCOTT, C. A. TAMMINGA;
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Abstract: Schizophrenia is a serious mental illness affecting approximately 1% of the world's population. Schizophrenia is characterized by a wide variety of distinct symptoms which can be broadly categorized as positive (e.g., delusion, hallucinations, psychosis), negative (e.g., anhedonia, alogia), and cognitive symptoms. The mechanisms underlying these symptoms, particularly psychosis, remain poorly understood. Findings from human schizophrenia tissue have demonstrated that molecular markers of hippocampal activity, particularly within the CA3 subfield, could represent a mechanism for *in vivo* whole hippocampal/CA1 hyperactivity, which correlates with the degree of psychosis; neuronal activity, as measured with *in vivo* imaging, is elevated in hippocampus in schizophrenia, and schizophrenia CA3 tissue shows increased glutamatergic receptors and post-synaptic proteins in CA3. Moreover, as elements of psychosis resemble features of memory, and the severity is correlated with activity in a region known to mediate aspects of memory, we therefore conceptualize psychosis as a memory disorder, induced by hippocampal hyperactivity, and hypothesize that hyperactivation in CA3 directly mediates specific behaviors associated with psychosis. In order to replicate this in a mouse and specifically induce a hyperactive state in CA3, we infused an AAV containing a Designer Receptor Exclusively Activated by Designer Drugs (DREADD), under the control of a pyramidal cell-specific promoter directly into the dorsal or ventral CA3 of wild-type mice. This approach allows us to induce firing of the infected neurons in a cell-type, spatially, and temporally specific manner, and assess the resulting animal behaviors and hippocampal pathology. We focus on behavioral paradigms assessing both classical animal behaviors associated with schizophrenia (prepulse inhibition), as well as episodic memory (fear conditioning). Our preliminary results assessing animal behaviors after acute activation of DREADD-expressing pyramidal cells suggest hyperactivity within both the dorsal and ventral CA3 enhances cued fear conditioning but does not modify contextual fear conditioning or prepulse inhibition. These results suggest a specific behavioral effect of CA3 hyperactivity, but recommend further research to determine the broader range of symptom correlates induced by hippocampal hyperactivity, as well as the role of abnormal activity within the other hippocampal

subfields and connected regions. The overall demonstration of the neural correlates of psychosis would satisfy a high medical need in schizophrenia research, and provide novel targets for therapy.

Disclosures: D. Scott: None. **C.A. Tamminga:** None.

Poster

844. Schizophrenia Circuits and Systems

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 844.11/LLL22

Topic: H.03. Schizophrenia

Support: MH57440

MH105782

Title: Hippocampal subregional differences in response to entorhinal cortex and amygdala input in MAM model of schizophrenia

Authors: *K. M. GILL, A. A. GRACE;
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Abstract: There are significant neurochemical and electrophysiological changes in the ventral hippocampus (vHPC) of the rat methylazoxymethanol acetate (MAM) neurodevelopmental model of schizophrenia. In the present study, extracellular field potential recordings were conducted in vivo from subregions of the vHPC (CA3, CA1, and vSub) in adult Saline and MAM-treated offspring. The goal was to observe whether there were alterations in the gating of afferent input arising from the basolateral amygdala (BLA) and entorhinal cortex (EC) in this model. For each hippocampal subregion, baseline evoked field potential responses were produced via EC stimulation (100 μsec pulse duration, 0.5 Hz pulse frequency). After baseline, a subthreshold BLA stimulation preceded EC stimulation at preset intervals (100, 30, 20, 10, 1 msec) and the effect on EC-evoked field potential amplitude (deviation between positive and negative phase components of evoked field potential) was measured. In Saline animals, shortening the latency between BLA and EC stimulation caused progressive changes in field potential amplitude, in particular there was increased field size in CA1 and decreased field size in vSub. In contrast, a different pattern was observed in MAM animals such that there were no discernible changes in field potential amplitude until the latency between stimulation was of sufficiently short duration (1 msec), and only in the CA1 and vSub subregions. The impact of high frequency stimulation to the BLA (0.5mA, 20 Hz, 10 sec) on subsequent EC-evoked

responses was also measured. In Saline animals, the largest effect was a sustained potentiation (>50% from baseline; 30 min) of field potential responses in CA1. In addition, there was a transient reduction in EC-evoked field potential responses in CA3 (>10% from baseline; <10 min) as well as a larger, longer lasting reduction in EC-evoked field potentials in the vSub (>15% from baseline). Unlike Saline animals, in MAM animals the tetanization of the BLA caused only a slight increase (10% from baseline) in field potential size in CA1 along with a larger sustained decrease in field potential size in CA3 (>20%; 30 min). Overall, the hippocampal subregions in Saline animals appeared more sensitive to the coincident stimulation of BLA and EC. Since the EC participates as a gateway for information between the neocortex and hippocampus, this would signify that strong amygdala activation can heterogeneously impact the influence of cortical inputs to the vHPC in normal subjects. This could indicate an inability of the BLA to modulate the responsiveness of vHPC to potential contextual changes signaled by the EC in MAM animals.

Disclosures: **K.M. Gill:** None. **A.A. Grace:** None.

Poster

844. Schizophrenia Circuits and Systems

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 844.12/LLL23

Topic: H.03. Schizophrenia

Support: NIMH grant F32MH106265

NIMH grant R01MH101218

NIMH grant R01 MH100561

NIMH grant R01 MH077235

Title: Mismatch negativity depends on somatostatin interneurons and is affected in a genetic model of schizophrenia

Authors: *J. P. HAMM, J. A. GOGOS, R. YUSTE;
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Abstract: Sensorineural processing dysfunction in schizophrenia undermines how affected individuals perceive and relate to a changing environment. The mismatch negativity (MMN), typically recorded with EEG during auditory or visual “oddball” paradigms, is among the best replicated biomarkers of this aspect of the disease. Since schizophrenia involves cortex-wide

alterations to microcircuitry and local interneurons, it is likely that the MMN biomarker reflects a circuit-level pathophysiology. Mouse research provides promising tools to investigate fine components of MMN with cell-level precision, but past attempts to examine key MMN components at this scale have been unsuccessful, perhaps complicated by anesthesia and the scope and resolution of neocortical recordings. First, in primary visual cortex of awake mice, local field potentials were recorded with 16-channel electrode arrays spanning layers 1-5. Two-photon calcium imaging of layer 2/3 neurons (GCaMP6s/f; 30Hz) was used to quantify population activity with single neuron resolution. Mice viewed full-field oriented squarewave stimuli in a typical oddball paradigm (12.5% oddballs) and a "many standards" control paradigm. Robust stimulus specific adaptation (SSA) and genuine deviance detection (the critical component of human MMN) was identified in local activity across all depths with current source density analysis and in single neuron responses with calcium imaging. These components were also observed in auditory cortex using a similar paradigm. Selectively suppressing somatostatin-containing interneurons (SOMs) with pharmacogetics (D.R.E.A.D.D.s) dramatically eliminated deviance detection, but left SSA intact. A similar deficit was observed in mutant mice (Df(16)A+/-) modeling 22q11.2 deletions in humans (a strong genetic risk factor for schizophrenia and cognitive dysfunction), involving again normal neuronal adaptation to repeated stimuli (SSA) but reduced deviance processing at the single cell level (60-80%). These results show that sensory cortex of awake mice could provide a rich model for understanding salience processing deficits paramount to schizophrenia. Further, this begins to link a non-invasive, highly translatable biomarker, the MMN, to the function of somatostatin-containing interneurons, a suspected cell-level pathophysiology present in some patients.

Disclosures: **J.P. Hamm:** None. **J.A. Gogos:** None. **R. Yuste:** None.

Poster

844. Schizophrenia Circuits and Systems

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 844.13/LLL24

Topic: H.03. Schizophrenia

Support: 1K23 MH102656-01A1 (Ivleva)

1R01MH083957-01A2 (Tamminga)

Title: Hippocampal hyperactivity: the driver for psychosis?

Authors: ***E. I. IVLEVA**[1], S. ASLAN[2], Y. FANG[1], C. B. SACCO[1], H. LU[3], M. D. RUGG[4], C. A. TAMMINGA[1];

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Abstract: Objective. Alterations in limbic system structure and function have long been implicated in psychotic disorders. In this study, conceptualizing psychosis as a learning and memory disorder and building on animal and tissue work from our lab, we examine how alterations in relational memory function and underlying brain circuitry may contribute to psychosis. We hypothesize that increased baseline hippocampal activity—specifically, activity in CA3 that is propagated onto downstream CA1 and subicular cell fields—coupled with weakened prefrontal cortex (PFC) function subserve both relational memory dysfunction and psychosis formation in schizophrenia.
Methods. 23 healthy comparison (HC) and 18 schizophrenia (SZ) subjects underwent multimodal brain MRI including whole brain perfusion [Arterial Spin Labeling (ASL)] and functional MRI (fMRI) with a relational memory task. ASL and fMRI analyses included both whole brain voxel-wise and region-of-interest (ROI)-based cerebral blood flow (CBF) and BOLD activity estimations. In an independent sample [24 H, 37 SZ], subfield-level hippocampal activity was estimated via regional cerebral blood volume (rCBV) using high resolution a Vascular Space Occupancy (VASO) perfusion technique.
Results. Compared to HC, SZ showed reduced CBF in bilateral dorsolateral prefrontal cortex (DLPFC) and the left anterior/middle cingulate gyrus, as estimated by whole brain voxel-wise ASL analyses [$p<.05$, FWE-corrected, $k\geq3848mm^3$]. In addition, SZ had increased CBF in the left parietal cortex/angular gyrus relative to HC. An ROI-based approach confirmed CBF reductions in SZ in bilateral DLPFC [left, $p=.03$; right, $p=.04$], and the left ventrolateral prefrontal cortex [$p<.001$] vs. HC. No between-group differences in hippocampal CBF were detected with this whole brain perfusion approach. However, high resolution hippocampal subfield VASO identified increased rCBV in SZ in the left CA3, CA1 and subiculum (combined) ($p=.08$, trend) but not in the dentate gyrus ($p=.48$), compared to HC.
Conclusions. Our findings identifiy increased baseline hippocampal activity/rCBV driven by CA3 and propagating onto CA1 and subiculum, coupled with reduced activity/CBF in PFC and anterior/middle cingulate in SZ. Notably, elevated hippocampal perfusion was detected by high resolution VASO but not by global ASL analyses, supporting the importance of high resolution hippocampal subfield-level approaches. These perfusion findings will be complemented by task-based fMRI outcomes. Furthermore, associations between imaging, relational memory and psychosis manifestation outcomes will be reported.

Disclosures: E.I. Ivleva: None. **S. Aslan:** None. **Y. Fang:** None. **C.B. Sacco:** None. **H. Lu:** None. **M.D. Rugg:** None. **C.A. Tamminga:** Other; Dr.Tamminga has served on the advisory board for drug development for Intra-Cellular Therapies, Inc; and as an ad hoc consultant for Eli Lilly Pharmaceuticals, Sunovion, Astellas, Pfizer, Merck.

Poster

844. Schizophrenia Circuits and Systems

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 844.14/LLL25

Topic: H.03. Schizophrenia

Support: PHS Award P50 MH086404

NIH T32MH018870

Title: Constitutively boosting dopamine neuron spike activity subtly alters indices of dopamine transmission some spontaneous and learned behaviors and attenuates amphetamine responsivity

Authors: *A. S. KALMBACH[1,5], M. O. CHOHAN[6], N. CHUHMA[5,1], S. MINGOTE[5,1], S. PASKEWITZ[6], S. E. GORHAM[1], J. LIZARDI-ORTIZ[2], K. TAYLOR[1], J. P. ADELMAN[8], D. L. SULZER[1,2,3], P. BALSAM[9,7,4], H. MOORE[6,1], S. RAYPORT[5,1];
[1]Psychiatry, [2]Neurol., [3]Pharmacol., [4]Psychology, Columbia Univ., New York, NY; [5]Mol. Therapeut., [6]Integrative Neurosci., [7]Cognitive Neurosci., New York State Psychiatric Inst., New York, NY; [8]Vollum Inst., Oregon Hlth. and Sci. Univ., Portland, OR; [9]Psychology, Barnard Col., New York, NY

Abstract: Several neuropsychiatric disorders involve aberrant dopamine signaling, and schizophrenia in particular involves increased striatal dopamine release. Dopamine neuron excitability and activity patterns evoke tonic and phasic release of dopamine in projection regions, and could contribute to the increased dopamine release. We sought to determine how a constitutive augmentation in dopamine neuron excitability would impact dopamine signaling and behaviors relevant to schizophrenia. With a DAT-driven knockout of the small conductance potassium channel, SK3, we eliminated SK3 immunoreactivity and apamin-sensitive currents in dopamine neurons. The conditional deletion of SK3 led to an increase in intrinsic excitability of dopamine neurons in vitro, with an increase in pacemaker activity in both the ventral tegmental area (VTA) and substantia nigra pars compacta (SNc). In vivo single-unit recordings in anesthetized mice further revealed an increase in spontaneous spike activity and shift from tonic irregular activity to bouts of sustained spiking at rates comparable to burst firing, which was more pronounced in the SNc. Eliminating SK3 channels resulted in increased dopamine content in the midbrain and ventral striatum, but not in the dorsal striatum. Using in vitro cyclic voltammetry, we found a modest increase in dopamine release in the striatum but no effect on reuptake of dopamine. In the open field, SK3 knock-out mice were hyperactive, but had a blunted response to amphetamine. Unexpectedly, loss of SK3 channel affected neither prepulse inhibition, a measure of sensory gating, nor the rates of probabilistic and reversal learning, measures of cognition. Together, these results indicate that constitutive loss of the SK3 potassium conductance in dopamine neurons leads to enhanced spike activity with evidence of

subtle changes at the levels of striatal DA transmission and spontaneous and learned behavior, and with a significantly attenuated behavioral response to amphetamine.

Disclosures: **A.S. Kalmbach:** None. **M.O. Chohan:** None. **N. Chuhma:** None. **S. Mingote:** None. **S. Paskewitz:** None. **S.E. Gorham:** None. **J. Lizardi-Ortiz:** None. **K. Taylor:** None. **J.P. Adelman:** None. **D.L. Sulzer:** None. **P. Balsam:** None. **H. Moore:** None. **S. Rayport:** None.

Poster

844. Schizophrenia Circuits and Systems

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 844.15/LLL26

Topic: H.03. Schizophrenia

Support: VA Schizophrenia Special Research Fellowship

U01EB017695

R01MH086638

Title: Schizophrenia genome-wide association studied with computer simulation: gamma oscillations and information flow in CA3

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Abstract: Brain oscillations, which play roles in memory and attention, are abnormal in schizophrenia (SCZ). Genome wide association studies (GWAS) in SCZ have identified 108 loci of possible mutations. We looked at two putative mutations, using multiscale modeling of hippocampal area CA3, to explore their effects on oscillations and information flow. Mutations at these 2 loci will alter network activity through changes in cell conductances: 1. HCN1 -- coding the channel mediating the h-current (Ih); 2. GRIN2A -- coding subunit 2A of the NMDA-type receptor (NMDAR). Our network model consisted of pyramidal neurons (PYR), basket cells (BAS) and Oriens Lacunosum Moleculare (OLM) interneurons. BAS and OLM also received inhibitory input from medial septum (MS). We varied the magnitude of Ih and NMDAR conductances (gh and gNMDAR respectively) at sites on each cell type (Table 1) and in

combinations. We evaluated the simulations for increase in gamma oscillation, a putative signature for SCZ. We also looked at decreased theta power as a possible secondary marker. Using multiple simulation wirings and drive, we found consistent gamma increase with increased Ih conductance at BAS, or with decreased gNMDAR conductance at OLM. These oscillatory changes were also associated with reduction of information transfer from CA3 input (mossy fibers of the trisynaptic pathway and perforant pathway) to output (Schaffer collaterals) as measured by normalized transfer entropy (nTE). We predict that the increase in gamma power seen in SCZ would be a consequence of HCN1 mutations that increase gh primarily on BAS, and/or GRIN2A mutations that decrease gNMDAR primarily on OLM cells. Our multiscale modeling of CA3 showed how 2 GWAS loci can produce oscillatory signatures of SCZ that would relate to alterations in information flow with implications for cognitive dysfunction. We propose that both HCN1 and GRIN2A are part of the same "clinical pathway" involved in generating oscillations (a potential biomarker), and producing cognitive impairment.
Table 1. Gamma-theta changes as unchanged 0, increase ↑, decrease↓

Conductance → gh increase				**gNMDAR decrease**		
	PYR	**BAS**	**OLM**	**PYR**	**BAS**	**OLM**
Gamma	0	↑	↓	↓	↓	↑
Theta	↑	0	↓	↓	↑	↓

Disclosures: **M.A. Sherif:** A. Employment/Salary (full or part-time): VA Connecticut Healthcare System, West Haven, Yale University - Dept. of Psychiatry. **S.A. Neymotin:** A. Employment/Salary (full or part-time): SUNY Downstate Medical Center, Brooklyn, NY. **W.W. Lytton:** A. Employment/Salary (full or part-time): SUNY Downstate Medical Center, Brooklyn, NY.

Poster

844. Schizophrenia Circuits and Systems

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 844.16/LLL27

Topic: H.03. Schizophrenia

Title: Selectively reduced dentate gyrus GluN1 is associated with hippocampal CA3 and CA1 hyperactivity and psychosis behaviors in a mouse genetic model

Authors: *C. TAN, S. SOUTHCOTT, M. YANAGI, W. LI, C. A. TAMMINGA;
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Abstract: Psychosis is the core symptom cluster in schizophrenia. Animal models for psychosis have been inadequate because of the unknown cellular and molecular disease mechanisms. Based on recently discovered hippocampal subfield-specific molecular pathology, reduced GluN1 in dentate gyrus (DG) and increased markers of synaptic strength in CA3, in schizophrenia subfield tissue, we created and are testing a reverse translational animal model for schizophrenia psychosis (SzP).
We crossed a POMC-Cre mouse line with a floxed P-GluN1 mouse line to create a DG-specific knock out of GluN1 mouse model (DG-GluN1 KO). In DG, the tissue showed a reduced level of GluN1 protein in the KO mice. To assess baseline cellular activity in hippocampal subfields, we recruited c-Fos, as a marker for neuronal activity, and performed the immunohistochemistry and stereological analysis on both groups. The coronal sections showed a trend towards a *decrease* in the number of c-Fos-positive neuronal nuclei in DG in KO mice compared to controls. However, a significant *increase* in the number of c-Fos-positive neuronal nuclei were identified in CA3 ($p=0.02$) and CA1 ($p=0.03$) subfields in KO mice. We examined the number of c-Fos-positive nuclei along the rostral-to-caudal distance from Bregma and found a significant increase in caudal CA3 and CA1 (-2.70mm and -2.92mm from Bregma). These CA3/CA1 hyperactivity indicators could be the source of the well demonstrated *in vivo* imaging in individuals with SzP. Behaviorally, the DG-GluN1 KO mice showed reduced pre-pulse inhibition and performance in Morris Water Maze, as well as increased freezing in the fear conditioning paradigm and latency to enter the shock-paired compartment in the passive avoidance task. These behavior results indicated the deficient sensorimotor gating and impaired hippocampal-dependent spatial memory, which are consistent with those detected in human SzP behavior tests, as well as an enhanced fear associated memory recall, which may be the consequence of hippocampal pathology and its associated pathology in the related limbic structures.
In this study, we demonstrate the presence of increased hippocampal CA3/CA1 activity associated with the DG-specific GluN1 depletion. In addition, we also identify the classical and novel animal psychosis behaviors. These findings support the further testing of the DG-GluN1 KO as an animal preparation for psychosis in schizophrenia.

Disclosures: C. Tan: None. **S. Southcott:** None. **M. Yanagi:** None. **W. Li:** None. **C.A. Tamminga:** None.

Poster

844. Schizophrenia Circuits and Systems

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 844.17/LLL28

Topic: H.03. Schizophrenia

Support: NIH Grant R01 MH095810

NIH Grant R01 MH097742

ALSAC

Title: Haploinsufficiency of the 22q11.2-microdeletion gene *Mrpl40* disrupts short-term synaptic plasticity and working memory through dysregulation of mitochondrial calcium

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Abstract: Hemizygous deletion of a 1.5- to 3-megabase region on chromosome 22 causes 22q11.2 deletion syndrome (22q11DS), which constitutes one of the strongest genetic risks for schizophrenia. Mouse models of 22q11DS have abnormal short-term synaptic plasticity (STP) that contributes to working memory deficiencies similar to those in schizophrenia. We screened mutant mice carrying hemizygous deletions of 22q11DS genes and identified haploinsufficiency of *Mrpl40* (mitochondrial large ribosomal subunit protein 40) as a contributor to abnormal STP. Two-photon imaging of the genetically encoded fluorescent calcium indicator GCaMP6, expressed in presynaptic cytosol or mitochondria, showed that *Mrpl40* haploinsufficiency dysregulates STP via impaired calcium extrusion from the mitochondrial matrix through the mitochondrial permeability transition pore. This led to abnormally high cytosolic calcium transients in presynaptic terminals and deficient working memory but did not affect long-term spatial memory. Thus, we propose that mitochondrial calcium dysregulation is a novel pathogenic mechanism of cognitive deficiencies in schizophrenia.

Disclosures: **P. Devaraju:** None. **J. Yu:** None. **D. Eddins:** None. **M.M. Mellado-Lagarde:** None. **L. Earls:** None. **J.J. Westmoreland:** None. **G. Quarato:** None. **D.R. Green:** None. **S.S. Zakharenko:** None.

Poster

844. Schizophrenia Circuits and Systems

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 844.18/LLL29

Topic: H.03. Schizophrenia

Support: Brain and Genomics Fund, University of Minnesota Foundation, University of Minnesota

American Legion Brain Sciences Chair, Univeristy of Minnesota

McKnight Presidential Chair in Cognitive Neuroscience, University of Minnesota

Title: Hemisphere- and lag-dependent differences in dynamic neural interactions in schizophrenia

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Abstract: We compared neural interactions in 21 schizophrenia patients and 23 matched healthy controls using cross-correlation function (CCF) analysis of prewhitened resting-state magnetoencephalographic (MEG) recordings. Data were acquired from 248 axial gradiometers (Magnes 3600WH, 4-D Neuroimaging) at 1.027 Hz (every 0.974 ms) for 45s while participants fixated a spot. MEG time series were prewhitened (i.e. converted to white noise innovations) using a (50,1,3) ARIMA model. For each participant, all possible pairwise CCFs between MEG sensors were computed at zero and up to 50 lags (= 48.7 ms, every 0.974 ms) and the CC distributions between the two groups of participants were compared at each lag using a t-test on the Fisher z-transformed CCs. We found the following. (a) CCs in schizophrenia (SZ-CC) were highly significantly stronger than in controls (C-CC) in all lags. (b) At zero and up to 15 lags (= 14.61 ms), SZ-CCs were significantly greater than C-CCs, with a peak at the 7th lag (= 6.82 ms); at lags >15, SZ-CCs were lower than C-CCs, with a peak at the 18th lag (= 17.53 ms). (c) This pattern was most prominent in the right hemisphere and in interhemispheric interactions. In contrast, in the left hemisphere, there was no systematic difference until the 10th lag (= 9.74 ms), after which SZ-CCs were lower than C-CCs until the 23rd lag (= 22.4 ms). These findings demonstrate for the first time significant hemisphere- and lag-dependent systematic differences in strength and polarity of dynamic neural interactions in schizophrenia.

Disclosures: C. Chorn: None. **A.P. Georgopoulos:** None. **A. Leuthold:** None.

Poster

844. Schizophrenia Circuits and Systems

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 844.19/LLL30

Topic: H.03. Schizophrenia

Support: NARSAD Young Investigator

Title: Duplication of hVIPR2 elicits cognitive and social behavorial deficits in a novel BAC transgenic mouse model

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Abstract: The lack of a credible animal model of Schizophrenia with good construct validity hinders the understanding of its pathogenic mechanisms and the development of therapeutics. Two large-scale GWAS studies identified a rare Copy Number Variant (CNV) at the chromosomal locus 7q36.6 in schizophrenia patients at a rate 14 times higher than in healthy individuals, with all of the microduplications occurring within a single gene: Vasoactive Intestinal Peptide Receptor 2 (VIPR2). The identification of such genetic lesion permits the generation of etiologically valid genetic animal models of schizophrenia. We have developed a conditional BAC transgenic mouse model of the susceptibility allele that faithfully recapitulates genetic microduplication of human VIPR2. Importantly, the first exon of VIPR2, which contains the endogenous translation initiation codon, was floxed by two loxP sites, and therefore the expression of VIPR2 can be switched-off in desired temporal and spatial patterns, controlled by crossing with Cre recombinase-expressing mice. Genetic microduplication of human VIPR2 elicits significant cognitive (spatial working memory) deficits and impaired social interaction and social cognition in mice. Neurocircuits underlying the behavioral deficits were dissected using conditional genetics and wireless optogenetic device. Such animal model offers the opportunity to explore the molecular, cellular and circuit-level abnormalities underlying the expression of psychopathology, and may facilitate translational studies for biomarkers and drug discovery.

Disclosures: **X. Tian:** None. **A. Richard:** None. **K. Holmes:** None. **I.V. Savage:** None. **W. Yang:** None. **N. Goeders:** None. **X. Lu:** None.

Poster

844. Schizophrenia Circuits and Systems

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 844.20/LLL31

Topic: H.03. Schizophrenia

Support: the National Center of Competence in Research (NCCR) “SYNAPSY - The Synaptic Bases of Mental Diseases” financed by the Swiss National Science Foundation (n° 51AU40_125759)

Title: Rescue of impaired CA1 hippocampal network dynamics in an animal model of schizophrenia

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Abstract: 22q11 Deletion Syndrome (22q11DS) is a rare genetic disease due to chromosomic alteration disrupting the expression of approximately 20 genes. Patients suffering from 22q11DS display a wide variety of abnormalities, including cardiac defects, facial malformations and learning deficits. Furthermore, the patients exhibit an exaggerated risk to develop schizophrenia. In order to study the mechanisms underlying the neuropsychiatric symptoms in 22q11DS, we used a transgenic mouse model reproducing the human chromosomal alteration. Using a combination of calcium imaging and patch-clamp recordings, we observed alterations of CA1 hippocampal network dynamics and of electrophysiological properties of specific neuronal populations. Using pharmacological and chemogenetic approaches targeting these neuronal populations, we reinstated normal electrophysiological properties and consequently restored hippocampal network dynamics. In conclusions, our data suggests that some neuronal dysfunctions associated to the 22q11 deletion may be restored by manipulating specific neuronal subpopulations.

Disclosures: **A. Carleton:** None. **T. Marissal:** None. **C. Bertollini:** None. **R. Salazar:** None. **S. Mutel:** None. **M. De Roo:** None. **D. Muller:** None.

Poster

844. Schizophrenia Circuits and Systems

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 844.21/LLL32

Topic: H.03. Schizophrenia

Support: NIH Grant DP50D012109-03

NIH Grant MH43775

NIH Grant MH077945

NIH Grant MH074797

NIAA Grant 2P50AA012870-11

NIMH Grant F30 MH107149

NIH Grant T32GM 007205

Title: Global signal representation is spatially shifted in schizophrenia

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Abstract: Schizophrenia (SCZ) is a severe neuropsychiatric illness associated with widespread disruptions across distributed neural systems. Functional magnetic resonance imaging (fMRI) studies have identified extensive abnormalities in the blood-oxygen level-dependent (BOLD) signal in SCZ patients, including significant alterations in the average gray matter signal (i.e. the 'global' signal, GS). It remains unknown, however, if these GS alterations follow a spatially preferential pattern. To test this, we examined if GS changes in SCZ show an identifiable spatial pattern in a sample of 161 patients and 164 matched healthy comparison subjects (HCS) who underwent resting-state fMRI. We found regions showing altered (increased or reduced) statistical relationship with GS (beta weight) in SCZ relative to HCS. Increases were preferential to frontal-parietal areas, whereas reductions localized to sensory cortices. The magnitudes of these bi-directional shifts were strongly correlated, suggesting a common source. Independent network overlap analyses confirmed that association regions showed preferential increases in GS beta weights while sensory regions showed preferential reductions. Additionally, a parallel network-level voxel-wise GS beta weight analysis in healthy subjects showed that GS beta values are generally higher in sensory compared to association regions. This effect was again altered bi-directionally in SCZ, adding independent convergent evidence. Findings revealed that GS spatial representation in sensory vs. association cortices is strongly anti-correlated in HCS, with significant attenuation of this relationship in SCZ. This overall loss of 'differentiation' in association vs. sensory networks with respect to GS representation may underlie disrupted information flow in SCZ.

Disclosures: G.J. Yang: None. **J.D. Murray:** None. **M.F. Glasser:** None. **G.D. Pearlson:** None. **C. Schleifer:** None. **G. Repovs:** None. **J.H. Krystal:** None. **A. Anticevic:** None.

Poster

844. Schizophrenia Circuits and Systems

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 844.22/LLL33

Topic: H.03. Schizophrenia

Title: Spatio-temporal alterations in working memory-related neuromagnetic activity in patients with schizophrenia while on and off antipsychotic medication

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Abstract: Background: While prefrontal abnormalities and the associated impairments in working memory and executive function are well established in schizophrenia, a detailed understanding of temporal (millisecond) characteristics of these abnormalities is still needed to clarify the pathophysiology and refine the treatment of this devastating disorder; therefore, we used magnetoencephalography (MEG) to detect specific alterations in neural activation during WM and evaluated its modulation by antipsychotic medication, in patients with schizophrenia.
Methods: Twenty-five psychiatric inpatients with schizophrenia or psychosis NOS and 100 healthy individuals group-matched for age, sex, ethnicity, handedness, and WM performance, completed 20-second trials of a 2-back WM and 0-back control task (six trials per task condition) during neuromagnetic recording with a 275-channel whole head MEG system. Controls completed the task once, and the patients twice: after at least 2 weeks of atypical antipsychotic medication treatment, and after at least 2 weeks of placebo treatment in a counterbalanced and double-blinded fashion. Synthetic aperture magnetometry, an adaptive beamforming technique, was used to localize beta band (14-30Hz) activity in 400ms windows time-locked to responses, in the 2-back relative to the 0-back condition. Voxelwise t-tests for group and medication comparisons were performed using AFNI.
Results: WM-related activation, measured by differences in beta band activity between 2-back and 0-back was reduced in unmedicated patients compared to controls in bilateral prefrontal cortex (PFC) and increased in visual and parietal cortex, specifically during the pre-response period ($p<0.05$, FDR corrected). Medication treatment significantly normalized these neural abnormalities ($p<0.05$), but did not alter task performance variables.
Conclusion: These results extend prior accounts of PFC dysfunction in schizophrenia by demonstrating that even when achieving similar WM accuracy as controls, during a specific epoch of task performance patients show reduced PFC beta band activation that may be ameliorated by antipsychotic treatment. The temporal specificity of this finding suggests that only select cognitive processes during WM task engagement may be particularly relevant to PFC dysfunction in schizophrenia, though better dissection of such cognitive components and delineation of the underlying - perhaps dopaminergic - mechanisms by which neuroleptic therapy modulates this particular abnormality await future translational work.

Disclosures: D.Y. Rubinstein: None. **D.P. Eisenberg:** None. **F.W. Carver:** None. **T. Holroyd:** None. **D.R. Weinberger:** None. **J.A. Apud:** None. **R. Coppola:** None. **K.F. Berman:** None.

Poster

844. Schizophrenia Circuits and Systems

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 844.23/LLL34

Topic: H.03. Schizophrenia

Support: P50MH103204

Title: Pyramidal neuron heterogeneity in dorsolateral prefrontal and posterior parietal areas of monkey neocortex

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Abstract: The functional specialization of primate neocortical areas is partly determined by area-specific electrophysiological and morphological neuronal properties, which depend on specific patterns of gene expression. Layer 3 pyramidal cells (L3PCs) are crucial for neocortical circuit function, by generating output signals conveyed to other neocortical regions via their long-distance axonal projections. L3PCs of primary sensory versus association areas of the primate neocortex, have significantly different properties, and such differences are thought to contribute to area-specific function. However, whether L3PCs have different features between the dorsolateral prefrontal (PFC) and posterior parietal (PPC) areas of the primate neocortex is poorly understood. While distinctively involved in cognition, PFC and PPC are co-activated in various cognitive tasks, and communicate via reciprocal connections furnished by L3PCs. Moreover, the interactions between PFC and PPC are altered in mental disorders that affect cognitive function, such as schizophrenia. Here we describe preliminary results from studies comparing the electrophysiological, morphological and transcriptional properties of L3PCs from the macaque monkey DLPFC and PPC. Whole-cell recordings were performed in acute slices from PFC area 46 or PPC areas 7a and LIP, to assess intrinsic membrane properties, morphology, and GABAA receptor-mediated synaptic inhibition in L3PCs. Recordings from n=24 PFC and n=25 PPC L3PCs showed that, in both areas, L3PCs were divided into regular spiking (RS) or burst spiking (BS) subtypes. The intrinsic electrophysiology parameters showed several differences between RS and BS neurons. However, within an electrophysiological subtype (RS or BS), most parameters did not differ between areas (PFC versus PPC). Interestingly, the proportions of RS and BS neurons differed significantly between areas, since BS L3PCs were more frequent in PFC (RS/BS in PFC: 14/10; RS/BS in PPC: 22/3; p=0.0187, Chi-Square test). These data suggest that the input/output transformation properties of L3PCs have greater heterogeneity in PFC than PPC. Ongoing work is assessing regional differences in the morphology of the L3PCs filled with biocytin during recording, and regional differences in

L3PC gene expression, using DNA microarray analysis of RNA samples collected from L3PCs using laser capture microdissection.

Disclosures: **G. Gonzalez-Burgos:** None. **T. Miyamae:** None. **D. Arion:** None. **D.A. Lewis:** F. Consulting Fees (e.g., advisory boards); David A. Lewis currently receives investigator-initiated research support from Pfizer. In 2013-2015, he served as a consultant in the areas of target identification and validation and new compound dev.

Poster

844. Schizophrenia Circuits and Systems

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 844.24/LLL35

Topic: H.03. Schizophrenia

Support: NIH T32-NS061847-08

Sloan Research Fellowship

NIH R01 5-R31-MH058251-06-10

CONTE 5-P50-MH06065-07-10

Title: Spectral 1/f noise differences account for apparent oscillatory band-specific effects in Schizophrenia

Authors: *B. Q. ROSEN[1], E. PETERSON[1], A. CAMPBELL[2], A. BELGER[2], B. VOYTEK[1]; [1]UCSD, San Diego, CA; [2]Univ. of North Carolina at Chapel Hill, Chapel Hill, NC

Abstract: Numerous electroencephalography (EEG) experiments have reported significant differences between patients diagnosed with schizophrenia and healthy controls. While time-domain event-related potential (ERP) results are mixed, there is a consensus that power in oscillatory sub-bands is altered in schizophrenia. Specifically, that power in the low frequency ranges of delta (1-4 Hz) and theta (4-8 Hz) are often increased; that power in the mid-frequency bands of alpha (8-12 Hz) and beta (12-30 Hz) remain unchanged, and that power in the gamma range (>30 Hz) is decreased. Each of these results is often interpreted as an independent phenomenon. Here we offer a unifying account, building on our previous work examining alterations of 1/*f* noise in the power spectrum. Variations in spectral 1/*f* noise can be quantified by measuring the slope of the power spectrum, giving a decay exponent χ. In this study we investigated event- and non-event-related χ in EEG data recorded during a selective attention task from three sample groups: schizophrenia (SZ) patients (n = 31), asymptomatic but

genetically predisposed participants (n = 25), and matched controls (n = 35). While traditional ERP analysis was sensitive to task condition, consistent with previous reports, there were no group ERP differences. In contrast, SZ patients had steeper χ compared to both non-SZ groups, who did not differ from one another. In agreement with previous studies, oscillatory power for the control and SZ groups did not differ except in the gamma band, which was attenuated in SZ. This difference is parsimoniously explained by a between-group difference in χ slope. These χ effects were also reflected in behavioral performance, as SZ patients were less accurate and had greater response time variability than controls. Changes to spectral slope have been hypothesized to reflect changes in neural excitation and/or inhibition. In sum, not only can we offer a simpler explanation for numerous band-specific changes in power by unifying them under χ, we can also begin to link these changes to concrete physiological variables.

Disclosures: B.Q. Rosen: None. **E. Peterson:** None. **A. Campbell:** None. **A. Belger:** None. **B. Voytek:** None.

Poster

844. Schizophrenia Circuits and Systems

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 844.25/LLL36

Topic: H.03. Schizophrenia

Title: Altered temporal structure of spontaneous brain activity in Schizophrenia

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Abstract: Background: Schizophrenia is one of the most unclear psychiatric disorders. Using resting-state functional magnetic resonance imaging (rs-fMRI), recent studies showed altered global signal power in schizophrenia (e.g., Yang et al., 2014). However, it remains unknown how the more fine-grained relationship across different frequencies, i.e. temporal structure, changes in schizophrenia. A comparison between temporal structure of schizophrenic brains and that of healthy controls will contribute to better understandings of abnormality of schizophrenia. **Methods:** The current study involved 10 healthy subjects and 28 schizophrenic patients. Each subject's resting-state brain was scanned in Siemens 3T fMRI scanner. 156 scans with a TR of 2s per brain volume were acquired. The data pre-processing steps were implemented in AFNI (Cox, 1996), including rigid body correction/realignment within and across runs, resampling to 3×3×3 mm^3 voxels. Next, we calculated the power-law exponent (PLE) of the power spectrum in two key region within the cortical midline structure, that is the medial prefrontal cortex (MPFC) and

posterior cingulate cortex (PCC). Additionally, we calculated the temporal variability of fMRI signal in two infra-slow frequencies: slow 5 (0.01-0.027 Hz) and slow 4 (0.027-0.073 Hz). **Results:** Schizophrenic patients showed significantly decreased PLE in MPFC, t (36) = 2.588, p =.014, but not in PCC, t (36) = .277, p = .784. Patients also showed reduced temporal variability in MPFC than healthy controls in slow 5. **Conclusions:** Our preliminary results suggest that schizophrenic patients have abnormal long-term temporal correlations of neural activity in the MPFC which may have diagnostic potential in psychiatric disorders.

Disclosures: F. Kondo: None. **Z. Huang:** None. **G. Northoff:** None.

Poster

844. Schizophrenia Circuits and Systems

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 844.26/LLL37

Topic: H.03. Schizophrenia

Support: NIH Grant NS13742 /NS/NINDS/NIH HHS

Postdoctoral Program Research grant from the University of Science and Technology in the Republic of Korea (UST PostDoctoral Research Program)

National Research Foundation of Korea grant funded by the Korean Government (NRF-2009-352-C00111)

Flagship grant of the Korea Institute of Science and Technology (2E25472)

Grant of the Global Frontier R&D Program (NRF-M1AXA003-2011-0031525)

Title: Severely dysregulated thalamocortical rhythms and psychotic-like behavior of mice lacking $Ca_V3.1$ T-type Ca^{2+} channel in N-methyl-D-aspartate receptor hypofunction, as an advanced schizophrenia model

Authors: *S. CHOI[1,3], E. YU[1,3], E. HWANG[4], R. CANCRO[2], R. R. LLINÁS[1,3];
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Abstract: Although the etiology of schizophrenia is not fully elucidated, there is considerable evidence to suggest that abnormal thalamocortical rhythms might be a pathophysiological mechanism for the psychotic symptoms. In order to assess the alteration of thalamocortical

rhythms in schizophrenia from a molecular perspective, behavioral and electrophysiological studies using mice lacking $Ca_V3.1$ T-type Ca^{2+} channel, one of key molecular components for thalamocortical rhythms, was implemented. Compared to wild-type control mice, $Ca_V3.1$ knockout mice showed significantly increased hyperactivity and psychotic-like behaviors in NMDA receptor hypofunction model of schizophrenia. Moreover, the recording of spontaneous activities from prefrontal cortex and mediodorsal thalamus revealed that $Ca_V3.1$ knockout mice had decreased low-frequency rhythms (e.g., delta and theta) and increased high-frequency rhythms (e.g., beta and gamma) in the thalamocortical network. Because the functional deficits in schizophrenia are most likely the consequence of dysregulated coherence between low- and high-frequency rhythms, we also examined the cross-frequency coupling between delta/theta and beta/gamma rhythms. Indeed, phase-amplitude coupling of low- and high-frequencies was found to be dramatically pronounced in the prefrontal cortex of $Ca_V3.1$ knockout mice following ketamine administration. Our results indicate that significantly increased psychotic-like behaviors in $Ca_V3.1$ knockout mice are associated with dysregulated interaction of low- and high-frequency rhythms in the thalamocortical network and raise the possibility that $Ca_V3.1$ T-type Ca^{2+} channels may serve as a triggering variable in psychotic episodes in schizophrenia.

Disclosures: S. Choi: None. **E. Yu:** None. **E. Hwang:** None. **R. Cancro:** None. **R.R. Llinás:** None.

Poster

844. Schizophrenia Circuits and Systems

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 844.27/LLL38

Topic: H.03. Schizophrenia

Support: NIH Grant R01MH085666

Title: NR2B subunit vulnerability in developing prefrontal cortex in a neurodevelopmental model for schizophrenia: physiology and mechanism

Authors: *Y. GULCHINA[1], M. A. SNYDER[1], S.-J. XU[2], F. ELEFANT[2], W.-J. GAO[1]; [1]Neurobio. and Anat., Drexel Univ. Col. of Med., Philadelphia, PA; [2]Dept. of Biol., Drexel Univ., Philadelphia, PA

Abstract: Cognitive functions, particularly working memory, rely on prefrontal cortical circuitry. Subsets of pyramidal neurons in the prefrontal cortex (PFC) are responsible for maintaining persistent firing for proper PFC-dependent cognition. This process strongly depends on the NMDAR, specifically the NR2B subunit. In these experiments, we describe the functional

state of layer V pyramidal neurons of the mPFC in the MAM-E17 neurodevelopmental model for schizophrenia. With particular focus on the juvenile and adolescent stages of development, we demonstrate significant loss of NR2B protein in synaptic fractions from MAM animals. Using whole-cell patch-clamp electrophysiology, we observe a significant reduction of amplitude and frequency of NMDA-miniEPSCs in both juvenile and adolescent animals, respectively. Using layer II/III evoked stimulation (10 pulses, 20 Hz), we confirm the significant loss of NR2B-NMDARs at synapses of layer V pyramidal cells in juvenile MAM animals. These data demonstrate an early vulnerability of the NR2B subunit in PFC of MAM animals, possibly underlying early cognitive impairments in working memory. To understand the mechanism of reduced NR2B protein expression in MAM animals, we investigated epigenetic processes that govern gene expression levels. A repressor protein, REST, selectively regulates expression of Grin2b, the NR2B encoding gene. Further, we elucidated an epigenetic contribution to this protein loss using chromatin immunoprecipitation. We confirm the selective repression of Grin2b by REST in juvenile MAM animals, concomitant with an increase in the repressive histone marker, H3K27me3. Thus, we propose an epigenetic contribution to NR2B downregulation at synapses of layer V pyramidal neurons in developing MAM animals.

Disclosures: **Y. Gulchina:** None. **M.A. Snyder:** None. **S. Xu:** None. **F. Elefant:** None. **W. Gao:** None.

Poster

844. Schizophrenia Circuits and Systems

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 844.28/LLL39

Topic: H.03. Schizophrenia

Support: Hungarian National Programme In Brain Sciences KTIA_NAP_13-2-2015-0011

Title: Investigation of resting state alpha-band oscillatory brain activity on a nonhuman primate model of schizophrenia

Authors: ***A. TRUNK**[1], V. OLÁH[1], G. STEFANICS[2], I. HERNÁDI[1];
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Abstract: According to WHO around 0.6 to 1% of the world population is affected by various symptoms associated with schizophrenia (SZ). Recent theories suggest that key symptoms of SZ result from dysfunction of the glutamatergic and/or dopaminergic neurotransmission resulting in reduced alpha power in the resting state electroencephalographic (rEEG) oscillatory activity. In

the present study, we investigated whether the acute administration of the N-methyl-D-aspartate receptor (NMDAR) antagonist ketamine induces such effects in adult non-human primates (NHPs). Non-invasive rEEG was recorded from two subjects using 20 Ag/AgCl scalp electrodes according to a concentric electrode layout scheme. Recording sessions were designed in a counterbalanced, repeated measure and placebo-controlled fashion after prior treatment with 1) intramuscular injection of 1 mg/kg b.w. ketamine; 2) injection of vehicle (saline) solution. Oscillatory activity (power spectra) in the alpha frequency band (8-12 Hz) was analyzed in EEGLAB. Hypotheses testing for possible treatment (ketamine vs. saline) effect in single trial responses were compared with non-parametric bootstrap statistics. We found that ketamine decreased the alpha activity compared to saline and that effect was sustained for at least 30 min after ketamine injection. The reduced alpha activity in the ketamine condition well corresponds to previous results obtained in human SZ patient studies. In summary, the present pharmacological SZ model in NHPs may be suitable for further analysis of SZ-like transient alterations of oscillatory brain function and may also become a valuable tool for preclinical drug development research.

Disclosures: **A. Trunk:** None. **V. Oláh:** None. **G. Stefanics:** None. **I. Hernádi:** None.

Poster

844. Schizophrenia Circuits and Systems

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 844.29/LLL40

Topic: H.03. Schizophrenia

Support: 5K22MH099164-03

Title: Aberrant ca^{2+} channel function in fast-spiking interneurons in an NMDAR hypofunction mouse model of schizophrenia

Authors: *V. JEEVAKUMAR, A. BOHANNON, J. HABLITZ, K. NAKAZAWA;
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Abstract: Cortical NMDAR hypofunction has been used to model the symptoms of schizophrenia. The parvalbumin (PV) expressing fast-spiking (FS) GABAergic interneurons are a prime target in this model. These cells provide perisomatic inhibition and mediate synchronous oscillatory activity. Abnormal neuronal synchrony is observed in schizophrenia, however the underlying cellular mechanisms are not fully understood. We generated a mouse line with postnatal conditional deletion of the NMDAR subunit GluN1 predominantly in cortical and hippocampal interneurons, a majority of which is PV containing. These mice display specific

behavioral characteristics of schizophrenia, and impairments in synchronous action potential (AP) firing *in-vivo*. We attempted to identify the critical cellular mediators involved in schizophrenia-related abnormal oscillations leading to cognitive dysfunction and focused our attention on the $Ca_v2.1$ channels (P/Q type) because they are highly expressed in PV interneurons and mediate GABA release onto excitatory neurons.
Using dual whole-cell patch clamp recordings we tested synchronous inhibitory postsynaptic currents (IPSC) – peak IPSC amplitudes within a 7ms window, between pairs of layer II/III pyramidal cells in the medial prefrontal cortex (mPFC) in order to measure the extent of impairments in perisomatic inhibition. mPFC slices were prepared from Ppp1r2-cre(+/-)/GluN1 (f/f) mutant/YFP (f/f) mice or their GluN1 (f/f) control littermates, male and female, 4-6 weeks old. IPSC synchrony in the mutant mice was ~ 30% lower than controls (ctl = 27.4±1.35 %, n=8, mut = 18.76±0.86 %, n=12 pairs; $p < 0.001$ t-test). Next, we explored the means for rescuing this impairment. Preliminary data suggested reduced levels of ω-agatoxin IVA-sensitive whole-cell currents in the mutant FS neurons compared to controls. To test this further, we used the $Ca_v2.1/2.2$ channel agonist GV-58 (100 μM) in combination with K^+ channel blocker 3,4-diaminopyrimidine (DAP, 3 μM for reliable increase of AP duration). Co-administration of GV-58 and DAP is required for enhancing depolarization of the cell because GV-58 preferentially affects Ca^{2+} channels in open conformation. Bath application of DAP + GV-58 significantly increased IPSC synchrony in the mutant mice (mut = 18.65±1.31 %, after GV-58 = 23.65±0.99 %, n = 5 pairs, $p < 0.01$, paired t-test). However, the L-type Ca^{2+} channel blocker nimodipine had no impact on synchrony. In conclusion, we show that impaired IPSC synchrony in the GluN1 mutant mice may be a consequence of P/Q channel dysfunction in the PV interneurons, and is rescued by augmenting the channel function.

Disclosures: V. Jeevakumar: None. **A. Bohannon:** None. **J. Hablitz:** None. **K. Nakazawa:** None.

Poster

845. Schizophrenia: Developmental Models

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 845.01/LLL41

Topic: H.03. Schizophrenia

Support: CIHR

OMHF

NSERC

Dept Psychiatry, UWO

Title: Developmental disturbances in thalamocortical connection are sufficient to produce almost all features of schizophrenia

Authors: *R. RAJAKUMAR;
Anat. & Cell Biol., Univ. Western Ontario, London, ON, Canada

Abstract: Partial ablation of subplate of the developing frontal cortex was achieved by two different approaches in PD1 S-D rat pups: infusions of either P75 receptor antibody-conjugated to saporin or β-nerve growth factor, and both resulted in identical changes: ~20% loss of subplate and aberrant distribution of thalamocortical fibers within the cortex. Control littermates received similar infusions of vehicle. Pups were allowed to grow under standard care. All animals survived, and showed no noticeable differences in milestones or activities. No differences were observed between lesioned and control groups in standard behavioral tests at 6-8 weeks of age. However, lesioned group showed significantly increased stress- or amph-induced locomotor activity, PPI deficit, social interaction deficits, and executive functional deficits after 9 weeks of age. A month-course of haloperidol or risperidon completely ameliorated locomotor abnormalities but did not affect social interaction deficit. Histological examination revealed several interesting changes: (1) 18% loss of gray matter thickness in the mPFC and no change in thickness in other cortical areas at 12 weeks, while at 20 weeks PFC loss remained at 18% but parietal and temporal cortices showed progressive thinning (20-36%); (2) significant loss of neuropil in the mPFC characterized by loss of synaptophysin and spinophilin labeling; (3) no changes in the number of neuronal cell bodies in PFC; (4) significantly increased lateral and third ventricular volume; (5) significant loss of dopaminergic fibers in lower layers of the PFC; (6) significant loss of GAD67-IR terminals in PFC; (6) significant decrease in the intensity of PAR labeling and abnormal distribution of PAR-IR terminals/cell bodies without loss of neurons; (7) significant loss of GAT-1-IR terminals only in upper layers of the PFC; (8) loss of PAR-IR terminals and cell bodies in the hippocampus; (9) abnormal distribution but no loss of CR-IR neurons in the entorhinal cortex; and (10) significantly reduced volume of basolateral amygdala. No changes were seen in ChAT neurons of the septum or N. basalis. All structural changes noted above were seen as early as 12 weeks and were not affected by antipsychotic treatment between 12 and 16 weeks. Results suggest that disturbances in thalamocortical pathfinding (due to genetic or other mechanisms) are sufficient to cause features of schizophrenia in normal animals.

Disclosures: **R. Rajakumar:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); patent holder.

Poster

845. Schizophrenia: Developmental Models

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 845.02/LLL42

Topic: H.03. Schizophrenia

Support: CIHR

Title: Role of Transforming growth factor beta in schizophrenia related behaviours in neonatal ventral hippocampus lesioned rats

Authors: *A. T. JOSEPH, S. K. BHARDWAJ, L. K. SRIVASTAVA;
Douglas Mental Hlth. Univ. Inst., Montreal, QC, Canada

Abstract: Components of transforming growth factor β (TGFβ) signaling are implicated in a number of psychiatric disorders including schizophrenia. The neonatal ventral hippocampus lesion (NVHL) is a heuristic model to study the effect of early hippocampal abnormalities on the development of schizophrenia related behaviors and pathology. Previous work has shown increased oxidative and inflammatory stress in the prefrontal cortex (PFC) of NVHL animals. Our preliminary study has shown a reduction in the mRNA and signaling by TGFβ1, an anti-inflammatory member of the TGFβ family, in the PFC of adult NVHL animals. Thus we hypothesised that upregulation of TGFβ1 may be able to rescue the behavioral deficits observed in NVHL animals, possibly through its anti-oxidative effects. In order to test this hypothesis, Sprague-Dawley rat pups at P7 were bilaterally microinjected with ibotenic acid (3μg/side) or saline in the ventral hippocampus to generate NVHL or sham animals. The recombinant TGF-β1 or saline were injected intraperitoneally (IP) twice daily from P7-P14 at a concentration of 200ng/kg making 4 groups - Sham-saline, Sham-TGF-β1, NVHL-saline and NVHL-TGF-β1. Both male and female pups were included for the experiment. The following behavioral tests were conducted- spontaneous locomotion, social interaction and pre pulse inhibition (PPI) at two time points - P31-P35 (periadolescence) and P60-P65 (post-pubertal). As previously reported post-pubertal NVHL group treated with saline exhibited an enhanced locomotor activity, deficit in PPI and impaired social behavior as compared to the control animals in both male and female groups. Neonatal administration of recombinant TGFβ1 prevented enhancement of locomotor activity, deficit in PPI and reduced social preference in male NVHL-TGFβ1 treated group at P60. The data suggest that TGFβ1 may act as a neuroprotective agent to confer protection against the NVHL induced behavioural deficit. The results also suggest that TGFβ1 deficit is a key molecular mechanism causing NVHL-induced behavioural deficits.

Disclosures: **A.T. Joseph:** None. **S.K. Bhardwaj:** None. **L.K. Srivastava:** None.

Poster

845. Schizophrenia: Developmental Models

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 845.03/LLL43

Topic: H.03. Schizophrenia

Title: Effects of sex and late embryonic methylazoxymethanol exposure on working memory

Authors: S. C. PENLEY[1], K. NESTOR[1], *S. W. THRELKELD[2];
[1]Neuroscience/Psychology, Wheaton Col., Norton, MA; [2]Psychology, Rhode Island Col., Providence, RI

Abstract: Prenatal exposure to Methylazoxymethanol (MAM) inhibits mitosis of neurons allowing for an examination of the role of specific groups of neurons in anatomical and behavioral development. Exposure to MAM in rats on embryonic day (E) 17 particularly impacts hippocampal and prefrontal neuroanatomy and has been proposed as a model for schizophrenia, a disorder that is characterized in part by deficits in working memory. There is evidence in humans that the incidence of Schizophrenia across sexes is similar, but the severity and time of onset are not. There is also ample evidence that cortical injury during development more severely impacts males than females. Here, we examined working memory performance between male and female rodents exposed to MAM on E17 as compared to controls. Results elucidate the role of late embryonic teratogen exposure and sex on the pathogenesis of working memory deficits.

Disclosures: S.C. Penley: None. **K. Nestor:** None. **S.W. Threlkeld:** None.

Poster

845. Schizophrenia: Developmental Models

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 845.04/LLL44

Topic: H.03. Schizophrenia

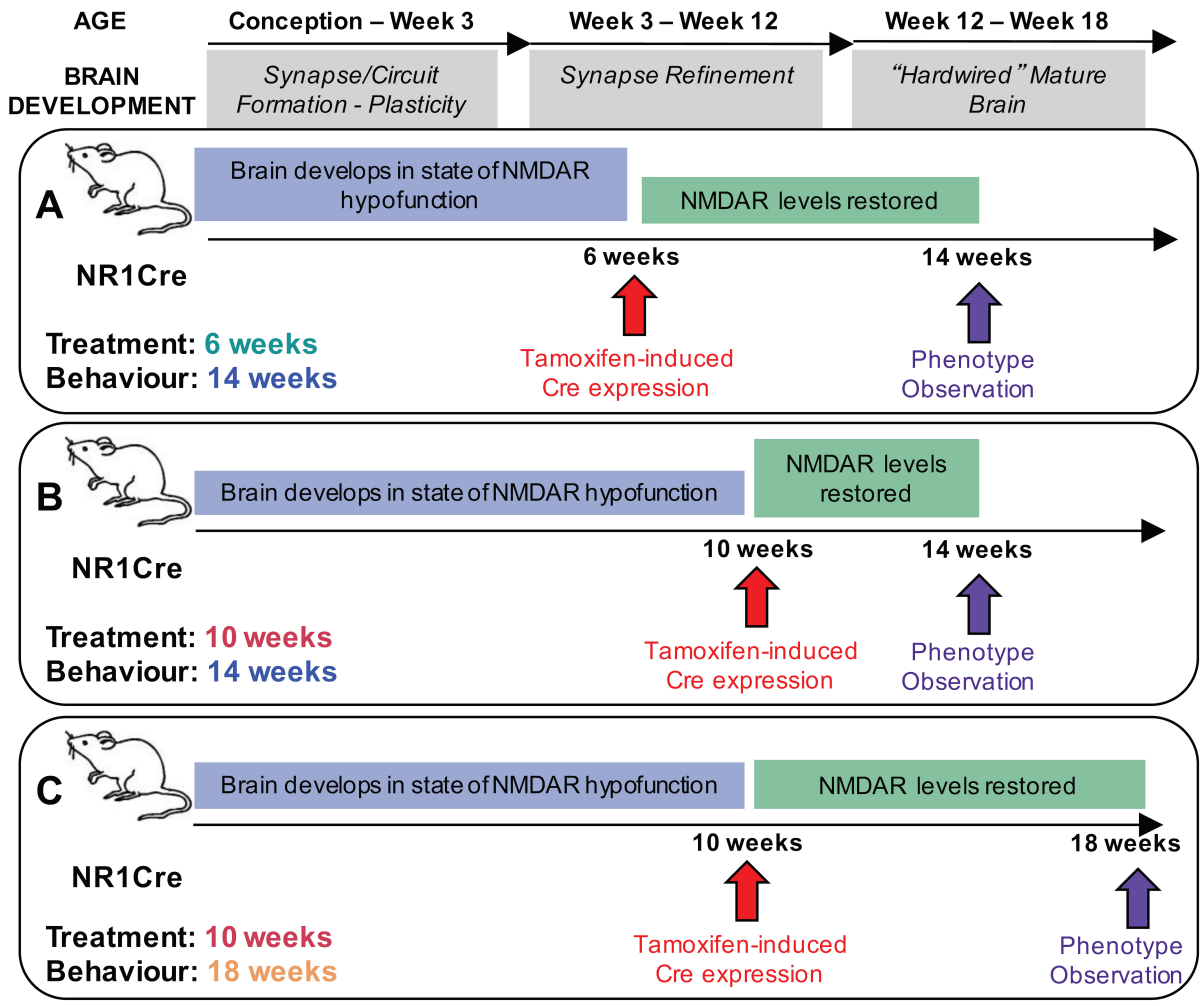
Support: CIHR MOP-119298

CIHR MOP-89825

Title: Inducible rescue of NMDA receptor deficiency to measure the plasticity of neural networks.

Authors: *C. MIELNIK[1], M. A. BINKO[2], R. ISLAM[2], M. MILENKOVIC[1], W. HORSFALL[1], E. K. LAMBE[2], A. J. RAMSEY[1,2];
[1]Pharmacol. and Toxicology, Univ. Of Toronto, Toronto, ON, Canada; [2]Physiol., Univ. of Toronto, Toronto, ON, Canada

Abstract: Schizophrenia poses challenges in its treatment, due to the differing timelines of etiology and symptom presentation. "Mis-wiring" occurs during developmental processes, whereas symptoms of the disorder do not manifest until adulthood. Negative and cognitive symptoms are particularly disabling and treatments remain ineffective. Therefore, we are presented with a challenge in treating this disorder: can therapeutic interventions in adults reverse symptoms, including treatment-resistant negative and cognitive symptoms, that arise from neurodevelopmental deficits? To address this question, we generated a mouse line capable of inducible-Cre mediated rescue of NMDAR deficiency. WT, NR1 and NR1Cre mice were treated with tamoxifen at either 6- or 10-weeks. Behavioural characterization of rescue was tested at 14- or 18-weeks: locomotor activity, stereotypy, executive function, anxiety, sociability, and sensorimotor gating. Biochemical and cellular levels of rescue were also measured: mutation excision rates and functional receptor levels. (See Binko et al., poster for electrophysiology.) Regardless of time of intervention, NR1Cre mice showed similar effects on behaviour and biochemical rescue. When compared to NR1 mice, hyper locomotion and increased stereotypic behaviour were decreased in NR1Cre mice. Cortex-linked behaviours (such as sociability, cognition, executive function) were rescued in NR1Cre mice similar to WT levels. This was in accordance with biochemical data that suggested the greatest biochemical rescue was in the cortex and hippocampus when compared to other brain regions. Therefore, regardless of time of intervention, NR1Cre mice showed similar rescue both behaviourally and biochemically. This suggests that plasticity may not be developmentally dependent, but rather brain-region specific. Therefore, normally treatment-resistant symptoms (negative/cognitive) show the greatest improvement in our model. This implies that the treatment-resistant nature of these symptoms may not be due to a lack of plasticity in the underlying circuits.



Disclosures: **C. Mielnik:** None. **M.A. Binko:** None. **R. Islam:** None. **M. Milenkovic:** None. **W. Horsfall:** None. **E.K. Lambe:** None. **A.J. Ramsey:** None.

Poster

845. Schizophrenia: Developmental Models

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 845.05/LLL45

Topic: H.03. Schizophrenia

Support: NSERC

Title: Disruption of neonatal neurogenesis produces cognitive deficits that are distinct from those observed in schizophrenia

Authors: *M. TSE[1], P. T. PIANTADOSI[2], M. AUGER[2], S. CAHILL[2], J. D. COLE[2], J. S. SNYDER[2], S. B. FLORESCO[2];
[2]Psychology, [1]Univ. British Columbia, Vancouver, BC, Canada

Abstract: Disruption of neonatal neural development via neonatal ventral hippocampal lesion or impeding early neurogenesis has been proposed to underlie pathophysiology that leads to cognitive deficits associated in schizophrenia in adulthood. In the present study, we sought to assess whether disrupting neonatal neurogenesis in transgenic rats that express herpes simplex virus thymidine kinase (TK) under control of the glial fibrillary-associated protein (GFAP) promotor may alter behavior and cognition in adulthood. TK transgenics and wide-type controls were treated with the antiviral drug valganciclovir (Valg; 10-20mg/kg) or saline on post-natal day (PND) 5/7/9, and tested on a number of cognitive/behavioral assays at 2 months of age. Interestingly, unlike other types of neonatal manipulations, Valg treated TK rats did not show enhanced sensitivity to the psychomotor stimulant effects of amphetamine. However, neonatal treatment of Valg induced various degrees of motor deficits as revealed with tests of locomotion, and this was associated with reduced cerebellar volume. Valg treatment in TK transgenic rats resulted in severe spatial learning deficits on a delayed-response version of the radial arm maze, which is mediated by the hippocampus and medial prefrontal cortex. Subsequently, rats were tested on an operant version of strategy set-shift task that assesses cognitive flexibility. TK-Valg-treated rats showed severe impairment during learning of an the initial visual cue discrimination, but curiously, were unimpaired when they had to alter their strategy and use an egocentric response discrimination during set-shift. In a discriminative conditioned fear discrimination assay, TK-Valg-treated rats showed reduced fear to conditioned stimulus (CS) associated with foot-shock, and also showed more rapid extinction relative to all other groups. Lastly, tests of anxiety using the elevated plus maze revealed that TK-Valg-treated rats showed reduced time spent in open arms. Interestingly, TK transgenics treated with Valg showed reduction of head size (microcephaly). Collectively, it is suggested that disruption of neonatal neurogenesis at PND5/7/9 causes severe cognitive/learning deficits accompanied with motor dysfunction and cranial abnormalities, revealing effects that are qualitatively distinct than that of schizophrenia. This suggests that neurodevelopmental disruptions that causes schizophrenic-like phenotype require more targeted disruption of the development of hippocampal-prefrontal circuitry.

Disclosures: **M. Tse:** None. **P.T. Piantadosi:** None. **M. Auger:** None. **S. Cahill:** None. **J.D. Cole:** None. **J.S. Snyder:** None. **S.B. Floresco:** None.

Poster

845. Schizophrenia: Developmental Models

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 845.06/LLL46

Topic: H.03. Schizophrenia

Support: MEXT Japan KAKENHI 15K08633

AMED Japan Brain/MINDS

Title: Developing novel blood-based protein biomarker for schizophrenia with MIA background

Authors: *A. OH-NISHI[1,2], T. MAEDA[3,2], T. SUHARA[4];
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Abstract: Maternal infection (maternal immune activation, MIA) is a risk factor for schizophrenia in the offspring, which subsequently seems to reveal the characteristic behavioral abnormality and immune system disturbances. Model animal studies showed that early treatment with anti-psychotic agents improved the MIA produced neuronal- and behavioral-dysfunctions (Piontkewitz 2009,2011), which suggests a possibility that, if early diagnosis were possible, anti-psychotic treatment of schizophrenia with MIA background might prevent the onset of the dysfunctions. Here, we report a serologic marker candidate found in the MIA animal model for early diagnosis of the MIA-associated neurodevelopmental disorders including schizophrenia. Serum proteome analysis of the mature MIA rat showed that the immunoglobulin (Ig) light chain is reproducibly augmented, which was also observed in neonatal MIA rat. The Ig light chain in sera takes two forms — free from or bound to the Ig heavy chain. Only the former is an inflammatory disease marker, but pro-inflammatory cytokines in the sera of the MIA rats were at less than detectable limits by the ELISA protocol we used. To confirm the results in commercially available human samples for research, we carried out serum assays of Ig light chains of schizophrenia patients. Although the number of samples was limited, we found augmentation of free Ig light chains (FLCs) in schizophrenia patient sera. Our findings suggest that assay of serum FLCs would provide a clue toward realization of an early serodiagnostic test for schizophrenia with MIA background.

Disclosures: **A. Oh-Nishi:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Stock; more than 5% of RESVO. inc.. **T. Maeda:** None. **T. Suhara:** None.

Poster

845. Schizophrenia: Developmental Models

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 845.07/LLL47

Topic: H.03. Schizophrenia

Title: Behavioral characterization of the mouse models of Ch16p11.2 microdeletion and duplication syndromes

Authors: T. SHIMADA[1], E. D. LAKE[1], N. M. WALTON[1], K. TAJINDA[1], M. MATSUMOTO[2], H. ITO[1], *M. ADACHI[1];
[1]CNS, Astellas Res. Inst. of America, Skokie, IL; [2]Neurosci., Astellas Pharma Inc, Tsukuba, Japan

Abstract: Psychiatric disorders such as schizophrenia, autism, and bipolar disorder, are prevalently affecting populations worldwide and are believed to result from genetic as well as environmental factors. Numerous efforts have been undertaken to elucidate the pathophysiological mechanism underlying these disorders; yet, no molecular targets that translate to therapeutic interventions have been identified thus far. This may be attributable, in part, to significant problems stemming from the lack of animal models that faithfully recapitulate symptoms observed in patients while mimicking the heterogeneity of clinical presentations among patients.
In an attempt to generate a mouse model of psychiatric disorders that more accurately recapitulates the disease state, here we investigated the role of copy number variation in chromosome16p11.2 locus, a region for which duplication frequently occurs in schizophrenia and bipolar disorder and deletion is associated with autism spectrum disorder. We engineered mouse lines either lacking or possessing an additional copy of a 378-kb segment in mouse chromosome 7qF3, which is highly conserved with the human Ch16p11.2 locus. This region encompasses over 25 genes, similar to human genome. To examine the interplay between gene copy number, gene expression and behavioral phenotypes, we measured mRNA levels of genes within the micro-duplicated/deleted region and will correlate them to behavioral phenotypes to assess the face validity of this construct as a model for schizophrenia, bipolar disorder, and autism. We will discuss the behavioral outcomes of the CNV at the Ch16p11.2 locus in detail at the presentation.

Disclosures: **T. Shimada:** A. Employment/Salary (full or part-time): Astellas Research Institute of America. **E.D. Lake:** A. Employment/Salary (full or part-time): Astellas Research Institute of America. **N.M. Walton:** A. Employment/Salary (full or part-time): Astellas Research Institute of America. **K. Tajinda:** A. Employment/Salary (full or part-time): Astellas Research Institute of America. **M. Matsumoto:** A. Employment/Salary (full or part-time): Astellas

Pharma Inc. **H. Ito:** A. Employment/Salary (full or part-time): Astellas Research Institute of America. **M. Adachi:** A. Employment/Salary (full or part-time): Astellas Research Institute of America.

Poster

845. Schizophrenia: Developmental Models

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 845.08/LLL48

Topic: H.03. Schizophrenia

Support: JSPS KAKENHI Grant Numbers 26860942

Title: Investigation of anatomical basis underlying working memory impairment in chronic phencyclidine-treated mice

Authors: *Y. ARIME, K. AKIYAMA;
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Abstract: Chronic phencyclidine (PCP) treatment induces impairments in several cognitive functions including working memory in rodents. The structural basis underlying working memory impairment in this model was fully understood. In the present study, we aim to clarify the brain regions underlying working memory impairment in chronic PCP-treated mice at the cellular level while they perform a working memory task, and to examine the quantitative analysis of cell morphology at the synaptic level. To assess working memory in mice, we used the discrete paired-trial variable-delay task in T-maze, which is dependent on the prefrontal cortex. Adult male mice, which were pre-trained with the discrete paired-trial delayed alternation training, were chronically administered PCP (10 mg/kg, s.c.) or saline (control) for 14 days. After withdrawal, their working memory was assessed at variable delays (5, 15 or 30 sec) in three consecutive days. After working memory task, we performed c-Fos mapping in various brain regions, including the prelimbic (PL) and infralimbic cortex (IL), which constitute the medial prefrontal cortex, and anterior cingulate cortex (ACC). To assess the effect of chronic PCP treatment on dendritic spine morphology such as spine types (thin, mushroom and stubby), spine density, head diameter and length, we also examined three-dimensional and laminar specific dendritic spine analysis using Thy1-EGFP transgenic mice. Mice with repeated PCP treatment displayed significant reduction in correct responses at all retention intervals (delay) compared to control mice. Between chronic PCP-treated mice and control, no changes in c-Fos positive cells were observed in various brain regions, including each cortical layer (layer 2-3, 5 and 6) of the IL and ACC. In the PL, chronic PCP-treated mice showed significantly increased c-Fos positive cells only in the layer 2-3 (not layer 5 and 6). The present data showed that chronic

PCP treatment induced the decrease in the number of dendritic spines in deep layer 3 (thin and mushroom spines) of the PL, also occurs, to a lesser degree, in layer 5 (mushroom spines). Our results suggest that anatomical and functional alterations in the layer 2-3 of the PL may underlie the basis of working memory impairment in chronic PCP-treated mice. This region is a major site for integration of cortico-cortical and thalamo-cortical excitatory inputs. Furthermore, considering that the excitatory pyramidal neurons in the PL also receive multiple inhibitory inputs from GABAergic interneurons, the excitatory-inhibitory balance in the PL (especially layer 2-3) may be altered by chronic PCP treatment.

Disclosures: **Y. Arime:** None. **K. Akiyama:** F. Consulting Fees (e.g., advisory boards); Taisho Toyama Pharmaceutical Co., Ltd..

Poster

845. Schizophrenia: Developmental Models

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 845.09/LLL49

Topic: H.03. Schizophrenia

Support: MH104800

Title: Superantigens as a T-cell-based model for maternal immune activation: cytokine responses of pregnant Balb/c and C57/BL6 mice to staphylococcal enterotoxin B

Authors: *R. GLASS, A. W. KUSNECOV, 08854;
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Abstract: Stimulation of the immune system during pregnancy, known as maternal immune activation (MIA), can cause long-lasting neurobiological and behavioral changes in the offspring. This phenomenon has been implicated in the etiology of developmental psychiatric disorders, such as autism and schizophrenia. Much of this evidence is predicated on animal models that rely on activation of the innate immune system using bacterial agents such as LPS and/or viral mimics such Poly I:C, both of which act through toll-like receptors. Fewer studies have examined the role of direct activation of maternal T-cells during pregnancy and whether this also results in altered neurobiological and behavioral outcomes in offspring. Bacterial 'superantigens', such as Staphylococcal Enterotoxin A and B (SEA; SEB), are microbial proteins that activate $CD4^+$ T-cells and cause prominent T-cell proliferation and cytokine production. Initially, we injected IP pregnant and non-pregnant adult female C57/BL6 and Balb/c mice with SEA or SEB (200 or 400g/kg respectively), or 0.9% saline, and measured splenic cytokine concentrations 2 hours later of IL-2, IFN-, IL-6 and IL-4. The results for SEB are available, and

showed induction of high amounts of IFN- and IL-2, with lesser amounts of IL-4 and IL-6. However, pregnant Balb/c mice had higher concentrations of IL-4 and IFN- than pregnant C57BL/6 mice. Within each strain, in response to SEB, pregnant Balb/c mice had higher levels of IL-4 than non-pregnant mice, while pregnant C57BL/6 mice produced marginally less IL-2 than non-pregnant mice (p=.063). Ongoing studies are looking at maternal cytokine responses to staphylococcal enterotoxin A (SEA) in these strains, in addition to the behavior of the adult offspring of pregnant mothers injected with these T-cell superantigens.

Disclosures: R. Glass: None. **A.W. Kusnecov:** None.

Poster

845. Schizophrenia: Developmental Models

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 845.10/LLL50

Topic: H.03. Schizophrenia

Support: P50MH080173

Title: Behavioral and molecular analysis of dysbindin-1 single point mutation mice

Authors: *E. H. CHANG, T.-S. S. CHANDON, L. E. YEUNG, K. BARBARI, K. FERNANDO, A. K. MALHOTRA;
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Abstract: The dystrobrevin binding protein 1 (DTNBP1) gene, located on human chromosome 6p22.3, is a known schizophrenia risk gene that encodes the dysbindin-1 protein. Dysbindin is widely expressed in the brains of both mice and humans and is localized synaptically. Furthermore, dysbindin protein and mRNA are reduced in post-mortem tissue from schizophrenia patients, specifically in the prefrontal cortex and hippocampus. For these reasons, dysbindin remains a protein of interest in the pathophysiology of schizophrenia. Here, we utilize dysbindin salt and pepper (spp) mice, which have a single point mutation on the Dtnbp1 gene and express diluted fur color in homozygous mutants. While the blood, plasma, and dendritic cells have been studied in these mice due to their importance for Hermansky-Pudlak syndrome, brain and behavioral alterations have never been examined. In this study, we examined adult (2-6 months of age) male and female dysbindin spp mice using multiple behavioral tests with videotracking (EthoVision XT 8.0). Open field testing of locomotion and anxiety showed that spp heterozygotes (n=26) and spp homozygotes (n=22) did not differ from wildtype controls (n=25) in their mean velocity or time spent in the center or peripheral zones. On the novel object recognition task, there were no difference between genotypes for novelty recognition across

genotypes. To test for anxiety and depressive-like symptoms, we used the elevated plus maze and tail suspension test. There were no differences across genotypes in either of these tests. To examine sociability, we used the three chamber social interaction task. Interestingly, we found that dysbindin spp heterozygotes ($P<0.005$) and homozygotes ($P<0.05$) spent more time than wildtype mice exploring a stranger mouse, compared to a familiar mouse. This suggests a preference for social novelty in the dysbidin spp mice. To examine protein, we performed Western Blots and found reduced dysbindin levels in the frontal cortex of dysbindin spp homozygotes ($P<0.01$), but no differences in the hippocampus. When examining soluble N-ethylmaleimide-sensitive factor attachment protein (SNAP)-25, we found lower levels in the frontal cortex of homozygous spp mice ($P<0.05$) compared to wildtype mice, with no differences in the hippocampus. Together our results represent the first molecular and behavioral characterization of dysbindin spp mice, demonstrating reduced dysbindin and SNAP-25 protein in the frontal cortex of spp homozygotes, but not spp heterozygotes. We continue to explore the behavioral and cognitive phenotypes of these mice in order to determine how these molecular brain changes affect functional measures.

Disclosures: **E.H. Chang:** None. **T.S. Chandon:** None. **L.E. Yeung:** None. **K. Barbari:** None. **K. Fernando:** None. **A.K. Malhotra:** F. Consulting Fees (e.g., advisory boards); Genomind, Takeda Pharmaceuticals, Forum Pharmaceuticals.

Poster

845. Schizophrenia: Developmental Models

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 845.11/LLL51

Topic: H.03. Schizophrenia

Support: VA Merit 1I01BX001356

VA Merit 1I01BX002774

VA CDA 1IK2BX002130

NIH Grant MH039683

NIH Grant HL095491

NIH Grant T32 HL007901

Title: Ketamine induced developmental schizophrenia model shows altered 40 Hz auditory steady-state response in adult mice

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Abstract: Abnormal cortical gamma band oscillation (GBO) linked to sensory and cognitive processing has been reported in schizophrenia (Sz) patients. Postmortem studies in Sz patients have shown deficits in parvalbumin (PV) containing GABAergic interneurons in several brain areas. PV interneurons are known as major contributors of GBO generation, and hypofunction of NMDA receptors (NMDARs) on PV interneurons is implicated in GBO deficits in Sz. Acute administration of NMDAR antagonists, such as ketamine, in adult animals is often used to mimic Sz-like symptoms and to investigate the role of NMDARs in GBO. However, since Sz has a significant neurodevelopmental component, investigation of models which mimic Sz-like impairment of neural development is vital to improve our understanding of Sz. Previous studies have shown that administration of ketamine at early postnatal stage of mice reduces PV expression in the prefrontal cortex and induces Sz-like symptoms in adulthood (Jeevakumar et al, 2015). Here we utilized this model to test whether developmental ketamine treatment alters 40 Hz auditory steady state responses (ASSR) which are widely used to assess GBO abnormalities. Ketamine (30mg/kg) or saline was administered to mice on postnatal days 7, 9, and 11. EEG/EMG electrodes were implanted on the skull once the mice reached adulthood (>2 month old). The ASSR task consisted of a 1-s of pre-stimulus epoch, a 1-s of 40 Hz auditory stimulus epoch, and a1-s of post-stimulus epoch, and was repeated for 120 times per experiment. EEG data was analyzed and compared between the ketamine-treated mice and the control mice.
The power spectrum was computed over 0.75 s of the auditory stimulus epoch, starting at 0.25 s after the stimulus onset. We found that 40 Hz ASSR was lower for the ketamine-treated mice compared to the control mice, consistent with studies of patients with Sz. We also analyzed amplitude of the event-related potentials around 50 ms (P50) and 100 ms (N100) relative to auditory stimulus onset where a large transient potential change was observed. P50 peak amplitude and peak-to-peak amplitude between P50 and N100 were both greater for the ketamine-treated mice than the control mice during the course of trials, a possible indication of sensory gating deficit, a characteristic of Sz phenotype.
These results show that developmental ketamine treatment that causes abnormal cortical PV expression in mice demonstrates similar ASSR deficits observed in Sz patients, suggesting potential use of this model for further investigating altered neural processing, related to deficits in sensory and cognitive processing in Sz.

Disclosures: F. Katsuki: None. **J.T. McKenna:** A. Employment/Salary (full or part-time): Merck MISP. B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution; Merck MISP. C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Merck MISP. **J.M. McNally:** None. **R.E. Strecker:** None. **R.W. McCarley:** None.

Poster

845. Schizophrenia: Developmental Models

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 845.12/LLL52

Topic: H.03. Schizophrenia

Support: MRC PhD Scholarship

Title: Mice haploinsufficient for Map2k7, a schizophrenia risk gene, show altered acquisition and performance on a touchscreen rodent gambling task

Authors: *R. L. OPENSHAW[1], D. M. THOMSON[2], J. A. PRATT[2], B. J. MORRIS[1];
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Abstract: Developing effective therapies to treat psychiatric disorders relies on animal models with appropriate face and construct validity. For this purpose, we investigated mice haploinsufficient for *Map2k7* (*Map2k7*$^{+/-}$), a gene functionally associated with schizophrenia (Winchester *et al*., 2012), in a rodent gambling task (rGT) that closely resembles the human Iowa Gambling Task (IGT).
Impaired decision making is frequently observed in the IGT in patients with schizophrenia, who make more disadvantageous choices, and show a reduced ability to adapt to shifting reward/punishment contingencies, compared to control subjects. In the rGT, mice choose between four options that differ in magnitude and probability of reward/punishment. To gain optimum amounts of reward in the time available, mice should select smaller, frequent rewards rather than large, infrequent rewards.
Mice (12 *Map2k7*$^{(+/-)}$(6 male), 12 WT (6 male)) were trained on the rGT using touchscreen apparatus (Campden Instruments) until they reached stable performance. Grid contingencies were counterbalanced across animals.
Map2k7$^{+/-}$ mice showed enhanced accuracy and fewer trials to reach criteria during task acquisition. Once they had reached stable % responding for each option, they displayed altered preference for the “high-risk, high-reward” option, and altered % optimal choices made on average. When the two most subtly different contingencies were switched, both groups of mice took a similar number of sessions to swap their responding accordingly, showing that all mice were capable of changing their decisions based on alterations in the probability and magnitude of reward and punishment. However, when the two most extreme contingencies were switched in conjunction with the punishment magnitude becoming less extreme, *Map2k7*$^{+/-}$ mice displayed a striking deficit in their ability to switch responding from the least optimal to the most optimal choice.
Overall, *Map2k7*$^{+/-}$ mice display alterations in gambling task acquisition and performance.

Additionally, *Map2k7*$^{+/-}$ mice show difficulty in shifting their decisions based on altered reward/punishment contingencies when punishment magnitude became more subtle. These results suggest MAP2K7 and/or other signalling components in its pathway have a role in decision making that may relate to perseveration. We previously reported that *Map2k7*$^{+/-}$ mice show an attentional deficit in the 5-CSRTT. These data support and extend these findings, showing promise for *Map2k7*$^{+/-}$ mice being a translatable model of cognitive dysfunction in psychiatric disorders.
We thank Prof. Penninger (IMBA, Vienna, Austria) for the gift of the mice.

Disclosures: R.L. Openshaw: None. **D.M. Thomson:** None. **J.A. Pratt:** None. **B.J. Morris:** None.

Poster

845. Schizophrenia: Developmental Models

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 845.13/LLL53

Topic: H.03. Schizophrenia

Support: NSERC

Title: Impaired attentional setshifting and reversal learning in a neurodevelopmental rat model of schizophrenia

Authors: *S. J. DESAI, B. ALLMAN, N. RAJAKUMAR;
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Abstract: Partial ablation of subplate neurons of the developing prefrontal cortex (PFC) in neonatal rat pups results in the adult emergence of positive and negative symptom-like features and structural abnormalities that are consistent with schizophrenia. Within the PFC, these changes include: 1) altered laminar distribution of GABAergic neurons; 2) decreased density of dopamine fibers in lower layers; 3) decreased synaptophysin and spinophilin immunolabeling, and; 4) loss of GABA transporter-1 immunoreactivity restricted to upper layers of the PFC. As glutamate, dopamine and GABA neurotransmitters play important role in executive functioning, we hypothesized that subplate-lesioned rats will show executive function deficits. At 10-12 weeks of age, lesioned and sham-operated (control) animals underwent an operant-based attentional set-shifting task, and reversal learning task. Set-shifting required the rats to learn a visual-cue discrimination (i.e., press the lever associated with the visual cue light), and then, shift to a response discrimination strategy (e.g., always press the left lever regardless of visual cue light) to obtain a sucrose pellet. For reversal learning, when rats were presented with two levers,

they first learned to press a given lever for every trial on training day, and then on the next day, they were required to switch to pressing the opposite lever. Compared to controls, the lesioned rats showed impaired executive function, as the total number of errors made, and the number of trials to achieve the performance criterion were significantly higher in the lesioned group for both tasks. Consistent with our hypothesis, rats whose subplate neurons were partially ablated during development showed increased perseverance in adulthood during task requiring cognitive flexibility; findings consistent with the deficits associated with schizophrenia.

Disclosures: **S.J. Desai:** None. **B. Allman:** None. **N. Rajakumar:** None.

Poster

845. Schizophrenia: Developmental Models

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 845.14/LLL54

Topic: H.03. Schizophrenia

Title: Behavioral characterization of neurodevelopmental MAM-E17 rat model

Authors: ***R. GRAF**, Z. A. HUGHES;
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Abstract: Schizophrenia (SZ) is a debilitating neuropsychiatric disorder with limited treatment options. Since the underlying causes are complex including genetic and environmental risk factors, the mechanism of the disorder is not yet fully understood. Exposure to methylazoxymethanol (MAM) at embryonic day 17 (E17) is hypothesized to induce deficits associated with positive, negative and cognitive symptoms observed in SZ patients. The aim of our research was to investigate whether the neurodevelopmental MAM rat model recapitulated any aspects of the cognitive and behavioral phenotype associated with SZ. Here we investigated adult offspring from E17 MAM-treated dams and their abilities to acquire and perform a location discrimination task utilizing touchscreen technology. The Location Discrimination Reversal (LD) task is a reward-based operant behavioral test that relies on the hippocampus, specifically the dentate gyrus to assess location memory by simultaneously displaying two identical stimuli in separate locations on a screen. The rats were trained to discriminate between the two illuminated images by pairing the correct response with a food reward; once learnt, the rule was then reversed. The MAM-treated rats acquired the task at a slower rate; however, when the discrimination index was reduced by decreasing the separation between the stimuli, the MAM rats exhibited modestly greater impairment compared to E17 vehicle treated controls (SHAM) only at the most challenging, adjacent, condition. In order to exacerbate cognitive symptoms, rats were challenged with the NMDA antagonist, MK-801 (0.032 and 0.056 mg/kg, SC) or

muscarinic antagonist, scopolamine (0.056 and 0.1 mg/kg, SC). While both MAM and SHAM groups were equally sensitive to MK-801, MAM-treated rats demonstrated greater sensitivity to the lower dose of scopolamine (0.056 mg/kg). Furthermore, hypersensitivity to psychostimulants is hypothesized to provoke positive-like symptoms. In order to test this theory, rats were exposed to either NMDA antagonist PCP (5 mg/kg, SC) or d-amphetamine (1.78 mg/kg, SC) and evaluated in a habituated locomotor activity assay. Both agents elicited a greater degree of hyperlocomotion in MAM vs SHAM animals. Taken together, here we demonstrated behavioral phenotype of the MAM exposure animal model in the pre-clinical assays of cognitive and positive symptoms. Further research needs to me conducted to determine if this model could be used for advancement of novel therapies.

Disclosures: R. Graf: None. **Z.A. Hughes:** None.

Poster

845. Schizophrenia: Developmental Models

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 845.15/LLL55

Topic: H.03. Schizophrenia

Support: CIHR 125984

Title: Perceptual oddity discrimination is impaired in the offspring of rats exposed to an inflammatory event during pregnancy

Authors: *B. R. LINS[1], Q. M. GREBA[1], R. K. THERA[1], S. E. CZINER[2], J. G. HOWLAND[1]; [1]Physiol., Univ. of Saskatchewan, Saskatoon, SK, Canada; [2]Byram Hills High Sch., Armonk, NY

Abstract: The medial temporal lobe is a critical brain region required for memory and is implicated in a variety of neurological disorders including schizophrenia. The perirhinal cortex (Prh) is a temporal lobe structure long known to be required for the discrimination of new and previously-experienced stimuli. Growing evidence suggests the Prh may have a non-mnemonic role in perception as well. Patients with schizophrenia exhibit impairments in perceptual category learning. The underlying cause of these deficits is unclear, and they exist despite preservation of occipital lobe function which suggests the involvement of other cortical areas. Involvement of the prefrontal cortex has been suggested based on correlational evidence, but the implication of a role in perception warrants examination of the Prh as well. The rodent oddity discrimination task depends on the integrity of the Prh and may be a useful tool to examine perceptual abnormalities in animal models of schizophrenia. The present experiment aims to

determine the effect of maternal immune insult during pregnancy on the adult offspring's performance in a simultaneous oddity discrimination task. Pregnant Sprague-Dawley dams were briefly anesthetised on gestational day 15 to receive a single intravenous injection of the viral mimetic polyI:C or physiological saline. Aside from acute follow-up (weight and temperature measurements), dams were left undisturbed to deliver their litters naturally and pups were weaned at 23 days old. Behaviour testing on the offspring began at adulthood (56 days old) and both male and female offspring were assessed. The oddity discrimination task took place in an open square arena following two days of habituation. On test day, rats were individually exposed to 3 identical objects and 1 "odd" object for 5 minutes of spontaneous exploration. Time spent exploring the odd object was expressed as a percent of total object exploration. Both male and female offspring of saline-treated dams showed significantly greater exploration of the odd object than male and female offspring of polyI:C-treated dams which performed near chance levels. PolyI:C-treated offspring were further divided into two categories based on the acute effects of polyI:C treatment on their mother's body weight. Offspring born to dams who experienced more than the average amount of weight loss were compared to those from dams who lost less than the overall average. The acute effects of polyI:C treatment on maternal weight did not affect the offspring's oddity preference. These data demonstrate the first evidence of impaired oddity discrimination in a model of maternal immune activation.

Disclosures: B.R. Lins: None. **Q.M. Greba:** None. **R.K. Thera:** None. **S.E. Cziner:** None. **J.G. Howland:** None.

Poster

845. Schizophrenia: Developmental Models

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 845.16/LLL56

Topic: H.03. Schizophrenia

Support: CIHR MOP 89825

CIHR MOP 119298

Title: Inducible rescue of NMDA receptors in a mouse model of schizophrenia: Neurophysiological consequences

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Abstract: Cognitive deficits in schizophrenia include impaired executive function, attention problems and distractibility. These deficits are not well addressed by current treatments and are disabling in terms of reintegration into the work place and society. Schizophrenia and its cognitive symptoms are thought to be developmental in origin, with a protracted period of aberrant development before the illness manifests in early adulthood. The transgenic mouse model of schizophrenia with reduced expression of the NR1 subunit of the NMDA receptor not only recapitulates these cognitive deficits and their emergence in early adulthood, but also many other endophenotypes of schizophrenia including increased locomotor activity, stereotypy, impaired sensorimotor gating, and deficits in sociability.
Here, we investigate whether normal cognitive performance can be restored after a lifetime of NMDA hypofunction, using an inducible transgenic approach to rescue NR1 subunit expression in adulthood. Strikingly, this partial adult rescue of the NR1 subunit largely normalized performance on tests of executive function, the symptom domain not well addressed by current treatments for schizophrenia. Our linked poster examines behavioral improvement and levels of protein rescue in different brain regions. This poster investigates the concomitant neurophysiological changes.
Since the medial prefrontal cortex is central to executive function, we probe its neurophysiology after adult rescue of NMDA receptor expression. Whole cell patch clamp recordings in acute brain slices showed significantly diminished NMDA receptor currents in layer V pyramidal neurons in the NR1 knockdown mice compared to wildtype. NMDA currents were almost completely restored in the conditional rescue mice after cre-recombinase activation. This finding is consistent with the normalized cognitive and social performance. Interestingly, behavioral rescue is not seen across all symptom domains. Stereotypy, an aberrant motor behavior, is not normalized by adult NR1 rescue. Consistent with this finding, electrophysiological recordings in the dorsal striatum show that medium spiny neurons have small NMDA currents in both knockdown and adult rescue, despite a significant rescue of NMDA binding. These results suggest targeting NMDA receptor function may be a key and specific step to achieving cognitive improvement in schizophrenia.

Disclosures: **M.A. Binko:** None. **C.A. Mielnik:** None. **A.J. Ramsey:** None. **E.K. Lambe:** None.

Poster

845. Schizophrenia: Developmental Models

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 845.17/LLL57

Topic: H.03. Schizophrenia

Support: Wellcome Trust WT0845921Z

Title: Do antipsychotic drugs influence only salience allocation processes that involve integration of information from prior experience ? Evidence from overshadowing and latent inhibition studies in dopamine d2 receptor deficient mice.

Authors: *P. M. MORAN[1], M. J. O'CALLAGHAN[2], C. BAY-RICHTER[4], C. M. P. O'TUATHAIGH[5], J. L. WADDINGTON[6], D. M. HEERY[3];
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Abstract: Salience allocation is the process whereby attention is directed towards stimuli in the environment to use in the formation of relevant associations. There is increasing evidence that salience allocation is abnormal in schizophrenia and may explain symptoms such as delusions and unusual thought patterns. Consequently, it has been suggested that antipsychotic drugs act to relieve some symptoms of schizophrenia by rebalancing abnormal salience allocation via dopamine D_2 receptor (D_2) antagonism. Salience is allocated to stimuli using different models and can be extrinsic (determined by what is previously known about stimuli) or intrinsic (determined by physical properties of stimuli such as loudness brightness etc; Cassaday & Moran 2010) which are likely to have different neural substrates.
Our previous findings suggest that D_2 plays a role in in the allocation of extrinsic salience based on prior knowledge and that antipsychotic drugs act via D_2 antagonism on extrinsic salience allocation. [Bay-Richter et al., (2013) *Neuropsychopharmacology, 38*(8),1512-1520; O'Callaghan et al., (2014) *J. Psychopharmacology*, 28(10): 973–977]. Here we investigated whether this is also the case for intrinsic salience.
Extrinsic (latent inhibition) and intrinsic (overshadowing) salience allocation were measured using drinking behaviour in thirsty mice (Table below describes 3 stage procedure that followed 7 days of lick training). Increased time to complete licks in thirsty mice in response to stimuli previously been paired with mild footshock (0.38mA) was the learning index.

	Preexposure	Conditioning	Test
Latent inhibition	Tone(85dB) (85dB)	Tone(85dB) + footshock (.38mA)	Tone(85dB)
Latent inhibition control	Place in box	Tone(85dB) + footshock	Tone(85dB)
Overshadowing	Lick training	Light+Tone (85dB) + footshock	Light (85dB)
Overshadowing control	Lick training	Light +footshock	Light (85dB)

D_2 deficient mice displayed good overshadowing but there was a strong trend towards reduced

overshadowing in D_1 deficient mice. Subsequent PCR analysis showed increased D_2 receptor mRNA expression in the striatum of D_1 deficient mice which may help to explain reduced overshadowing. Using a novel protocol that induces low overshadowing in controls we found that D_2 deficient mice but not mice treated acutely with the D_2 antagonist haloperidol show potentiated overshadowing. Taken together these data suggest that while the D_2 receptor may be important in both intrinsic and extrinsic salience allocation, antipsychotic drugs may act specifically on extrinsic salience processes.

Disclosures: **P.M. Moran:** None. **M.J. O'Callaghan:** None. **C. Bay-Richter:** None. **C.M.P. O'Tuathaigh:** None. **J.L. Waddington:** None. **D.M. Heery:** None.

Poster

845. Schizophrenia: Developmental Models

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 845.18/LLL58

Topic: H.03. Schizophrenia

Support: DAAD scholarship

CMPB

Heisenberg fellowship

Title: Schizophrenia-relevant ‚endophenotypes' in response to hyperstimulated NRG1/ErbB4 signaling

Authors: M.-C. SOTO-BERNARDINI[1], T. UNTERBARNSCHEIDT[1], E. DERE[1], C. DULLIN[1], A. RONNENBERG[1], M. M. BRZÓZKA[2], A.-K. MARTENS[3], F. ALVES[1], M. ROSSNER[2], H. EHRENREICH[1], K.-A. NAVE[1], *M. H. SCHWAB[1];
[1]Max-Planck Inst. of Exp Med., Goettingen, Germany; [2]Ludwig-Maximilians-Universität München, München, Germany; [3]Hannover Med. Sch., Hannover, Germany

Abstract: The *neuregulin 1* (*NRG1*) gene encodes a family of growth and differentiation factors with an epidermal growth factor (EGF)-like signaling domain that serve as ligands for the receptor tyrosine kinase ErbB4, the most prominent neuronal NRG1 receptor in the brain. NRG1/ErbB4 signaling has been implicated in the regulation of multiple aspects of nervous system development as well as synaptic functions in the mature brain. Variants of the human *NRG1* and *ErbB4* genes are possible genetic risk factors for schizophrenia. Increased NRG1 expression and ErbB4 hyperphosphorylation was found in postmortem brains of schizophrenia patients, suggesting that NRG1/ErbB4 hyperstimulation represents a possible pathomechanisms

with relevance for schizophrenia.
We recently showed that 'global' overexpression of NRG1 type I or type III isoforms under control of the neuronal Thy1.2 promoter causes brain 'endophenotypes' with relevance for schizophrenia. To investigate the consequences of NRG1/ErbB4 hyperstimulation in more specific *in vivo* models, we generated two conditional transgenic mouse lines, which permit conditional, Cre recombinase-dependent overexpression of NRG1 type I and type III isoforms. In contrast to ‚global' overexpression in the brain, cortex-restricted NRG1 type III overexpression in glutamatergic projection neurons was not associated with weight loss, ventricular enlargement, and defects in sensorimotor gating. Biochemical and behavioral investigation revealed distinct profiles in the recruitment of downstream signaling pathways and behavioral changes in conditional NRG1 type I and type III transgenic mice. These findings suggest NRG1 functions in subcortical networks and NRG1 isoform-specific consequences of NRG1-ErbB4 hyperstimulation in the cortex with relevance for schizophrenia 'endophenotypes'.

Disclosures: **M. Soto-Bernardini:** None. **T. Unterbarnscheidt:** None. **E. Dere:** None. **C. Dullin:** None. **A. Ronnenberg:** None. **M.M. Brzózka:** None. **A. Martens:** None. **F. Alves:** None. **M. Rossner:** None. **H. Ehrenreich:** None. **K. Nave:** None. **M.H. Schwab:** None.

Poster

845. Schizophrenia: Developmental Models

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 845.19/LLL59

Topic: H.03. Schizophrenia

Support: CB-2011-01- 166241

INFR-2012-01-187757

Title: Alterations in the synaptic plasticity associated to behavioral impairment in a schizophrenia like model

Authors: ***M. G. HERNANDEZ**, L. LARA VALDERRABANO, C. LÓPEZ RUBALCAVA, E. GALVÁN;
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Abstract: The sub-chronic, neonatal administration of MK-801 (NMDA receptor antagonist) in rats is a model that mimics schizophrenia-like symptoms. Nevertheless, the relationship between changes in the synaptic transmission and behavioral alterations in this model remains unclear. To explore this issue, pups on postnatal day (PND) 7 were injected with MK-801 (0.2 mg/kg for 5

days); thereafter, the animals were evaluated at 30 and 90 PND. MK-801 pretreated animals consistently displayed a reduction in new object recognition (NOR), social interaction (SI) and pre-pulse inhibition of the acoustic startle response (PPI) tests only at 90 PND. In addition, hippocampal slices from MK-801 animals were used to evaluate alterations on cellular excitability and synaptic plasticity. Whole cell experiments performed on CA1 pyramidal cells revealed alterations in the fire pattern and changes in the firing frequency of pretreated animals. Although paired-pulse facilitation did not exhibit changes at 30 PND, a reduction in the facilitation index was observed at 90 PND. In a similar vein, at 30 PND, the animals exhibited stable LTD; nevertheless, at 90 PND, induction of LTD is blunted. In another series of experiments, tetanic stimulation to Schaffer collaterals failed to induce LTP at 30 and 90 PND on the MK-801 animals. Lastly, we also explored alterations in the protein synthesis required for the late-phase of LTP. For this, the adenylyl cyclase-cAMP-PKA signaling pathway was stimulated with Forskolin for 30 min. In control, postsynaptic responses exhibited a long-lasting potentiation that lasted up to 6 hours. In contrast, MK-801 pretreated animals exhibited a transient and unstable potentiation. These results indicate that neonatal administration of MK-801 yield to the onset of deficits that mimics the schizophrenic symptoms at 90 PNDs. The behavioral impairment is accompanied by alterations in the neuronal excitability and synaptic plasticity.

Disclosures: **M.G. Hernandez:** None. **L. Lara Valderrabano:** None. **C. López Rubalcava:** None. **E. Galván:** None.

Poster

845. Schizophrenia: Developmental Models

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 845.20/LLL60

Topic: H.03. Schizophrenia

Support: NIH R01-NS060125-5

SFARI Innate Immune System Impact Grant #321998

NIH P50 MH106438-01

The MIND Institute Intellectual and Developmental Disabilities Research Center (U54 HD079125)

Title: Challenges for reproducibility in a mouse maternal immune activation model and recommendations for standardization

Authors: *M. ESTES[1], D. JOHN[1], D. VAN DER LIST[1], L. HAAPANEN[2], I. SHAFFER[1], A. MARTINEZ-HORTA[1], M. FOOTE[3], R. F. BERMAN[3], J. VAN DE WATER[2], A. MCALLISTER[1];
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Abstract: Infections during pregnancy are associated with increased risk of psychiatric disorders in offspring. The viral mimic Poly(I:C) is often used in models of maternal immune activation (MIA). However, the level of immune activation induced in the dam and resulting phenotypes in offspring vary widely from lab to lab, even using the same source and dose of Poly(I:C). We have identified two factors contributing to this variability: lot to lot variation in immunogenicity of the Poly(I:C) and variability in immune responsiveness within a mouse strain. To overcome these issues, we designed a protocol to determine the appropriate dose of any source of Poly(I:C) for inducing reproducible levels of MIA and disease-relevant changes in offspring.
The Poly(I:C) model was originally designed to cause elevations in interleukin-6 (IL-6) in maternal serum to levels comparable to those induced by influenza. However, many laboratories using this model do not measure maternal IL-6, and those that do report widely varying levels using the same dose and source of Poly(I:C). Reported MIA-induced maternal IL-6 levels have also been steadily decreasing over the past few years. Recently, we discovered that most of the available sources of the kind of Poly(I:C) used in the original published model elicited an IL-6 response in pregnant mice that ranged from no difference compared to saline injections to a maximum increase of only 2% of the originally reported MIA values.
In order to determine the magnitude of IL-6 induction that is sufficient to cause disease-related phenotypes, we tested 3 doses of Poly(I:C) in pregnant mice that were high, medium, or low responders to immune challenge based on a priming procedure with low doses of Poly(I:C) prior to breeding. Glutamatergic synapse density and the protein levels of neuronal MHC class I molecules and whole brain MEF2 transcription factors and STAT activation were quantified from groups of MIA and control offspring from each combination of dose and immune responsiveness. The biologically-relevant dose of Poly(I:C) was determined as the lowest concentration that minimized litter loss while eliciting reproducible changes in the biological measures obtained when Poly(I:C) was more immunogenic. Current efforts are underway to add behavioral assessments to these outcome measures, and to screen for cytokine changes in maternal serum that consistently reflect these biological measures. We recommend that labs perform a similar optimization protocol for every new lot of Poly(I:C) in order to determine the effective dose to elicit MIA and report these measures in each paper to enable comparison of results between labs within the field.

Disclosures: M. Estes: None. **D. John:** None. **D. van der List:** None. **L. Haapanen:** None. **I. Shaffer:** None. **A. Martinez-Horta:** None. **M. Foote:** None. **R.F. Berman:** None. **J. Van de Water:** None. **A. McAllister:** None.

Poster

845. Schizophrenia: Developmental Models

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 845.21/LLL61

Topic: H.03. Schizophrenia

Support: NIH Grant MH097997

Title: NEAT1- long noncoding RNA associated with paraspeckles: role in oligodendrogenesis and angiogenesis - relevance to schizophrenia.

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Abstract: Long noncoding RNA - NEAT1 is a structural component of paraspeckles, subnuclear bodies in interchromatin regions that control sequestration of paraspeckle proteins. Microarray studies of multiple cortical regions from individuals with schizophrenia (SZ) showed strong downregulation of NEAT1 levels compare to controls. Evaluation of two animal models ("quaking" and mutant human DISC1) implicated in myelin function alterations showed that NEAT1 expression is strongly associated with oligodendrocyte transcription profiles. OLG/myelin -related gene/protein expression decline is among the most corroborated observations in the pathophysiology of SZ. To gain insight into biological processes affected by deficiency of NEAT1 expression we performed analysis of RNA-Seq data from frontal cortex of adult NEAT1-KO and controls mice. As expected, cortical samples from NEAT1-KO mice show dramatic reduction of NEAT1 (13.8 fold change). Near identical decrease was also detected for one of the other lncRNA - Malat1 (14.8 fold change), suggesting that NEAT1 may play a role in transcriptional regulation of Malat1. Myelin specific genes (Olig1-2, Nfasc, Cldn11, Mal, Pllp) were significantly downregulated in NETA1-KO mice ($ps \leq 0.05$). According to the results of the WGCNA analysis, a weighted correlation network analysis tool, several modules highly enriched for biological processes related to RNA post-transcriptional modification, cellular assembly-translation initiation showed positive module-trait relationships with NEAT1-KO mice. Modules enriched with vascular/endothelial cells and myelinating OLGs markers were inversely correlated with deficit of NEAT1 expression. Endothelin-1, VEGF signaling pathways and ECM-cell interactions in OLG differentiation were among the significantly downregulated pathways, while mTOR/EIF2 signaling and cholesterol biosynthesis pathways showed upregulation. Disruption of Wnt signaling, implicated in both OLG- and vascular- related functions, offered mechanistic insights into the consequences of NEAT1 deficit in CNS. Multiplex RNA *in situ* hybridization (ViewRNA) demonstrated co-localization of NEAT1 with

Sox10 (OLG marker) and Flt1 (vascular/endothelial cells marker) in cerebral cortex of control mice. These findings suggest strong involvement of NEAT1 in oligodendrocyte and vascular function. Evaluation of the identified signaling pathways in postmortem brains of individuals with SZ will deepen and advance our understanding of the mechanisms underlining pathophysiology of SZ.

Disclosures: P.L. Katsel: None. **P. Roussos:** None. **P. Fam:** None. **W. Tan:** None. **M. Pletnikov:** None. **S. Nakagawa:** None. **V. Haroutunian:** None.

Poster

845. Schizophrenia: Developmental Models

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 845.22/LLL62

Topic: H.03. Schizophrenia

Support: SNSF Grant 31-116689

SNSF Grant 310030_135736/1

NCCR SYNAPSY SNSF 51AU40_125759

Avina Foundation

Damm-Etienne Foundation

Alamaya Foundation

Title: Oxidative stress-driven parvalbumin interneuron impairment as a core mechanism in psychiatric disorders

Authors: *J. CABUNGCAL[1], M. CUENOD[1], J. T. COYLE[2], M. D. PUHL[2], M. DIDRIKSEN[3], A. A. GRACE[4], K. GILL[4], T. HENSCH[5], H. MORISHITA[6], A. S. LAMANTIA[7], T. MAYNARD[7], L. LINDEMANN[8], U. MEYER[9], S. GIOVANOLI[9], P. O'DONNELL[10], P. STEULLET[1], K. Q. DO[1];
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Neuroscience, Opthalmology & Rare Dis. (NORD) DTA, F. Hoffmann-La Roche Ltd, Basel, Switzerland; [9]Inst. of Pharmacol. and Toxicology, Univ. of Zurich-Vetsuisse, Zurich, Switzerland; [10]Neurosci. and Pain Res. Unit, BioTherapeutics Res. and Development, Pfizer Inc., Cambridge, MA

Abstract: Parvalbumin interneurons (PVI) are a class of fast spiking inhibitory cortical interneurons essential to maintain proper excitatory/inhibitory balance and cortical synchronization, and their activity supports cognitive functions. These cells are surrounded by perineuronal nets (PNN) and have been implicated in schizophrenia pathophysiology. During neurodevelopment, the highly metabolically active PVIs are particularly sensitive to reactive oxygen species (ROS). We tested whether known genetic and environmental risk factors converge on brain redox dysregulation, yielding oxidative stress as a central core mechanism leading to specific cellular and circuit dysfunctions. Thirteen animal models relevant to autism and schizophrenia, ranging from genetic manipulations to environmental insults and their combinations were investigated for oxidative stress with immunohistochemistry (8-oxo-DG), along with assessing integrity of PVI and their PNN. These models included: fmr1 KO, 15q13.3 microdeletion: Df(h15q13)/+, *LgDel* model of 22q11DS, 1q21.1 deletion, serine racemase (SR) KO, GRIN2A KO, Gclm KO; Gclm KO + GBR12909, PV-Gclc KO, GRIN2A KO + GBR12909, neonatal ventral hippocampal lesion (NVHL), methylazoxymethanol acetate developmental rodent model (MAM) and poly:IC maternal immune activation. With the exception of the 1q21.1 CNV model, they all presented an increase in oxidative stress associated with a decrease of PVI- and PNN- immunoreactivity in the anterior cingulate cortex. Changes in oxidative stress and in PVI/PNN were negatively correlated. In some models, antioxidants such as N-acetyl-cysteine prevented these cellular anomalies as well as physiological and behavioral alterations. These results suggest a convergence of various genetic and environmental risk factors on oxidative stress induced PVI/PNN impairment as a "final common pathway" in the pathophysiological development of psychiatric disorders. Indeed, oxidative stress in reciprocal interaction with dopamine dysregulation, inflammation, and NMDA receptor hypofunction could be central to damage of the highly metabolically active PVI. Antioxidant systems are therefore potential therapeutic targets, assuming that redox regulators could be applied to vulnerable individuals early, close to environmental impacts, before the clinical emergence of diseases.

Disclosures: **J. Cabungcal:** None. **M. Cuenod:** None. **J.T. Coyle:** None. **M.D. Puhl:** None. **M. Didriksen:** None. **A.A. Grace:** None. **K. Gill:** None. **T. Hensch:** None. **H. Morishita:** None. **A.S. LaMantia:** None. **T. Maynard:** None. **L. Lindemann:** None. **U. Meyer:** None. **S. Giovanoli:** None. **P. O'Donnell:** None. **P. Steullet:** None. **K.Q. Do:** None.

Poster

845. Schizophrenia: Developmental Models

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 845.23/LLL63

Topic: H.03. Schizophrenia

Support: CIHR Grant 125984

Title: Degradation of perineuronal nets in medial prefrontal cortex impairs prepulse inhibition and crossmodal object recognition memory: implications for schizophrenia

Authors: *J. G. HOWLAND[1], Q. GREBA[1], J. W. PAYLOR[2], N. K. ZABDER[3], B. G. MURRAY[3], I. R. WINSHIP[2];
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Abstract: Schizophrenia is a particularly costly brain disorder given its typical onset in early adulthood and persistence throughout life. Studies in humans with schizophrenia show reduced expression of perineuronal nets (PNNs), a specialized extracellular matrix component, in corticolimbic brain areas. The consequences of altered PNNs in the disorder are unclear, although hypotheses regarding the dys-regulation of parvalbumin-expressing interneuron (PV-cell) activity have been proposed. In some neurodevelopmental models of schizophrenia, reduced perineuronal nets have been reported in medial prefrontal cortex (mPFC), which may contribute to the behavioural changes observed in these models. Given these considerations, the present experiments were designed to assess the effects of degrading perineuronal nets in mPFC on two behaviours relevant to schizophrenia: prepulse inhibition of the acoustic startle response and crossmodal (tactile to visual) recognition memory. Briefly, young adult, male Long Evans rats received an intracranial infusion of the enzyme chondroitinase-ABC (ChABC, n=8), which degrades perineuronal nets, or the control enzyme penicillinase (n=8) into mPFC. Two weeks later, the rats were tested on prepulse inhibition using a standard protocol (120 dB pulse, prepulses 3, 6, and 12 dB above background noise level). Prepulse inhibition was impaired in rats injected with ChABC on trials with a 3 dB prepulse without changes in startle amplitude. Crossmodal recognition memory was tested using a test based on rats' innate preference for novelty. After a series of habituation sessions, the rats were allowed to explore two copies of an object in the dark (3 min, sample phase). Sixty minutes later with the room lights on, rats were exposed to a copy of the sample object and an additional novel object and allowed to explore them visually but not touch them (test phase). Rats injected with ChABC were profoundly impaired on the crossmodal test and failed to show a preference for the novel object. No changes in exploration time were observed between groups for either the sample or test phases. Following behavioral testing, rats were sacrificed and we used immunohistochemistry with the lectin

Wisteria Floribunda Agglutinin to assess perineuronal nets. Rats injected with ChABC had reduced expression of perineuronal nets around the injection site in mPFC. These results indicate that the acute loss of perineuronal nets in mPFC is sufficient to produce behavioral changes in adult rats. On-going experiments will relate these behavioural alterations to the activity of neurons in mPFC during task performance.

Disclosures: J.G. Howland: None. **Q. Greba:** None. **J.W. Paylor:** None. **N.K. Zabder:** None. **B.G. Murray:** None. **I.R. Winship:** None.

Poster

845. Schizophrenia: Developmental Models

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 845.24/LLL64

Topic: H.03. Schizophrenia

Support: NRF- funding

URC- funding University Research Committee

Title: Male rats are susceptible whilst females are resilient to developing schizophrenia like neophobic responses following social isolation

Authors: *K. ATMORE[1], V. RUSSELL[2], D. STEIN[1], F. HOWELLS[1];
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Abstract: The socially isolated rat model is a developmental animal model of schizophrenia. Neophobia or avoidance of novelty is a common feature of the human disorder – schizophrenia. A few studies have investigated the response to novelty in socially isolated rats, largely only in male rats. In the present study we investigated the novelty response in both male and female rats that had been socially isolated, using a novel object recognition (NOR) task.
Sprague Dawley rats (25 per group; male-socialised, male-isolated, female socialised, female-isolated) were housed by sex in cages of 4 animals or alone from postnatal day (p) 21 and subjected to minimal handling. From p78-82 rats underwent NOR testing. This test involved three parts, initial open field exploration, familiarisation/habituation to two identical objects in the open field, and in the final phase one familiar object was replaced by a novel object. These trials were video recorded and analysed using Noldus tracking software to measure distance travelled and time spent exploring different zones in the arena where the objects were located. In the first minute of the NOR test isolated males entered the zone containing the novel object

less frequently than their group counterparts. Male isolates also covered a significantly shorter distance than group males in the first minute of the NOR test consistent with reduced tendency to explore a novel environment. In this study, males were shown to be more susceptible to environmental manipulations than females, as isolated males weighed significantly more than group animals from p28 onwards. No significant difference was found between female isolates and group subjects.
Inability to attend to novel and relevant environmental stimuli is a characteristic trait of schizophrenia. The results of the present study reinforce the usefulness of the social isolation rat model of schizophrenia and support the inclusion of both sexes in future experiments to help identify the neurochemistry underlying sex specific resilience to displaying symptoms. This will provide useful translational information for understanding and treating the human disorder.

Disclosures: K. Atmore: None. **V. Russell:** None. **D. Stein:** None. **F. Howells:** None.

Poster

845. Schizophrenia: Developmental Models

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 845.25/LLL65

Topic: H.03. Schizophrenia

Support: National Health and Medical Research Council of Australia

Title: The BDNF Val66Met genotype interacts with glucocorticoid stress hormone to regulate prepulse inhibition of acoustic startle, an endophenotype of schizophrenia

Authors: *M. VAN DEN BUUSE[1], M. NOTARAS[2], R. HILL[2], J. GOGOS[3];
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Abstract: Reduced expression of Brain-Derived Neurotrophic Factor (BDNF) has been implicated in the pathophysiology of schizophrenia. The BDNF Val66Met polymorphism, which results in deficient activity-dependent secretion of BDNF, has been reported to mediate stress sensitization and clinical features of schizophrenia, although clinical studies have been inconsistent (Notaras et al., 2015). Here we investigated whether chronic stress may be a factor that determines allele of risk within this disorder.
We studied the effect of this polymorphism on Prepulse Inhibiton (PPI), a translational model of sensorimotor gating which is disrupted in schizophrenia. We utilized $BDNF^{Val66Met}$ mice genetically modified to carry a humanized BDNF transcript expressing the Val66Met

polymorphism ($hBDNF^{Val66Met}$) and studied the long-term effect of chronic corticosterone (CORT) exposure in these animals as a model of history of stress. PPI was assessed at both 100msec and 30msec inter-stimulus intervals (ISI). Mice were assessed at baseline and after acute injection of apomorphine or MK-801.
Analysis of PPI at the commonly used 100msec ISI identified that, irrespective of CORT treatment, the $hBDNF^{Val/Met}$ genotype was associated with significantly reduced PPI. In contrast, PPI was not different in $hBDNF^{Met/Met}$ mice compared to the $hBDNF^{Val/Val}$ genotype. At the 30msec ISI, a significant genotype x CORT interaction reflected that CORT treatment selectively disrupted sensorimotor gating of $hBDNF^{Val/Met}$ heterozygote mice but not $hBDNF^{Val/Val}$ or $hBDNF^{Met/Met}$ mice. Analysis of startle reactivity revealed a significant $hBDNF^{Val66Met}$ genotype x CORT x sex interaction, reflecting that chronic CORT reduced startle reactivity of $hBDNF^{Val/Val}$ male mice by 51%. However, ANCOVA suggested that this was independent of the effect of CORT and $hBDNF^{Val66Met}$ genotype on PPI. The effects of apomorphine and MK-801 in this model will be presented.
We provide the first robust evidence of a distinct BDNF 'heterozygote disadvantage' phenotype using the sensorimotor gating endophenotype of schizophrenia, and that a history of stress hormone exposure interacts with BDNF Val66Met genotype.

Disclosures: **M. Van den Buuse:** None. **M. Notaras:** None. **R. Hill:** None. **J. Gogos:** None.

Poster

845. Schizophrenia: Developmental Models

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 845.26/LLL66

Topic: H.03. Schizophrenia

Support: MaineINBRE

Colby College Office of the Dean of Faculty

Title: Investigation of Disc1 gene status and stress exposure in female rats on behavior and hippocampal plasticity

Authors: *J. MITCHELL, M. J. GLENN;
Psychology, Colby Col., Waterville, ME

Abstract: The goal of the present study was to characterize the behavioral and neural effects of a biallelic deletion within the Disc1 (disrupted in schizophrenia 1) gene in female rats as a function of chronic stress exposure or control conditions. Mutations in the Disc1 gene are associated with

increased incidence of psychiatric illness, particularly schizophrenia but also depression and bipolar disorder. A common feature of these disorders is the contributing factor of stress. Thus, this study tested the Two-Hit Hypothesis of schizophrenia; that exposure to chronic unpredictable stress would significantly worsen the effects of the gene deletion. To do this, DISC1 knockout and wildtype rats were exposed to either 3 weeks of chronic unpredictable stress or maintained under normal colony conditions. At the end of the stress period, all rats underwent a battery of tests to evaluate emotionality and cognition. Rats were then sacrificed and brains retained for analyses of neural and genomic markers. Both behavioral and biological findings support the hypothesis; rats that had a DISC1 KO gene and were exposed to chronic stress were significantly worse off than control animals. Data from behavioral and biological assays give further support of the DISC1 model of schizophrenia as a reliable way to investigate schizophrenia in rats. In addition, this study found that females, in response to stress, exhibit hyperactivity, a symptom that is not seen in males exposed to stress. The results from this study supported the Two-Hit Hypothesis, the DISC1 KO model of schizophrenia in rats, and exemplified the importance of including females in biomedical research.

Disclosures: J. Mitchell: None. **M.J. Glenn:** None.

Poster

845. Schizophrenia: Developmental Models

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 845.27/LLL67

Topic: H.03. Schizophrenia

Support: NIH Grant R01MH075916

NIH Grant K23MH079498

NIH Grant R01DA023210

Title: NMDA receptor blockade has differential effects on the synaptic proteome in juvenile versus adult mice.

Authors: K. BORGMANN-WINTER[1,2], N. BOWMAN[1], A. BANERJEE[1], W. BILKER[1], S. SIEGEL[3], *C.-G. HAHN[3];
[1]Univ. of Pennsylvania, Philadelphia, PA; [2]Children's Hosp. of Philadelphia, Philadelphia, PA; [3]Dept Psychiat, Univ. Pennsylvania Sch. Med., Philadelphia, PA

Abstract: Previously we observed that chronic ketamine decreased N-methyl-D-aspartame (NMDA) receptor signaling n adult mice but increased it in juveniles. In addition, we found that

NMDA receptor signaling changes persisted following cessation of treatment at least for 2 weeks in juvenile animals. Such differential effects of NMDA receptor blockade between juveniles and adults are of interest from the perspective of schizophrenia pathophysiology as well as increasing prevalence of ketamine abuse among adolescents. In this study we examined the proteome of synaptic membrane fractions in juvenile and adult mice at 24 hours and two weeks after cessation of a 2 week ketamine treatment. Ketamine (20mg/kg) was administered to adult (10 week) and juvenile (4 week) C3H male mice daily for 2 weeks. Mice were sacrificed after either 24 hours or a two week washout period. Crude synaptic membrane fractions were isolated by centrifugation of the post nuclear extracts of homogenized mouse cortical tissues. Ten µg of synaptic membrane extracts were mixed with [13C6]lysine-labeled internal standards. Samples were trypsin-digested, and processed for LC-SRM/MS on a triple quadrupole mass spectrometer for 200+ synaptic proteins. Peak areas for "light" endogenous peptides and "heavy" standard peptides were calculated, and ratios (l/h) between the two were used as dependent variables. Repetitive ketamine injection started in the juvenile period compared to adulthood (daily injection for 14 days followed by 24 hrs drug washout) led to alterations in more than 60 proteins that differed between the groups including SRC, GluN2B and GluR3 along with multiple mitochondrial proteins ($p<0.03$, Wilcoxin Rank Sum; multiple comparisons were accounted for using the FDR). Some protein alterations persisted two weeks later in animals exposed to NMDA receptor blockade during the juvenile period. These results point to interesting differences in the effects of the onset of NMDA receptor hypofunction in the juvenile period compared to that in the adult period.

Disclosures: **K. Borgmann-Winter:** None. **N. Bowman:** None. **A. Banerjee:** None. **W. Bilker:** None. **S. Siegel:** None. **C. Hahn:** None.

Poster

845. Schizophrenia: Developmental Models

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 845.28/LLL68

Topic: H.03. Schizophrenia

Support: NIH NCRR 5P20RR016463-12

NIH NIGMS 8P20GM103423-12

Title: Progression of schizophrenia-like symptomology during periadolescent development is sexually dimorphic in DISC1 knockout Sprague Dawley rats

Authors: *M. J. GLENN, W. YU, A. A. BATALLAN;
Psychology, Colby Col., Waterville, ME

Abstract: The DISC1 gene contributes to the development and function of the central nervous system and alterations in it are linked to psychiatric disorders, particularly schizophrenia. In humans, DISC1 translocation affects brain areas dysfunctional in schizophrenia (hippocampus, frontal cortex); at the subcellular level (centrosome, mitochondria) the gene product is important in neuron migration, branching, and signal transduction. Assessing the impact of knockouts to candidate risk genes, like DISC1, in animal models provides valuable insights into the significance of that gene for the kind and magnitude of symptoms, neural and genomic effects, and the relation between those behavioral and physiological outcomes. Previous research has relied on mouse models and these may not yield as reliable or rich a behavioral analysis as can be obtained using rats. Thus, the overall aim of the present study was to characterize the effects of a biallelic deletion of the DISC1 gene in the Sprague Dawley rat and two key goals were addressed: 1) to detect potential early markers in the behavior of DISC1 knockout rats comparable to the subtle behavioral and intellectual abnormalities observed in otherwise healthy human adolescents who later develop schizophrenia; and 2) to search for biological sex differences in symptom kind, emergence, and severity. To do this, female and male wildtype and DISC1 knockout rats were assessed beginning just prior to weaning and during the post-weaning periadolescent period. The primary outcomes evaluated were overall activity, exploratory behavior, response to novel objects, response to novel conspecifics, and pre-pulse inhibition. These behaviors were selected as analogous indices of positive, negative, and cognitive symptoms in schizophrenia as it occurs in humans. The results revealed that both female and male DISC1 knockout rats differed from wildtypes on numerous measures. However, the magnitude and kind of deficits was sexually dimorphic: female rats were hyperactive, averse to novel objects, and exhibited a modest impairment in pre-pulse inhibition, whereas male rats were anxious, averse to novel objects and rats, and showed a severe impairment in pre-pulse inhibition. These data confirm that the DISC1 knockout rat model is an excellent way to reproduce and study symptoms of schizophrenia and additionally reveal that the deletion of this gene has differential consequences on the progression and emergence of specific schizophrenia-like symptoms clusters in females and males.

Disclosures: **M.J. Glenn:** None. **W. Yu:** None. **A.A. Batallan:** None.

Poster

845. Schizophrenia: Developmental Models

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 845.29/LLL69

Topic: H.03. Schizophrenia

Support: USPHS grant P50-MH103222

Title: Kynurenic acid in the fetal mouse brain: on the role of mother-placenta-fetus dynamics

Authors: *F. M. NOTARANGELO[1], N. GOEDEN[2], A. POCIVAVSEK[1], S. BEGGIATO[1], K. WONS[1], A. BONNIN[2,3], R. SCHWARCZ[1];
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Abstract: The kynurenine pathway (KP), which constitutes the main catabolic route of the essential amino acid tryptophan in mammals, contains several neuroactive compounds ("kynurenines"), including kynurenic acid (KYNA), an endogenous inhibitor of both NMDA and α7nACh receptors, and 3-hydroxykynurenine (3-HK), a free radical generator. Elevation of KYNA levels in the fetal brain during the last week of gestation causes cognitive deficits in the adult offspring (Pocivavsek et al., 2014). As there is little known about KP metabolism during the gestational period, we now investigated its dynamics in mice *in vivo*. To this end, kynurenine (100 mg/kg; n = 3), KYNA (10 mg/kg; n = 3) or saline (n = 3) were administered orally to pregnant CD1 mice on gestational day 18. Ninety minutes later, the animals were euthanized, and the levels of KP metabolites were measured in maternal plasma, placenta, fetal plasma and fetal brain. Administration of kynurenine significantly increased kynurenine, KYNA and 3-HK levels in the maternal plasma (by 30-, 6- and 15- fold, respectively) and in the placenta (by 9-, 3- and 15-fold, respectively) compared to controls. Notably, this treatment also raised kynurenine levels (10-fold), as well as KYNA (4-fold) and 3-HK (17-fold) levels, in the fetal plasma, demonstrating the ability of systemic kynurenine to cross the placenta and reach the fetus. KYNA administration increased KYNA levels in both the maternal plasma (43-fold) and in the placenta (4-fold), but caused only a small, non-significant KYNA elevation (+28%) in the fetal plasma. Measurements of KP metabolites in the fetal brain revealed qualitatively and quantitatively similar effects as seen in the fetal plasma. Thus, we detected increased levels of kynurenine (11-fold), KYNA (5-fold) and 3-HK (17-fold) following maternal kynurenine administration, but no significant change in KYNA (+52%) after maternal KYNA treatment. Both individually and jointly, these data provide new insights into the roles of maternal, placental and fetal compartments with regard to the prenatal disposition of KP metabolites. The present findings are not only of interest with regard to the possible physiological role of kynurenines during gestation but may be especially relevant for conceptualizing the effects of abnormal maternal KP metabolism in the etiology of various neurodevelopmental disorders, including schizophrenia and autism.

Disclosures: F.M. Notarangelo: None. **N. Goeden:** None. **A. Pocivavsek:** None. **S. Beggiato:** None. **K. Wons:** None. **A. Bonnin:** None. **R. schwarcz:** None.

Poster

845. Schizophrenia: Developmental Models

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 845.30/LLL70

Topic: H.03. Schizophrenia

Title: A schizophrenia-associated SNP in zinc transporter SLC39A8 causes deficits in glutamate receptor activity and elevates the innate immune response

Authors: *W. TSENG[1], M. L. WEBER[1], V. R. BIEBER[1], T. A. LANZ[1], H. XI[1], R. D. BELL[1], E. L. HONG[2], D. L. BUHL[1];
[1]Neurosci. and Pain Res. Unit, Pfizer, Cambridge, MA; [2]Dept. of Psychiatry, Univ. of Maryland Sch. of Med., Baltimore, MD

Abstract: Genome-wide association studies (GWAS) identifying nonsynonymous single nucleotide polymorphisms (nsSNPs) in schizophrenia patients compared to control subjects have revealed a risk allele in gene SLC39A8 (rs12107325), which encodes metal-ion transporter protein Zip8 of the ZIP family. Despite the discovery and cloning of Zip8 nearly 10 years ago, most of its physiological functions in the CNS have remained under-characterized. Here we show that the human nsSNP A391T of SLC39A8 is a loss-of-function allele that leads to deficits in cellular zinc import in a time-dependent manner. The human nsSNP Zip8 A391T also results in impairment of pharmacologically-isolated NMDAR and AMPAR spontaneous firing activity, which is consistent with data indicating a mislocalization of GluA1 subunit containing AMPAR to the surface. Lastly, the knock-in of the human nsSNP Zip8 A391T recapitulates the phenotype of Zip8 knockout cells in which there is an increased release of inflammatory cytokines and elevated innate immune responses. The disruption in glutamate signaling is consistent with an observed decrease in glutamate using magnetic resonance spectroscopy in schizophrenic subjects carrying the mutation. Understanding how Zip8 regulates zinc levels and affects downstream messengers will elucidate the role of Zip8 in brain metal homeostasis and inflammation, uncovering potential disease mechanisms of schizophrenia and novel targets for therapeutics.

Disclosures: **W. Tseng:** A. Employment/Salary (full or part-time): Pfizer. **M.L. Weber:** A. Employment/Salary (full or part-time): Pfizer. **V.R. Bieber:** A. Employment/Salary (full or part-time): Pfizer. **T.A. Lanz:** A. Employment/Salary (full or part-time): Pfizer. **H. Xi:** A. Employment/Salary (full or part-time): Pfizer. **R.D. Bell:** A. Employment/Salary (full or part-time): Pfizer. **E.L. Hong:** None. **D.L. buhl:** A. Employment/Salary (full or part-time): Pfizer.

Poster

846. Biochemical Techniques

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 846.01/MMM1

Topic: I.01. Molecular, Biochemical, and Genetic Techniques

Title: Quantification of circulating Aβ40 and Aβ42 levels in blood and CSF in human and rodents using ultra sensitive single molecule counting (SMC™).

Authors: *L. CHEN[1], A. VAHEDI[2], S. HAMREN[2], J. MISTRY[3], Q. XIAO[3], J. HWANG[3]; [1]R&D, MilliporeSigma, Saint Charles, MO; [2]R&D, MilliporeSigma, Hayward, CA; [3]R&D, MilliporeSigma, St. Charles, MO

Abstract: Alzheimer's disease (AD) is the most common cause of dementia that affects millions of patients. Amyloid beta (Aβ) deposition is a pathological hallmark of Alzheimer's disease. The previous research suggested that Aβ1-40 and Aβ1-42 in cerebrospinal fluid (CSF) and plasma can be biomarkers to monitor AD progression. Accurate quantification of these two peptides becomes very critical for pre-clinical animal study and clinical research. Here we report on the performance of our newly developed Singulex Erenna® Aβ40 and Aβ42 immunoassay kits, using Single Molecule Counting (SMC™) technology. These SMC™ Aβ40 and Aβ42 immunoassay kits can accurately quantitate Aβ40 and Aβ42 levels in human plasma and CSF from normal individuals and Alzheimer's disease patients, as well as from mouse and rat samples. The lower limits of quantification (LLOQ) of Aβ40 and Aβ42 in these novel assay kits are 7.81pg/mL and 0.59 pg/mL, respectively. The SMC™ Aβ40 and Aβ42 kits are robust and allow for quantification from discovery, through drug development, to clinical trials using one platform. The analytical performance characteristics reported here include assay sensitivity, intra- and inter-assay precision, sample dilution linearity, spike recovery, and species specificity. In summary, these sensitive Aβ40 and Aβ42 assay kits provide a powerful non-invasive biomarker tool for studying the pathogenesis of neurodegenerative diseases such as Alzheimer's disease.

Disclosures: **L. Chen:** A. Employment/Salary (full or part-time): MilliporeSigma. **A. Vahedi:** A. Employment/Salary (full or part-time): MilliporeSigma. **S. Hamren:** A. Employment/Salary (full or part-time): MilliporeSigma. **J. Mistry:** A. Employment/Salary (full or part-time): milliporeSigma. **Q. Xiao:** A. Employment/Salary (full or part-time): MilliporeSigma. **J. Hwang:** A. Employment/Salary (full or part-time): MilliporeSigma.

Poster

846. Biochemical Techniques

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 846.02/MMM2

Topic: I.01. Molecular, Biochemical, and Genetic Techniques

Title: Fast and sensitive detection of DA, 5-HT and metabolites using the UHPLC ALEXYS Neurotransmitter Analyzer

Authors: *M. EYSBERG[1], L. VAN HEERWAARDEN[1], H.-J. BROUWER[1], F. CACCIAPAGLIA[2], N. REINHOUD[1];
[1]Antec, Zoeterwoude, Netherlands; [2]Antec USA, Boston, MA

Abstract: In the field of neurotransmitter analysis, there is a continuing demand for faster and more sensitive detection. A number of multi-component analyses have been developed optimized for low neurotransmitter concentrations in small sample volume (<2µL).The ALEXYS™ is a UHPLC system with the DECADE Elite (electrochemical detector) and SenCell (electrochemical flow cell) that has been designed to meet the highest demands for detection sensitivity and performance. The DECADE Elite uses Antec's workstation concept, keeping the column and flow cell (separation and detection) at a very accurate and stable temperature. Stable working conditions are a prerequisite for trace analysis. The SenCell has an Adjustable Spacer Technology (AST) that enhances the sensitivity and improves detection limits.Three fast methods (1-3 min) are presented for analyzing different sets of monoamine neurotransmitters and their metabolites that are applicable to microdialysate samples and brain tissue extracts. .
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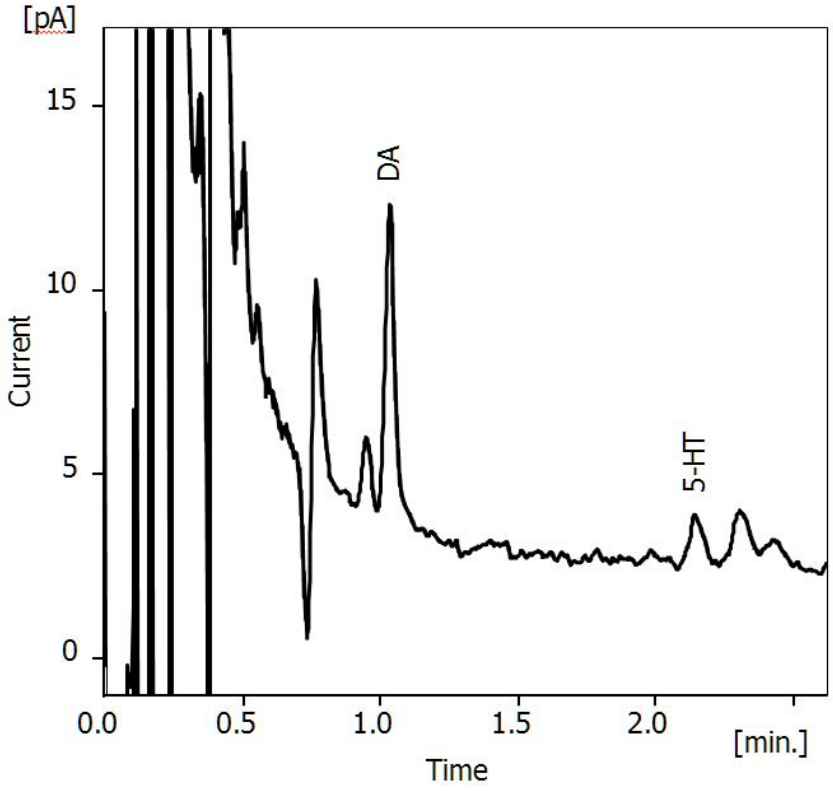

Example chromatogram of basal level rat brain microdialysate sample.

Disclosures: **M. Eysberg:** None. **L. van Heerwaarden:** None. **H. Brouwer:** None. **F. Cacciapaglia:** None. **N. Reinhoud:** None.

Poster

846. Biochemical Techniques

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 846.03/MMM3

Topic: I.01. Molecular, Biochemical, and Genetic Techniques

Support: NIH NEI R01EY017699 to SK

NIH NEI R21EY023565 to SK

PNI Innovation Award to SK

Title: A Method for MRI-guided reversible inactivation of thalamic regions

Authors: ***M. K. ERADATH**[1], M. A. PINSK[1], S. KASTNER[1,2];
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Abstract: Reversible inactivations using GABA agonists like muscimol are an effective tool in causally exploring the functional roles of particular brain regions in complex behavioral tasks. However, targeting deep brain structures in the primate brain for inactivation studies poses several technical challenges. Primarily, it is often difficult to confirm the location of deep subcortical targets and to precisely demarcate the extent and spread of inactivation zones over space and time. To address these challenges, we have developed a novel method that utilizes a custom-made drug delivery system and uses magnetic resonance imaging with contrast enhancing agent Gadolininium to visualize the extent and spatio-temporal spread of the inactivation agent within and around the targeted area. Our method uses tungsten microelectrode (75μm) threaded through a fused silica cannula (outer diameter: 360μm) to constitute the basic setup of the injectrode assembly. The setup also includes measures for accurately monitoring the infused volume. The injectrode assembly is inserted through a custom developed grid tube implanted over the skull. The grid tube system allows us to accurately aim the deep structures across multiple acute penetrations. Our injectrode assembly and specific procedural protocols allow us to confirm the accuracy and spread of drug at the targeted site before and after the inactivation sessions and to simultaneously obtain high quality single unit and local field data. We are currently validating our method by inactivating the pulvinar nucleus of the thalamus.

Disclosures: **M.K. Eradath:** None. **M.A. Pinsk:** None. **S. Kastner:** None.

Poster

846. Biochemical Techniques

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 846.04/MMM4

Topic: I.01. Molecular, Biochemical, and Genetic Techniques

Support: BBSRC Grant BB/J0153691/1

Title: Free-flow calibration of microelectrode biosensors substantially underestimates analyte concentration in tissue

Authors: ***A. NEWTON**[1], M. J. WALL[2], M. J. E. RICHARDSON[1];
[1]Systems Biol. Ctr., [2]Life Sci., Univ. of Warwick, Coventry, United Kingdom

Abstract: Amperometric biosensors are widely used to measure concentrations of a variety of analytes in solution and tissue, including; dopamine, acetylcholine, adenosine and glucose. A great deal of experimental and modelling effort has been directed at quantifying the response of the biosensors themselves; however, the influence that the tissue environment has on biosensor response has not been subjected to the same level of scrutiny. Here we identify an important issue in the way microelectrode biosensors are calibrated that is likely to have led to a significant underestimation of analyte tissue concentrations.
Concentration in tissue is typically determined by comparing the biosensor signal to that measured in free-flow calibration conditions. In a free-flow environment the concentration of the analyte at the outer surface of the biosensor can be considered constant. However, in tissue the analyte reaches the biosensor surface by diffusion through the extracellular space. Because the enzymes in the biosensor break down the analyte, a density gradient is set up resulting in a significantly lower concentration of analyte near the biosensor surface. This effect is compounded by the diminished volume fraction (porosity) and reduction in diffusion due to obstructions (tortuosity) in tissue. We demonstrate this effect through detailed modelling and experimentally verify our predictions in diffusive environments.
The biosensor-in-tissue response to concentration dynamics are also affected by the diffusive environment. The low concentration of analyte around the biosensor means a transient increase in tissue concentration results in a proportionally larger increase in the biosensor signal, resulting in a band-pass filtering of the underlying tissue analyte dynamics.
While biosensors provide accurate quantitative information about analyte concentration at their surface, it is essential to account for the effect the biosensor has on analyte concentration in surrounding tissue to better estimate its value away from the sensor.

Disclosures: **A. Newton:** None. **M.J. Wall:** None. **M.J.E. Richardson:** None.

Poster

846. Biochemical Techniques

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 846.05/MMM5

Topic: I.01. Molecular, Biochemical, and Genetic Techniques

Title: The effect of low molar excess of 4-oxo-2-nonenal and 4-hydroxy-2-nonenal on alpha-synuclein oligomerization

Authors: *L. ALMANDOZ GIL[1], H. WELANDER[1], E. IHSE[1], C. LENDEL[4], M. KARLSSON[2], J. SIGVARDSON[5], L. LANNFELT[1], M. INGELSSON[1], K. KULTIMA[3], J. BERGSTRÖM[1];

[1]Dept. of Publ. Hlth. and Caring Sci., [2]Dept. of engineering sciences, [3]Dept. of Med. Sci., Uppsala Univ., Uppsala, Sweden; [4]Dept. of Chem. and Biotech., Swedish Univ. of Agr. Sci., Uppsala, Sweden; [5]Bioarctic Neurosci., Stockholm, Sweden

Abstract: Aggregated alpha-synuclein is the main component of Lewy bodies, intraneuronal inclusions found in Parkinson's disease and dementia with Lewy bodies. A body of evidence implicates oxidative stress in the pathogenesis of these diseases. For example, a large excess (30:1, aldehyde:protein) of the lipid peroxidation end products 4-oxo-2-nonenal (ONE) or 4-hydroxy-2-nonenal (HNE) can induce alpha-synuclein oligomer formation. The objective of the study was to investigate the effect of these reactive aldehydes on alpha-synuclein at a lower molar excess (3:1) at both physiological (7.4) and acidic (5.4) pH. ONE rapidly induced the formation of alpha-synuclein oligomers at both pH values, but the effect was less pronounced under the acidic condition, as observed by size-exclusion chromatography. In contrast, only a small proportion of alpha-synuclein oligomers were formed with low excess HNE-treatment at physiological pH and no oligomers at all under the acidic condition. With prolonged incubation times, more alpha-synuclein was oligomerized at physiological pH for both HNE and ONE. The ONE-oligomers were more SDS-stable and to a higher-degree cross-linked as compared to the HNE-induced oligomers when analyzed by Western blot, but exhibited a less compact structure as evident by a higher sensitivity to proteinase K treatment. Mass spectrometry showed that both aldehydes modified the His50 residue, whereas ONE modified more Lys residues than HNE at both pH values. Taken together, our results show that the aldehydes ONE and HNE can modify alpha-synuclein and induce oligomerization, even at low molar excess, but to a higher degree at physiological pH.

Disclosures: L. Almandoz Gil: None. **H. Welander:** None. **E. Ihse:** None. **C. Lendel:** None. **M. Karlsson:** None. **J. Sigvardson:** None. **L. Lannfelt:** None. **M. Ingelsson:** None. **K. Kultima:** None. **J. Bergström:** None.

Poster

846. Biochemical Techniques

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 846.06/MMM6

Topic: I.01. Molecular, Biochemical, and Genetic Techniques

Support: NIDA Intramural Research Program, NIH

Title: Fluorescence activated cell sorting (FACS) and gene expression analysis of Fos-expressing neurons from fresh and frozen rat brain tissue

Authors: *F. RUBIO[1], X. LI[1], Q.-R. LIU[1], R. CIMBRO[2], B. T. HOPE[1];
[1]Behavioral Neurosci. Res. Branch, NIDA IRP, NIH, Baltimore, MD; [2]Div. of Rheumatology, Sch. of Medicine, Johns Hopkins Univ., Baltimore, MD

Abstract: The study of neuroplasticity and molecular alterations in learned behaviors is switching from the study of whole brain regions to the study of specific sets of sparsely distributed activated neurons called neuronal ensembles that mediate learned associations. Fluorescence Activated Cell sorting (FACS) has recently been optimized for adult rat brain tissue and allowed isolation of activated neurons using antibodies against the neuronal marker NeuN and Fos protein, a marker of strongly activated neurons. Until now, Fos-expressing neurons and other cell types were isolated from fresh tissue, which entailed long processing days and allowed very limited numbers of brain samples to be assessed after lengthy and complex behavioral procedures. Here we found that yields of Fos-expressing neurons and *Fos* mRNA from dorsal striatum were similar between freshly dissected tissue and tissue frozen at -80^{o}C for 3-21 days. In addition, we confirmed the phenotype of the NeuN-positive and NeuN-negative sorted cells by assessing gene expression of neuronal(*NeuN*), astrocytic (*GFAP*), oligodendrocytic (*Oligo2*) and microgial (*Iba1*) markers, which indicates that frozen tissue can also be used for FACS isolation of glial cell types. Overall, it is possible to collect, dissect and freeze brain tissue for multiple FACS sessions. This maximizes the amount of data obtained from valuable animal subjects that have often undergone long and complex behavioral procedures.

Disclosures: F. Rubio: None. **X. Li:** None. **Q. Liu:** None. **R. Cimbro:** None. **B.T. Hope:** None.

Poster

846. Biochemical Techniques

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 846.07/MMM7

Topic: I.01. Molecular, Biochemical, and Genetic Techniques

Title: Examining common laboratory methods that may alter sensitivity of carbon fiber electrodes in amperometric recordings of dopamine

Authors: W. T. PRATER, W. M. MCDONALD, M. D. BEANE, *D. B. LESTER;
Psychology Dept., Univ. of Memphis, Memphis, TN

Abstract: Carbon fiber microelectrodes (CFEs) are useful when combined with electrochemical techniques such as constant-potential amperometry and fast-scan cyclic voltammetry for

measuring rapid changes in neurotransmitter concentrations. Electrodes in the present study were constructed by threading a carbon fiber (7 μm o.d.) through a borosilicate glass tube, which was then heat-pulled to form a seal around the carbon fiber. Graphite powder was packed into the pulled glass tip and a wire inserted to make contact with the carbon fiber. The protruding fibers were cut under a stereomicroscope to extend 500um past the pulled glass. While most labs construct their own CFEs, and consequently variations in construction methods exist, the steps used by the present study are relatively standard. The present study was aimed at addressing less consistent or rarely discussed details regarding the use of CFEs and determining whether such details influence CFE sensitivity. For example, researchers rarely discuss the lag time between CFE construction and use, and methods vary regarding whether CFEs are cleaned prior to use and whether CFEs are calibrated before or after experiments. The present study utilized constant potential amperometry and a flow injection system to calibrate CFEs for the measurement of dopamine, which was tested at 4 known concentrations in phosphate-buffered saline (0.2, 0.4, 0.8, and 1.2 uM). Our CFEs consistently measured 0.138 nA/uM (SEM = 0.006) per 100um of exposed carbon fiber. Sensitivity did not significantly differ between CFEs used 2 months, 1 month, or 1 week after construction ($p = 0.18$), and quickly rinsing CFEs in solvents such as isopropyl alcohol or xylene did not alter sensitivity compared with untreated CFEs ($p = 0.16$ and 0.30, respectively). The calibration process, however, did significantly decrease CFE sensitivity in regards to dopamine measurement. On the second calibration, CFE responses (measured nA/uM per 100um of exposed carbon fiber) were attenuated by 48.8% from the initial calibration ($p = 0.002$). In summary, the present results indicate that CFEs may be used at least 2 months following construction without reduced sensitivity and cleaning electrodes (at least using solvents such as isopropyl alcohol and xylene) may not be necessary. Results also indicate that calibrating CFEs weakens the amperometric response and should be conducted after experimental data collection if sensitivity is an issue. Further studies will be conducted to determine the degree to which CFE sensitivity is attenuated after dopamine measurement in brain tissue.

Disclosures: **W.T. Prater:** None. **W.M. McDonald:** None. **M.D. Beane:** None. **D.B. Lester:** None.

Poster

846. Biochemical Techniques

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 846.08/MMM8

Topic: I.01. Molecular, Biochemical, and Genetic Techniques

Support: NIH 1U01NS090455-01

Title: The enhancement of the accuracy of absolute quantification of dopamine using tailored fast-scan cyclic voltammetry

Authors: *Y. KANG[1], Y. OH[1], H. SHIN[1], C. PARK[1], M. DEWAELE[1], I. KIM[1], K. E. BENNET[2], K. H. LEE[2], D. JANG[3];
[1]Biomed. Engin., Hanyang Univ., Seoul-City, Korea, Republic of; [3]Dept. of Neurosurg., [2]Mayo Clin., Rochester, MN 5590, NY

Abstract: Fast Scan Cyclic Voltammetry (FSCV) is the electrochemical technique that detect the neurotransmitter in vivo or in vitro by measuring the background current from Carbon fiber microelectrode (CFM). Background current contains the information of not only neurotransmitter but also solution. Therefore, background derived from the solution need to be eliminated, in order to estimate the neurotransmitter concentration. This method has limitations that it is hard to estimate the basal level of neurotransmitter, and has high error rate caused by larger background current from solution than neurotransmitter-oxidation and reduction current. Fast Scan Controlled-Adsorption Voltammetry (FSCAV) lead the adsorption around the CFM by 10 seconds holding, and 1-second scan using 100-times-repeated triangle waveform to increase the detecting sensitivity. However, there was still a large background current caused by negative 0.4V-holding-potential waveform. To minimize the background current, we proposed the adjusted holding potential to 0.0V, and use Charged-Balanced waveform which balances the positive and negative potential. By utilizing Charged-Balanced waveform, it leads smaller capacitive background current than what FSCAV leaded. For further enhancement, we developed "tailoring technique" to make identical cyclic voltammogram between 3rd and last background voltammogram by minutely manipulated waveform. As a result, tailored-FSCV showed significantly lower estimate error to quantify dopamine than other two methods by minimize background current differences.

Disclosures: **Y. Kang:** None. **Y. Oh:** None. **H. Shin:** None. **C. Park:** None. **M. DeWaele:** None. **I. Kim:** None. **K.E. Bennet:** None. **K.H. Lee:** None. **D. Jang:** None.

Poster

846. Biochemical Techniques

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 846.09/MMM9

Topic: I.01. Molecular, Biochemical, and Genetic Techniques

Support: W.M. Keck Foundation Medical Research Award

NIDA Grant 1RO1DA077525

Title: Continuous, real-time monitoring of drugs *In vivo* using electrochemical aptamer-based sensors

Authors: *P. A. VIEIRA[1,3], N. ARROYO-CURRAS[2], J. SOMERSON[2], K. L. PLOENSE[1], K. W. PLAXCO[2], T. E. KIPPIN[1];
[1]Psychological & Brain Sci., [2]Chem., Univ. of California Santa Barbara, Santa Barbara, CA;
[3]Dept of Psychology, California State Univ. Dominguez Hills, Carson, CA

Abstract: We developed an electrochemical aptamer-based indwelling sensor that achieves continuous, real-time pharmacodynamic measurements of therapeutic drugs in living animals. Our sensor combines the selectivity of aptamer biomolecular recognition with the sensitivity of electrochemical measurements in a low-cost (~$10/sensor) architecture approximately the size of a human hair. The sensor responds in a matter of seconds to fluctuating concentrations of aminoglycosides, doxorubicin, and cocaine, both in vitro and in vivo, and allows rapid adjustments of dosing based on the individualized pharmacodynamics of each test subject. This preliminary work is a first step in creating biosensors that are selective to specific drug targets, durable and long-lasting. By measuring therapeutic doses of aminoglycosides, doxorubicin and cocaine, we have developed a physiologically relevant biosensor that can be applied to the study of the biochemical processes underlying drug addiction as well as pharmaceutical therapies. By measuring the pharmacokinetic/toxicokinetic profile of a specific drug for each subject, we can better understand how individual drugs interact with individual factors (e.g. drug metabolism) that impact the efficacy of drug use.

Disclosures: P.A. Vieira: None. **N. Arroyo-Curras:** None. **J. Somerson:** None. **K.L. Ploense:** None. **K.W. Plaxco:** None. **T.E. Kippin:** None.

Poster

846. Biochemical Techniques

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 846.10/MMM10

Topic: I.01. Molecular, Biochemical, and Genetic Techniques

Support: FAPESP

CNPq

CAPES

Title: NO and H_2S modulate heme oxygenase (HO) activity during *In vitro* hyperosmotic stimulus

Authors: *R. COLETTI[1], F. M. V. VECHIATO[1], J. B. M. DE LIMA[1], F. LUCIO-OLIVEIRA[2], G. ALMEIDA-PEREIRA[1], L. L. K. ELIAS[1], J. ANTUNES-RODRIGUES[1];
[1]Sch. of Med. of Ribeirao Preto/Usp, Ribeirao Preto, Brazil; [2]Southern Minas Federal Inst., Muzambinho, Brazil

Abstract: NO, CO and H_2S are gaseous molecules produced in the central nervous system (CNS) by NO synthase (NOS), heme oxygenase (HO) and cystathionine beta-synthase (CBS)/3-mercaptopyruvate sulfurtransferase (3MST). It's known fluid deprivation increases such gases production in the hypothalamus, in which CO and H_2S acts increasing vasopressin (AVP) and oxytocin (OT) release, whereas NO plays an inhibition role. Also, it's been already demonstrated *in vivo* H_2S reduces hypothalamus nitrates content, which's typically found increased in response to extracellular hyperosmolality. On the other hand, little is known about the interactions NO and H_2S keep with CO-generating enzyme, HO.Our objective was to evaluate HO in vitro activity in extracellular iso- and hypertonicity, in media containing NO and H_2S donors, and NOS and CBS antagonists, so that it's possible to understand how CO pathway responds to increases and decreases of the other two CNS main gaseous neuromodulators.Male Wistar rats' (270-300g) medial-basal hypothalami (MBH) were collected and kept in oxygenated isotonic Krebs-Ringer bicarbonate buffer (KRBG, 280 mOsm/Kg H_2O) for pre-incubation (37°C, 60 min.). Then, medium was changed by a new iso- or hypertonic (340 mOsm/Kg H_2O) KRBG, w/ or w/o NO (600 μM SNP) and H_2S (10 mM Na2S) donors, or NOS (300 μM LNMMA) and CBS (100 μM AOA) antagonists, in a new 30-min. incubation. After that, MBH was submitted to HO enzymatic activity assay, in which the metabolizing capacity of hemin (200 nmol) into bilirubin was assessed after 1h. Results were analyzed by Student's *t*-test and ANOVA, followed by Newman-Keuls post-hoc test. Experimental protocols performed were previously approved by Ribeirao Preto Medical School's Ethics Committee (#027/2013-1).Hyperosmotic stimulus increased by itself hypothalamic HO enzymatic activity when compared to control group (t_9 = 4.40, $p < .01$). Interestingly, exogenous NO supply ($F_{1,20} = 5.48$, $p < .05$) reduced bilirubin generation; while, on the other hand, both sulfide content increase (drug: $F_{1,19} = 96.62$, $p < .0001$, osmolality: $F_{1,19} = 10.57$, $p < .01$) and NOS activity inhibition ($F_{1,21} = 6.84$; $p < .05$) increased hemin metabolism in MBH.Although it's been demonstrated both NO and H_2S act on hypothalamic magnocellular neurons directly, our results highlight such molecules also act indirectly modulating HO activity, changing, thus, hypothalamus CO content, another gaseous molecule which has AVP and OT secretion facilitating capacity. Such evidences make it clear the interaction among the three systems is important for the fine modulation of hormonal release in response to acute osmotic stimulus.

Disclosures: R. Coletti: None. **F.M.V. Vechiato:** None. **J.B.M. de Lima:** None. **F. Lucio-Oliveira:** None. **G. Almeida-Pereira:** None. **L.L.K. Elias:** None. **J. Antunes-Rodrigues:** None.

Poster

846. Biochemical Techniques

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 846.11/MMM11

Topic: I.01. Molecular, Biochemical, and Genetic Techniques

Support: MEXT

Title: *In vivo* regulation of glycogen synthase kinase 3b activity unveiled by the quantitative measurement of its phosphoisotype

Authors: *S.-I. HISANAGA[1], A. KRISHNANKUTTY[1], T. KIMURA[1], T. SAITO[1], A. ASADA[1], K. ANDO[1,2], K. AOYAGI[2], M. OHARA-IMAIZUMI[2,3], K. ISHIGURO[3]; [1]Tokyo Metropolitan Univ., Tokyo, Japan; [2]Kyorin Univ., Mitaka, Japan; [3]Juntendo Univ., Bunkyo, Japan

Abstract: Glycogen synthase kinase 3b (GSK3b) is a multifunctional protein kinase, which is involved in cell proliferation, survival, development and differentiation. GSK3b is also associated with diseases such as diabetes and Alzheimer's disease. Therefore, it is important to understand the regulation mechanism of its in vivo activity. GSK3b is thought to be constitutive active by autophosphorylation of Tyr216, and inactivated by phosphorylation at Ser9 downstream of many signaling pathways. The kinase activity of GSK3b has been evaluated by inhibitory phosphorylation at Ser9, but it does not measure the the kinase activity properly. Here, we applied the Phos-tag SDS-PAGE technique, which separates proteins depending on phosphorylation states, to the analysis of phospho-isotypes of GSK3b in cells and brains. There were three phospho-isotypes in GSK3b; double phosphorylation at Ser9 and Tyr216, single phosphorylation at Tyr216 and the nonphosphorylation, Active GSK3b with phosphorylation at Tyr216 was most abundant, half or more of total GSK3b. While increase in phospho-Ser9 was detected in insulin-treated cells by immunoblotting with anti-phospho-Ser9 antibody, the increase was a minor fraction of total GSK3b and most GSK3b remained as an active phospho-isotype. Adult mouse brains showed highly active GSK3b with a little Ser9 phosphorylation, and the phospho-isotypes of GSK3b changed depending on the regions of brain, age, sex and disease condition. These results indicate that the Phos-tag SDS-PAGE method provides the simple and appropriate measurement of *in vivo* active GSK3b and the activity is regulated independently on phospho-Ser9.

Disclosures: **S. Hisanaga:** None. **A. Krishnankutty:** None. **T. Kimura:** None. **T. Saito:** None. **A. Asada:** None. **K. Ando:** None. **K. Aoyagi:** None. **M. Ohara-Imaizumi:** None. **K. Ishiguro:** None.

Poster

846. Biochemical Techniques

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 846.12/MMM12

Topic: I.01. Molecular, Biochemical, and Genetic Techniques

Title: Evaluating the effectiveness of alternative fbs on neuroblastoma cells

Authors: *S. M. PECK, D. P. BALUCH;
ASU/SOLS, W.M. Keck Lab/Sols, Tempe, AZ

Abstract: Cell culture based research is one of the foundational forms of experimentation which transitions to future study's involving tissue and eventually animal and human trials. It is estimated that the R&D market cost for cell culture was valued at 16.35 billion in 2014 and costs related specifically to media, sera and reagents were 23% of that total. One of the largest costs involved in cell culture work is sera [i.e. fetal bovine serum, newborn calf and adult bovine serum] which provides nutrients, growth factors and hormones to cells to simulate their natural environment. It is reported that since 2003 the cost of fetal bovine serum has tripled which has affected the research efforts of many labs. A few pharma companies have begun developing an alternative serum where they have identified key factors that are most required by cell cultures in an attempt to reduce cost, overuse of cattle for serum production, and create a consistent product that should not vary in content between seasons or herds. This study compared the affects that standard FBS and the alternative serum supplemented media had on neuroblastoma cell growth, differentiation and behavior. Cells were imaged using confocal microscopy to observe any morphological changes, including the cytoskeleton, and were labeled for the neuroblastoma cell lineage markers, Nestin and Sox2, which have reduced expression in transformed cells. To evaluate any change in behavior, cells were also observed through live cell, time lapse microscopy. From these results it appears that alternative serum is an acceptable substitute for FBS in culture media for short periods of time but for prolonged growth the cells may require a small fraction of the hormones and growth factors provided through FBS for sustained healthy growth.

Disclosures: S.M. Peck: None. **D.P. Baluch:** None.

Poster

846. Biochemical Techniques

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 846.13/MMM13

Topic: I.01. Molecular, Biochemical, and Genetic Techniques

Title: The characterization of calf brain isolated celularl nuclear membrane Gal-specific lectin

Authors: *T. MACHARADZE, L. KHARAZISHVILI, R. AKHALKATSI;
Tbilisi State Univ., Tbilisi, Georgia

Abstract: The study of carbohydrate specificity of calf brain isolated cellular nuclear membrane protein fraction with hemmaglutination activity reveals inhibition with three carbohydrates:N-acetyl-D-glucosamin, D-galactose and D-mannose. This fact indicates that this protein fraction contains lectins with three different specifisity.
Our aim was the isolation Gal-specific lectin from above mentioned fraction and study some of biochemical characteristics. Gal-specific lectins obtained by Akhalkatsi et al. from calf (1-1,2 years old) brain cell nuclear membrane fraction, using Chaveau method without chaotropic and reductive substances. So obtained protein fraction hemagglutination activity showed, that titre is equal 256 and specific activity is 341. From this protein fraction calf brain cell nuclear membrane Gal-specific lectin has been obtained by affinity chromatogtaphy with column Gal immobilized on tris-acrylle. After further rechromatography which was obtained by HPLC (Waters, USA) on tandem columns Protein PAK 300 SW, U 60 showed fractions with molecular masses 70kD, 10kD and 5kD.
Rechromatography of all three fractions showed maximum absorbtion in the ultravioet area at 208-212nm, which points to the absence or presence of amino acids tyrosine and tryptophan in a very low concentration. The exception is the only 10kD fraction, which has the second maximum at 280nm. The calf brain cell nuclear membrane Gal-specific lectins are glycoproteins and contain carbohydrate 2,55mkg/100mkg protein.
Calf brain isolated cellular nuclear membrane gal-specific lectins specific activity is 320 and they are less termostabile then nuclear membrane GlcNAc-specific lectins. In the structure of carbohydrate binding center of calf brai cell nuclear membrane Gal-specific lectins take part Ca^{2+} and Mg^{2+}ions 9,68mkg and 3,14mkg/100mkg protein correspondingly, which was showed with the influance different concentration of EDTA and EGTA on the hemagglutination activity. Gal-specific lectins do not contain Mn^{2+} ions as GlcNAc-specific lectins obtained from the same sourses. The ion content in calf brain nuclear membrane lectins was measured by the atomic absorbtion method.

Disclosures: T. Macharadze: None. **L. Kharazishvili:** None. **R. Akhalkatsi:** None.

Poster

846. Biochemical Techniques

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 846.14/MMM14

Topic: I.01. Molecular, Biochemical, and Genetic Techniques

Title: Probing gapdh and siah-1 interactions in mammalian cell lines using proximity ligation assay

Authors: *H. SINGH;
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Abstract: Glyceraldehyde -3 -phosphate dehydrogenase (GAPDH), a key glycolytic enzyme known to exist primarily in cytoplasm, has often been viewed as a housekeeping enzyme. Interestingly, recent studies have implicated the enzyme in a number of neurodegenerative diseases, necessitating the need for a deeper understanding of its biological functions. GAPDH has been shown to have functions in critical nuclear events such as gene transcription, RNA transport, and DNA replication. Molecular studies have revealed that prevention of GAPDH nuclear translocation reduces cellular toxicity. However, a lack of nuclear localization signal (NLS) in GAPDH raises questions about the underlying mechanism of this movement. Recent studies showed that GAPDH, under stress conditions, binds with SIAH1 - an E3 ubiquitin ligase that contains an NLS. While several studies to date have shown GAPDH-SIAH-1 interactions using conventional methods, no convincing data has shown these interactions in cells, under native conditions. Here, we use proximity ligation assay (PLA) to probe GAPDH-SIAH-1 interactions in mammalian cell lines. We first use PLA to show that GAPDH and SIAH-1 proteins exist endogenously in the cytoplasm of Abelson murine leukemia virus-induced tumor and human colon adenocarcinoma cell lines. Next, we use PLA to probe the conditions and stimulus which facilitate the interaction of these proteins and their translocation to the nucleus. We further use R-()-Deprenyl (deprenyl), a known inhibitor of GAPDH, that abrogates GAPDH-SIAH-1 PLA complex. Our studies show that proximity ligation assay could be a method of choice to study protein-protein interactions in live cells and potentially open avenues for biomedical research.

Disclosures: **H. Singh:** A. Employment/Salary (full or part-time): MilliporeSigma.

Poster

846. Biochemical Techniques

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 846.15/MMM15

Topic: I.01. Molecular, Biochemical, and Genetic Techniques

Title: Comparison of Synaptech versus CMA probes for the quantification of extracellular acetylcholine, dopamine and its metabolites by cerebral microdialysis in freely-moving rats

Authors: *H. L. ROWLEY[1], R. S. KULKARNI[1], L. PINDER[1], D. J. HEAL[1], P. SEGLUND[2]; [1]Renasci Ltd, Nottingham, United Kingdom; [2]Synaptech Inc, Marquette, MO

Abstract: We investigated whether concentric Synaptech and CMA microdialysis probes yield comparable results when measuring neurotransmitters and metabolites in microdialysis in freely-moving rats. Dopamine (DA), DOPAC and HVA were measured in the nucleus accumbens (ACB) and acetylcholine (ACh) in the medial prefrontal cortex (PFC). d-Amphetamine (0.5mg/kg sc) was the pharmacological intervention. Experiment 1: 2 probes were stereotaxically implanted in ACB (relative to bregma [mm] AP +2.2, ML ±1.5, DV -8.0) and PFC (AP +3.2, ML ±2.5, DV -4.0) of isoflurane-anaesthetised male, Sprague Dawley rats (~300-350g). Two groups of 4 rats were implanted either with Synaptech 2.0mm probes (polyacrylonitrile membrane) via guide cannulae or CMA Elite 2.0mm probes (polyarylethersulfone membrane). Experiment 2: single 2.0mm Synaptech or CMA probes were implanted in PFC of groups of 8 rats. After ≥16hr recovery, 20min microdialysate samples (1.2µl/min artificial CSF [aCSF] or aCSF+1.0µM neostigmine) were taken for 3hr after d-amphetamine. DA, DOPAC and HVA were measured by ALEXYS™ hplc-ecd and ACh by ALEXYS™ uhplc-ecd (Antec). Results are mean ± SEM. In Experiment 1, basal concentrations of neurotransmitters and metabolites were comparable for Synaptech and CMA probes: DA = 9.4±0.1fmol/5ul vs 9.5±0.2; DOPAC = 2191±26fmol/5ul vs 2261±38; HVA = 1011±3fmol/5ul vs 1019±23; ACh = 228±22fmol/10ul vs 164±14. d-Amphetamine rapidly increased DA efflux in ACB with a peak at 40min: 544% baseline ($p<0.001$) (Synaptech) vs 347% ($p<0.001$) (CMA). There were concomitant decreases in DOPAC 55% baseline ($p<0.001$) (Synaptech) vs 51% ($p<0.001$) (CMA) and HVA 71% baseline ($p<0.001$) (Synaptech) vs 79% ($p<0.001$) (CMA). d-Amphetamine increased ACh efflux in PFC with a peak effect at 40min: 465% baseline ($p<0.001$) (Synaptech) vs 476% ($p<0.001$) (CMA). In Experiment 2, the vehicle-treated basals were stable for the 3hr experiment: 56.8±6.5fmol/5ul (Synaptech) vs 67.8±8.4 (CMA). d-Amphetamine increased ACh efflux to a peak of 609% at 60min ($p<0.001$) (Synaptech) vs 519% at 80min ($p<0.001$) (CMA). The head to head comparisons demonstrate that Synaptech and CMA probes have comparable performance levels in terms of measuring absolute concentrations of extracellular neurotransmitters and metabolites in microdialysates. The pharmacodynamic effects of d-amphetamine on extracellular concentrations of DA, DOPAC and HVA in ACB and ACh in

PFC were comparable using either probe. These experiments demonstrate that these 2 types of probe can be used interchangeably in microdialysis experiments and the results either in absolute or percentage baseline terms are to all intents and purposes identical.

Disclosures: **H.L. Rowley:** A. Employment/Salary (full or part-time): RENASCI LTD. **R.S. Kulkarni:** A. Employment/Salary (full or part-time): RENASCI LTD. **L. Pinder:** A. Employment/Salary (full or part-time): r. **D.J. Heal:** A. Employment/Salary (full or part-time): RENASCI LTD. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); RENASCI LTD. **P. Seglund:** A. Employment/Salary (full or part-time): Synaptech Inc. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Synaptech Inc.

Poster

846. Biochemical Techniques

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 846.16/MMM16

Topic: I.01. Molecular, Biochemical, and Genetic Techniques

Support: Nipissing University

Title: Revised methodology for SYNORF-1 antibody staining in planarians

Authors: T. MCCHARLES[1], A. HAGHGOO[2], E. REPO[2], A. STILLAR[2], *M. J. SAARI[2]; [1]Psychology, Nipissing UNiversity, North Bay, ON, Canada; [2]Nipissing Univ., North Bay, ON, Canada

Abstract: Planarians have extraordinary regenerative properties which make them a potentially useful organism for developing various developmental models in neuroscience. Immunohistochemistry allows the visualization of various projections of the planarian nervous system using the SYNORF-1 antibody, which selectively binds to the protein synapsin found in synaptic active zones. We have recently developed a modified staining method for *Dugesia dorotocephala* using the SYNORF-1 antibody. Specifically, we have added a bleaching step to remove the dark pigmentation in the worm. This bleaching step before the initial antibody incubation also allows the tissue to become more permeable, significantly increasing the intensity of the stain. Other alterations to the procedure, described more fully in the poster, allow better resolution and specificity of the stain.

Disclosures: **T. McCharles:** None. **A. Haghgoo:** None. **E. Repo:** None. **A. Stillar:** None. **M.J. Saari:** None.

Poster

846. Biochemical Techniques

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 846.17/MMM17

Topic: I.01. Molecular, Biochemical, and Genetic Techniques

Support: NIH 1U01NS090455-01

Title: Prolonged *In vivo* monitoring of extracellular change of dopamine

Authors: ***C. PARK**[1], Y. OH[1], Y. KANG[1], M. DEWAELE[1], H. SHIN[1], D. KIM[1], K. BENNET[2], I. KIM[1], K. LEE[3], D. JANG[1];
[1]Biomed. Engin., Hanyang Univ., Seoul-City, Korea, Republic of; [2]Div. of Engin., [3]Dept. of Neurosurg., Mayo Clin., Rochester, MN

Abstract: The background current of fast-scan cyclic voltammetry is subtracted from the overall signal detected to monitor small changes of dopamine. The subtraction reference point has to be renewed every 30~60 seconds to monitor phasic activity because the background signal drifts over the course of a minute. Herein, we developed charge-balanced multiple waveform fast-scan cyclic voltammetry (CBM-FSCV) to monitor extracellular dopamine concentration change over a prolonged time (> 1hour) with a fixed background subtraction reference point. By using CBM-FSCV, we confirmed the background from CBM-FSCV was stable for 2 days *in vitro*. In a pharmacological *in vivo* test, we were able to detect the final concentration of dopamine efflux using nomifensine (reuptake inhibitor, +235±60nM, SEM) and α-Methyl-DL-tyrosine (αMPT, synthesis inhibitor, -72.5±4.8nM, SEM) over 2 hours. In this study, we successfully measure the long term change of dopamine in vivo, both positive and negative, and we show that CBM-FSCV is an essential technique to monitor dopamine concentration changes over a prolonged time period. Keywords: Fast-scan cyclic voltammetry (FSCV); Charge-balanced multiple waveform fast-scan cyclic voltammetry (CBM-FSCV); Dopamine; Nomifensine; α-Methyl-DL-tyrosine (αMPT) **Acknowledgement** This research was supported by the NIH 1U01NS090455-01 award.

Disclosures: **C. Park:** None. **Y. Oh:** None. **Y. Kang:** None. **M. DeWaele:** None. **H. Shin:** None. **D. Kim:** None. **K. Bennet:** None. **I. Kim:** None. **K. Lee:** None. **D. Jang:** None.

Poster

846. Biochemical Techniques

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 846.18/MMM18

Topic: I.01. Molecular, Biochemical, and Genetic Techniques

Title: High throughput assay for identification of aggregating compounds

Authors: *S. M. NIELSEN;
Mol. Screening, H Lundbeck A/S, Valby, Denmark

Abstract: Small drugable compounds dissolved in aqueous buffers will appear as simple monomers. However at high concentrations these compounds may unexpectedly also appear as soluble aggregates. These aggregates have been shown to inhibit enzymes as well as membrane-embedded proteins such as G-protein coupled receptors and therefore, in a screening setup, these aggregates may appear as false positives. More worrying is that the appearance of soluble aggregates instead of higher concentrations of the monomer may be a cause of false negatives in a screening setup. Consequently, identification of aggregating compounds and optimizing the assay conditions to reduce the risk of compound aggregation, are critical. We have established an enzyme-based assay, which is sensitive to compound aggregation and has a high throughput. The assay uses a commercially available beta-lactamase enzyme and the commercially available substrate Fluorocillin Green with optimal excitation/emission wavelengths of 495/525 nm. These parameters make the substrate suitable for kinetic studies using high throughput instruments such as the Functional Drug Screening System (FDSS) and similar instruments, where the addition of the Fluorocillin Green substrate to the beta-lactamase enzyme can be handled in 384-well format with the enzyme activity being recorded simultaneously in all wells over time. We will present data from the profiling of known aggregating and non-aggregating compounds and suggest using the assay for evaluation of various assay conditions prior to screening campaigns as well as characterization of hits identified during a screening campaign.

Disclosures: S.M. Nielsen: None.

Poster

846. Biochemical Techniques

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 846.19/MMM19

Topic: I.01. Molecular, Biochemical, and Genetic Techniques

Support: NIH Grant 1NU01NS090455-01

Title: Desorption and reduction kinetic analysis using multi-waveform cyclic voltammetry

Authors: *H. SHIN[1], D. KIM[1], Y. OH[1], C. PARK[1], Y. KANG[1], M. DEWAELE[1], I. KIM[1], K. E. BENNET[2], K. H. LEE[3], D. JANG[1];
[1]Hanyang Univ., Seoul, Korea, Republic of; [2]Div. of Engin., [3]Dept. of Neurosurg., Mayo Clin., Rochester, MN

Abstract: Recently, Fast Scan Cyclic Voltammetry (FSCV) utilizing carbon fiber microelectrodes (CFMs) has been used as a catecholamine chemical sensor for neuroscience studies and has now been widely utilized for in vivo electroactive neurotransmitter detection. However, FSCV in vivo still has some selectivity problems due to complex circumstances such as, influences by pH transient, changes in non-faradaic background current, and other gross environmental changes at the CFM surface. Herein, we present a new method which uses multiple pulses in a single scan to calculate the kinetic properties of neurochemicals, called multi-waveform cyclic voltammetry. It consists of multi pulse (10 pulses per scan) cyclic voltammetry with voltage change from -0.4V to +1.0V and returning to -0.4V, at a scan rate of 1000 V/s. These successive cyclic voltammograms within a short duration have a rapidly decreasing pattern as the time for equilibrium adsorption decreases[KEB1] . This means that the amount of adsorbed analyte has a lower saturation as scan repetition rates increasefor the same concentration of the neurotransmitter. In this study, we also derived a theoretical equation for the decreasing pattern analysis of Dopamine (DA). As a result, the differences of consecutive voltammogram could be fit to the exponential form. This was expanded to all[KEB2] voltages for making the new type of pseudo color maps. These maps are composed of two features: the kinetic maps (K-maps) that show the specific kinetic characteristics of a particular analyte and the concentration maps (A-maps) for analyte quantification. We applied multi-waveform cyclic voltammetry to the three other electroactive species groups: catecholamines, indolamines and ascorbic acid (AA). These three groups showed different desorption-reduction constant characteristic. The results were coincided with derived theoretical values, which showed the usability of multi-waveform cyclic voltammetry to identify specific analytes.

Disclosures: **H. Shin:** None. **D. Kim:** None. **Y. Oh:** None. **C. Park:** None. **Y. Kang:** None. **M. DeWaele:** None. **I. Kim:** None. **K.E. Bennet:** None. **K.H. Lee:** None. **D. Jang:** None.

Poster

847. Genetic Techniques

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 847.01/MMM20

Topic: I.01. Molecular, Biochemical, and Genetic Techniques

Support: HFSP LTF

Title: A TIGRE reporter mouse line driving Cre- and tTA-dependent expression of the red calcium indicator R-CaMP1.07

Authors: *P. BETHGE[1], L. EGOLF[1], D. A. LORENZO[1], D. GONIOTAKI[2], L. MADISEN[3], F. F. VOIGT[1], M. OHKURA[4], J. NAKAI[4], H. ZENG[3], A. AGUZZI[2], F. HELMCHEN[1];
[1]Brain Res. Inst., Univ. of Zurich, Zurich, Switzerland; [2]Inst. of Neuropathology, University of Zurich, Switzerland; [3]Allen Inst. for Brain Sci., Seattle, WA; [4]Brain Sci. Inst., Saitama Univ., Saitama, Japan

Abstract: Genetically encoded calcium indicators (GECIs) are a common tool for two-photon calcium imaging in the mouse neocortex due to their high sensitivity, genetic targeting capabilities, and their ability to report activity of hundreds of cells in awake, behaving animals. Recently, Cre- and tTA-dependent reporter mouse lines for expression of green GECIs have been introduced, which can be crossed with Cre driver and tTA driver lines to provide high and stable levels of expression in a cell-type specific and inducible manner (Madisen et al. 2015, Neuron 85, 942). However, green GECIs have limitations, especially with regard to two-photon excitation using long wavelengths above 1000 nm, which are beneficial for deep imaging due to reduced light scattering. Here we introduce a novel TIGRE reporter line expressing the red-shifted GECI R-CaMP1.07 (Ohkura et al. 2012, PLoS One), which is two-photon excitable by fixed wavelength lasers operating at 1040-1060 nm. We combined this new R-CaMP1.07 mouse with various Cre driver lines to generate specific expression in excitatory neurons of the different layers of mouse cortex (L2/3, L4, L5, and L6). We find strong and stable expression over many weeks and demonstrate chronic neuronal calcium imaging across all layers of the mouse neocortex over several months. Functional calcium signals recorded in vivo were of high fidelity with large amplitudes (>100%) and fast kinetics (<1s decay), comparable to results obtained with virally-delivered R-CaMP1.07. In particular, we successfully acquired functional signals from L4, which has been difficult to target with viruses, and L6, which is challenging to reach for imaging with green GECIs. Red-shifted excitation of R-CaMP1.07 facilitates deep imaging due to reduction of light scattering in tissue, and does not require Ti:Sapphire lasers but can be achieved with less expensive fixed-wavelength lasers. Thus, the R-CaMP1.07 reporter mouse line is a valuable addition to the collection of transgenic mouse lines designed for studying neural network activity; it offers unique opportunities for imaging in deep cortical, or even

subcortical, regions and to perform dual-color calcium imaging in combination with virally expressed green GECIs.

Disclosures: **P. Bethge:** None. **L. Egolf:** None. **D.A. Lorenzo:** None. **D. Goniotaki:** None. **L. Madisen:** None. **F.F. Voigt:** None. **M. Ohkura:** None. **J. Nakai:** None. **H. Zeng:** None. **A. Aguzzi:** None. **F. Helmchen:** None.

Poster

847. Genetic Techniques

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 847.02/MMM21

Topic: I.01. Molecular, Biochemical, and Genetic Techniques

Support: NIH R21GM114852

Title: A genetic labeling tool to depict the complete neuronal lineages in individual *Drosophila* brains

Authors: ***Y. LI**[1], M. GHAZZI[2], Y. ZHAO[2], T. CHEN[2], B. YE[1,3], D. CAI[1];
[1]Cell and Developmental Biol., [2]Col. of Literature, Science, and the Arts, [3]Life Sci. Inst., Univ. of Michigan, Ann Arbor, MI

Abstract: During development, neural stem/progenitor cells replicate and differentiate into many lineages, which give rise to precise number and subtypes of cells. Defects in lineage development can cause severe developmental diseases. Currently, the state-of-the-art lineage analysis uses mosaic labeling techniques to study one or a few lineages at a time to avoid ambiguity. While the small number of highlighted cells can be investigated extensively, complications in the unlabeled adjacent lineages are hidden from analysis. The ability of unambiguously labeling large number of lineages in situ is highly desired, since it is extremely exhausting, if not impossible to use the available tools to study the precise spatial-temporal relationship of all related lineages in one animal.
We developed a multispectral and subcellular-coding system (MACS), which permits unambiguous genetic labeling of large number of cell lineages in the same animal. We used MACS to map all of the ~100 neural lineages in single Drosophila central brains and depict the developmental processes of all Drosophila neural lineages precisely in space and time. MACS can be easily adapted to other transgenic animal models, including fish, mouse and rat. MACS will create new opportunities in lineage studies, such as investigating lineage variations among individuals, and between hypomorphic alleles or different sex; as well as cell non-autonomous effects of gene mutations in stem/progenitor cells.

Disclosures: **Y. Li:** None. **M. Ghazzi:** None. **Y. Zhao:** None. **T. Chen:** None. **B. Ye:** None. **D. Cai:** None.

Poster

847. Genetic Techniques

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 847.03/MMM22

Topic: I.01. Molecular, Biochemical, and Genetic Techniques

Support: NIH Grant 1R01CA195770

Swedish Research Council (Vetenskapsrådet)

Title: Trace reconstruction of ancestral cells by enzymatic recoding

Authors: ***M. ÅKERBLOM**[1], M. T. MCMANUS[2];
[1]UCSF Diabetes Ctr., San Francisco, CA; [2]UCSF, Diabetes Ctr., San Francisco, CA

Abstract: A population of neural stem/precursor cells (NSCs) persists in the adult brain to produce large numbers of neuroblasts that differentiate into local circuit interneurons. Increasing evidence emphasizes profound heterogeneity within the NSC population, where NSCs located in different regions generates distinct interneuron subtypes. Inconsistent conclusions and the cumbersome and labor-intensive protocols associated with cell lineage tracing have limited the study of NSCs. To address fundamental questions that define NSCs and their relationship to adult neurons, new approaches are desperately needed.
Lineage tracing is the identification of all progeny of a single cell. A single cell is marked in such a way that all descendants will contain the mark, providing powerful means of stem cell biology, the number and location of progeny as well as of the differentiation process. The challenge of today's lineage tracing approaches is that a lineage tree usually is not linear but instead branches into tree-like lineages comprising numerous different cell types. The vast number of cells and their diverse lineages poses a daunting challenge for lineage tracing methods. To address fundamental questions that define NSCs and their relationship to adult neurons, new approaches are needed.
We are developing a new tool that will help us track the ancestry of individual cells, using a novel DNA barcoding technology. This project describes a new approach for tracking the evolutionary history of individual cells - at the most possible granular level, the individual cells. We take advantage of new technologies (deep sequencing and programmable DNA binding enzymes) and combine them in a way to create a single cell lineage tracer in which each cell writes its own unique barcode. This system is comprised of a molecular 'typewriter' that types a

unique barcode every time a cell goes into cell cycle. Moreover, this written barcode accumulates with each future generation. Using our novel tracer approach we expect to eventually delineate cell ancestries on a large scale and consequently map the lineages of adult NSCs in the brain *in vivo*. This will answer fundamental and important questions related to adult neurogenesis. Insights into the developmental origins that underlie the regional specification of NSCs are necessary to understand the origin of brain tumors as well as to develop regenerative therapies.

Disclosures: M. Åkerblom: None. **M.T. McManus:** None.

Poster

847. Genetic Techniques

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 847.04/MMM23

Topic: I.01. Molecular, Biochemical, and Genetic Techniques

Title: The characterization of a genetic toolbox for neuroscience: neuron-specific cre, fluorescent cre activity reporter and conditional optogenetics knock-in rats

Authors: *Z. LIU, G. ZHAO, 63146, X. CUI, 63146;
Horizon Discovery, Saint Louis, MO

Abstract: Mouse models have been extensively used for biomedical research largely due to the fact of being the only mammalian species with easy access of genetic tools to manipulate their genome. The rat, on the other hand, makes better models for many research fields such as cognitive neuroscience, cardiovascular diseases, diabetes and drug metabolism and were the main model system before the genetic modification era. Now with the advent of programmable nuclease-based gene editing technologies, the modification of rat genome is on par with that of mouse and the return of the rat models for research is highly likely. Yet there are few rat models available as universal tools so far. We have previously reported our efforts on the creation of a rat genetic toolbox, including nine neuron-specific Cre lines, a fluorescent Cre activity reporter line and two conditional opsin lines for optogenetics studies, which express excitatory Channel Rhodopsin and inhibitory Halorhodopsin respectively in a Cre-dependent manner. To recapitulate the neuron-specific expression patterns, 2A peptide or IRES-Cre cassette was inserted into the end of coding sequence of each of the following genes: tyrosine hydroxylase (Th), dopamine active transporter (DAT), tryptophan hydroxylase 2 (Tph2), somatostatin (Sst), vesicular inhibitory amino acid transporter(Slc32a1 or VGAT), vasoactive intestinal polypeptide, (VIP), 5-hydroxytryptamine receptor 3A (HTR3A), calcium/calmodulin-dependent protein kinase II alpha (CamKIIA) and parvalbumin (PValb). The reporter and opsin lines were

generated by inserting CAG promoter driving, floxed stop cassette-preceding tdTomato or opsin-Tdtomato fusion protein coding sequence into the Rosa26 locus. Here we will present our ongoing expression analysis on these Cre and optogenetics lines using a combination of mRNA in situ hybridization and immunohistochemistry methods.

Disclosures: **Z. Liu:** A. Employment/Salary (full or part-time): Horizon Discovery. **G. Zhao:** A. Employment/Salary (full or part-time): Horizon Discovery. **X. Cui:** A. Employment/Salary (full or part-time): Horizon Discovery.

Poster

847. Genetic Techniques

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 847.05/MMM24

Topic: I.01. Molecular, Biochemical, and Genetic Techniques

Support: Ellison Foundation

Cure Alzheimer's Fund

Title: Efficient introduction of hetozygous and homozygous disease-related mutations into human iPSCs using CRISPR/Cas9 to model Alzheimer's disease

Authors: ***D. KWART**[1], D. PAQUET[1], A. CHEN[1], A. SPROUL[2], S. JACOB[3], S. TEO[1], K. OLSEN[1], A. GREGG[1], S. NOGGLE[3], M. TESSIER-LAVIGNE[1];
[1]Tessier-Lavigne Lab., The Rockefeller Univ., New York, NY; [2]Columbia Univ. Med. Ctr., New York, NY; [3]The New York Stem Cell Fndn., New York, NY

Abstract: CRISPR/Cas9 allows sequence-specific gene editing in many organisms and is a promising tool to generate models of human diseases, e.g. in human pluripotent stem cells (iPSCs). CRISPR/Cas9 introduces double stranded breaks (DSBs) with high efficiency and locus specificity, which are typically repaired by non-homologous end-joining (NHEJ) resulting in nonspecific indel mutations, useful for generating gene knockouts. In rare cases, DSBs can also be repaired by homology-directed repair (HDR) using a DNA repair template, such as an introduced single-stranded oligo DNA nucleotide (ssODN), allowing knock-in of specific mutations. Although CRISPR/Cas9 is used extensively to engineer gene knock-outs through NHEJ, editing by HDR remains inefficient and can be corrupted by additional indels, preventing its widespread use for modeling genetic disorders by introducing disease-associated mutations. Furthermore, targeted mutation knock-in at single alleles, to model diseases caused by heterozygous mutations, such as early-onset Alzheimer's disease (EOAD), has not been reported.

We developed an efficient CRISPR/Cas9-based genome-editing framework that allows selective introduction of mono- and bi-allelic sequence changes with high efficiency and accuracy into iPSCs. We show that HDR accuracy is dramatically increased by incorporating silent CRISPR/Cas-blocking mutations together with pathogenic mutations, and establish a method we termed "CORRECT" for scarless editing. Furthermore, by characterizing and exploiting a stereotyped inverse relationship between the incorporation rate of a mutation and its distance to the DSB, we achieve predictable control of zygosity. Homozygous introduction require targeting a guide RNA close to the intended mutation, whereas heterozygous introduction can be achieved by distance-dependent suboptimal mutation incorporation or by using mixed repair templates. Using this approach, we establish human induced pluripotent stem cells (iPSCs) with homozygous and heterozygous dominant EOAD mutations in amyloid precursor protein (APP^{Swe}) and presenilin 1 ($PSEN1^{M146V}$) and derive cortical neurons, which display genotype-dependent disease-associated phenotypes. Our findings enable efficient introduction of homo- and heterozygous disease-associated mutations with CRISPR/Cas9, facilitating the study of molecular mechanisms of dementia in human in vitro models.

Disclosures: **D. Kwart:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); A patent has been filed. **D. Paquet:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); A patent has been filed. **A. Chen:** None. **A. Sproul:** None. **S. Jacob:** None. **S. Teo:** None. **K. Olsen:** None. **A. Gregg:** None. **S. Noggle:** None. **M. Tessier-Lavigne:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); A patent has been filed.

Poster

847. Genetic Techniques

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 847.06/MMM25

Topic: I.01. Molecular, Biochemical, and Genetic Techniques

Support: U01MH109107

Title: Systemic delivery of AAVs driving patterned gene expression by ultra-conserved enhancer elements

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School/Boston Children's Hosp., Boston, MA; [3]Harvard Med. School/Boston Children's Hospitla, Boston, MA

Abstract: The use of transgenic animals to observe and manipulate specific cellular populations has been fundamental to the advance in understanding the function of the nervous system in normal and diseased animals. While, a vast assortment of such resources currently exists, in mammals these tools are largely restricted to mice. We are using ubiquitous viral delivery coupled with across-species conserved enhancer elements to drive reporter gene expression in an effort to circumvent the generation of transgenic animals by achieving region-specific and cell-type specific gene expression. Using two near ubiquitous viral delivery systems (neonatal intraventricular injection of AAV9, and tail vein injection of AAVPHP.B) we are characterizing the expression patterns driven by ultra-conserved enhancer elements. Reproducible cell-type and region specific patterns of GFP expression have been observed in neurons and glial cells of mice for multiple enhancers. For select enhancer elements, these patterns have also been tested in rats and identical or nearly identical expression patterns were observed. Thus, we believe this system could be applied across species once a thorough catalogue of virally delivered ultra-conserved enhancer elements has been established.

Disclosures: **P.R. Williams:** None. **C. Wang:** None. **Y. Li:** None. **Z. Junjie:** None. **Z. He:** None.

Poster

847. Genetic Techniques

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 847.07/MMM26

Topic: I.01. Molecular, Biochemical, and Genetic Techniques

Title: Magnetogenetics: remote non-invasive magnetic activation of neuronal activity with a magnetoreceptor (MAR)

Authors: *S.-J. ZHANG;
SZU-CUHKSZ Joint Res. Ctr. for Artificial Intelligence & Brain Engin., Shenzhen Univ., Shenzhen, China

Abstract: Current neuromodulation techniques such as optogenetics and deep-brain stimulation are transforming basic and translational neuroscience. These two neuromodulation approaches are, however, invasive since surgical implantation of an optical fiber or wire electrode is required. Here, we have invented a non-invasive magnetogenetics that combines the genetic targeting of a magnetoreceptor with remote magnetic stimulation. The non-invasive activation of

neurons was achieved by neuronal expression of an exogenous magnetoreceptor, an iron-sulfur cluster assembly protein 1 (Isca1). In HEK-293 cells and cultured hippocampal neurons expressing this magnetoreceptor, application of an external magnetic field resulted in membrane depolarization and calcium influx in a reproducible and reversible manner, as indicated by the ultrasensitive fluorescent calcium indicator GCaMP6s. Moreover, the magnetogenetic control of neuronal activity might be dependent on the direction of the magnetic field and exhibits on-response and off-response patterns for the external magnetic field applied. The activation of this magnetoreceptor can depolarize neurons and elicit trains of action potentials, which can be triggered repetitively with a remote magnetic field in whole-cell patch-clamp recording. In transgenic *Caenorhabditis elegans* expressing this magnetoreceptor in *myo-3*-specific muscle cells or *mec-4*-specific neurons, application of the external magnetic field triggered muscle contraction and withdrawal behavior of the worms, indicative of magnet-dependent activation of muscle cells and touch receptor neurons, respectively. The advantages of magnetogenetics over optogenetics are its exclusive non-invasive, deep penetration, long-term continuous dosing, unlimited accessibility, spatial uniformity and relative safety. Like optogenetics that has gone through decade-long improvements, magnetogenetics, with continuous modification and maturation, will reshape the current landscape of neuromodulation toolboxes and will have a broad range of applications to basic and translational neuroscience as well as other biological sciences. We envision a new age of magnetogenetics is coming.

Disclosures: S. Zhang: None.

Poster

847. Genetic Techniques

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 847.08/MMM27

Topic: I.01. Molecular, Biochemical, and Genetic Techniques

Support: JSPS KAKENHI Grant Number 15H02442

Title: Generation of oxytocin receptor modified prairie voles by using CRISPR/Cas

Authors: *K. HORIE[1], T. HIRAYAMA[1], S. SUZUKI[1], T. FUKUDA[2], S. HIDEMA[1], K. NISHIMORI[1];
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Abstract: Prairie voles (Microtus ochrogaster) are socially monogamous rodents that form enduring pair between mates. Additionally, prairie voles exhibit biparental behaviors to their

pups. These social behaviors are completely different from mice and rats commonly used as animal models for the studies of social behaviors in laboratory. In prairie voles, it is suggested that these behaviors are regulated by neurotransmitters such as oxytocin, vasopressin and dopamine and the species-specific distribution of their receptors in their brains. In particular, recent studies imply oxytocin/oxytocin receptor (*Oxtr*) plays a dominant role for the regulation of pair bonding behavior in prairie voles. Although many reports indicate relationships between the functions of neurotransmitters and the phenotypes in prairie voles by using pharmacological methods, there are no reports using genetically engineered prairie voles to uncover molecular mechanisms of their social behaviors. Especially, the details of the neural regulatory mechanisms by their receptors are elusive. To further elucidate the neural mechanisms of social behaviors in prairie voles, it is useful to generate genetically modified prairie voles. We focused on *Oxtr* and tried to generate *Oxtr* KO, tagged and floxed prairie voles by using CRISPR/Cas, and then successfully generated *Oxtr* KO prairie voles.
First, we established developmental engineering and reproductive technologies of prairie voles. We succeeded to collect embryos from super-ovulated female voles (7.2 embryos/ a vole). We also succeeded to culture vole embryos efficiently from one cell stage to blastocyst stage in G-1/G-2 PLUS medium (81% efficiency). Next, we applied these techniques to generation of *Oxtr* knock-out (KO) prairie voles by using CRISPR/Cas. We designed CRISPR/Cas target sites against *Oxtr* locus of prairie voles, and evaluated targeting efficiencies of each single-guide RNA (sgRNA) by single strand annealing assay in HEK293T cells, and then choose two sgRNAs that showed high activities. Finally, we succeeded to generate *Oxtr* KO prairie voles by microinjection of sgRNA and Cas9 RNA into cytosol of one-cell embryos. We obtained 6 pups that carried mutations in their target locus. The T7E1 assay and direct sequencing showed 100% (6/6) targeting efficiencies, and sub-cloned *Oxtr* locus showed a variety of mutated genotypes. We confirmed the efficient transmission of mutated genotypes to the next generation. We are now trying to generate *Oxtr*-flag tagged and *Oxtr* floxed prairie voles by CRISPR/Cas mediated DNA vector knock-in (KI) strategy and successfully confirmed that the KI efficiency was high (>50%) in embryos of prairie voles.

Disclosures: **K. Horie:** None. **T. Hirayama:** None. **S. Suzuki:** None. **T. Fukuda:** None. **S. Hidema:** None. **K. Nishimori:** None.

Poster

847. Genetic Techniques

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 847.09/MMM28

Topic: I.01. Molecular, Biochemical, and Genetic Techniques

Support: Michael J. Fox Foundation

Target ALS

Title: Viral vector mediated transdifferentiation of resident oligodendrocytes into functional neurons.

Authors: *T. J. MCCOWN[1], M. S. WEINBERG[2], H. E. CRISWELL[3];
[1]Gene Therapy Ctr., Univ. of North Carolina, Chapel Hill, NC; [2]Gene Therapy Ctr., [3]Ctr. for Alcohol Studies, Univ. of North Carolina at Chapel Hill, Chapel Hill, NC

Abstract: Resident cell reprogramming has emerged as a potential strategy for neuronal replacement, but to date *in vivo* approaches required transgenic mice or retroviral vectors (Heinrich et al., Nat. Cell Biol. 17:204,2015). Because selective *in vitro* inhibition of poly-pyrimidine-tract binding (PTB) protein expression reprograms fibroblasts into neuronal-like cells (Xue et al. Cell 152:82,2013), we utilized a novel oligodendrocyte trophic AAV vector in order to determine if *in vivo* inhibition of PTB protein expression would reprogram resident oligodendrocytes into functional neurons. First we developed an miRNA-GFP that significantly reduced PTB protein expression in HEK293 cells. Subsequently this miRNA-GFP construct was packaged into a recombinant AAV vector with the oligotrophic capsid, where expression was driven by a hybrid chicken beta actin promoter. One week after striatal infusion in rats GFP positive cells exhibited oligodendrocyte morphology with little or no NeuN/GFP co-localization. However, at 6 weeks post-vector infusion, most of the GFP positive cells exhibited a neuronal morphology with very few GFP positive oligodendrocyte-like cells. The majority of GFP positive cells co-localized with the neuronal marker NeuN while subsets of GFP positive cells exhibited co-localization with DARRP-32, a cellular marker of medium spiny neurons or parvalbumin, a marker for a subclass of GABAergic interneurons. This apparent oligodendrocyte to neuron transdifferentiation remained at the 3 or 6 month survival time points. When striatal slices were obtained from rats at 6 weeks or 3 months post-vector infusion, patch-clamp studies established that the GFP positive cells exhibited electrophysiological properties indicative of a mature neuron. Current-clamp recordings from GFP positive striatal cells identified spontaneous action potentials typical of functional neurons, while voltage-clamp recordings found spontaneous inhibitory postsynaptic currents indicative of GABAergic currents. These findings suggest that the oligodendrocytes transdifferentiated into functional striatal neurons. Also, 3 months after vector infusion, fluorescent beads were infused into the ipsilateral globus pallidum. Two weeks later, several GFP positive cells exhibited the presence of the fluorescent beads in the cell body, indicating retrograde transport within intact globus pallidum projections from transdifferentiated striatal cells. Thus, this viral vector approach appears capable of harnessing resident oligodendrocytes for *in vivo* neuronal replacement. (Supported by grants from the Michael J. Fox Foundation and Target ALS to TJM)

Disclosures: **T.J. McCown:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Thomas J. McCown. **M.S. Weinberg:** None. **H.E. Criswell:** None.

Poster

847. Genetic Techniques

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 847.10/MMM29

Topic: I.01. Molecular, Biochemical, and Genetic Techniques

Support: NIH Grant R21MH093914

NIH Grant UO1MH104974

NIH Grant F31NS093917-01

Title: Cre -dependent DREADD (designer receptors exclusively activated by designer drugs) mice

Authors: *R. H. J. OLSEN[1], H. ZHU[1], D. K. ARYAL[1], D. J. URBAN[1], B. L. ROTH[1], U. HOCHGESCHWENDER[2];
[1]Dept. of Pharmacol., UNC Chapel Hill Med. Sch., Chapel Hill, NC; [2]Neurosci. Program and Col. of Med., Central Michigan Univ., Mt. Pleasant, MI

Abstract: Designer Receptors Exclusively Activated by Designer Drugs (DREADDs), are engineered G protein-coupled receptors which can control GPCR signaling pathways (for example, Gq, Gs and Gi) to modulate important cellular functions. These chemogenetic tools have been successfully used *in vivo* across species to study the activity and function of neurons, glia, pancreatic β-cells, cancer cells, fat cells, and others. Presently, DREADDs are most typically introduced into an experimental condition via viral technologies. Here we present the generation and functional characterization of novel hM3Dq and hM4Di strains of mice which allow for Cre-recombinase-mediated restricted expression of these pathway-selective DREADDs. With the many well-characterized Cre-driver lines now available these DREADD lines will be applicable to studying a wide array of research and preclinical questions.

Disclosures: R.H.J. Olsen: None. **H. Zhu:** None. **D.K. Aryal:** None. **D.J. Urban:** None. **B.L. Roth:** None. **U. Hochgeschwender:** None.

Poster

847. Genetic Techniques

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 847.11/MMM30

Topic: I.01. Molecular, Biochemical, and Genetic Techniques

Support: KAKENHI(15H01431)

KAKENHI(25250003)

Title: Use of an optimized chimeric envelope glycoprotein enhances the efficiency of retrograde gene transfer of a pseudotyped lentiviral vector in the primate brain

Authors: M. FUJIWARA[1], S. TANABE[1], H. TSUGE[1], S. UEZONO[1], K. NAGAYA[1], M. SUGAWARA[2], S. KATO[2], K. KOBAYASHI[2], *K.-I. INOUE[1], M. TAKADA[1];
[1]Primate Res. Inst., Kyoto Univ., Inuyama, Japan; [2]Fukushima Med. Univ., Fukushima, Japan

Abstract: Lentiviral vectors have been used not only for various basic research experiments, but also for a wide range of gene therapy trials in animal models. The development of a pseudotyped lentiviral vector with the property of retrograde infection allows us to introduce foreign genes into neurons that are localized in brain regions innervating the site of vector injection. This enables pathway-selective gene manipulation in the brain. Recently, it has been demonstrated in mice that the use of a novel type of fusion glycoprotein (FuG-E) of which segmental junction was optimized results in increased retrograde gene transfer relative to the parental fusion glycoprotein (FuG-C). Here, we report the efficiency of retrograde gene transfer of the FuG-E pseudotyped lentiviral vector based on human immunodeficiency virus type 1 (HIV-1) in the primate brain by comparing its transduction pattern with the pattern induced by the parental FuG-C pseudotyped vector. After injection of the FuG-E vector encoding green fluorescent protein (GFP; 4.5 x 10^9 genome copies) into the striatum of macaque monkeys, many GFP-immunoreactive neurons were found in regions innervating the striatum, such as the cerebral cortex, thalamus, and substantia nigra. Quantitative analysis revealed that the number of neurons retrogradely transduced with the FuG-E vector was approximately 2.2, 1.7, or 1.2 times larger than the FuG-C vector case in the cerebral cortex (primary motor cortex and prefrontal cortex), thalamic nuclei (CM-Pf and CL), or substantia nigra pars compacta, respectively. We also confirmed that the FuG-E vector displays explicit neuron specificity to the same extent as the FuG-C vector. The present results indicate that pseudotyping of the HIV-1-based lentiviral vector with FuG-E glycoprotein greatly enhances the efficiency of gene transfer through retrograde axonal transport in the primate brain. This vector might promote approaches to pathway-selective gene manipulation and provide a powerful tool for effective gene therapeutic trials against neurological disorders through enhanced retrograde delivery.

Disclosures: **M. Fujiwara:** None. **S. Tanabe:** None. **H. Tsuge:** None. **S. Uezono:** None. **K. Nagaya:** None. **M. Sugawara:** None. **S. Kato:** None. **K. Kobayashi:** None. **K. Inoue:** None. **M. Takada:** None.

Poster

847. Genetic Techniques

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 847.12/MMM31

Topic: I.01. Molecular, Biochemical, and Genetic Techniques

Support: This study was supported by the Research Grant Program at Escuela de Medicina, Universidad Anáhuac Mayab given to E.M.-R.

Title: Global DNA methylation variation induced by cannabidiol in cerebral cortex of rats

Authors: *D. MORALES-LARA[1], F. DUARTE-AKÉ[3], J. PASTRANA TREJO[2], C. DE LA PEÑA[3], R. MECHOULAM[4], E. MURILLO RODRIGUEZ[2];
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Abstract: Several pieces of evidence have shown that the non-psychoactive compound of marihuana, cannabidiol (CBD), displays wake-promoting properties. Our group has reported that central microinjections of CBD promotes wakefulness and decreases sleep in rats during the lights-on periods. Despite that CBD does not bind to the cannabinoid receptors described at this date, recent evidence has suggested that this compound might be inducing several physiological effects via epigenetic DNA methylation. Thus, in the present study, global DNA methylation was analyzed in CBD-treated rats: Male Wistar rats (n=12) received an ip injection either of the following treatments: Vehicle (n=3), CBD (5mg/Kg, n=3; 10 mg/Kg, n=3; or 20mg/Kg, n=3). All experimental challenges were carried out at the beginning of the lights-on period (8:00h). One hour after injections, rats were sacrificed by decapitation and cerebral cortex was collected and immediately stored for further DNA methylation analysis. Global 5mC levels were detected by reversed-phase high performance liquid chromatography (RP-HPLC). We found that cerebral cortex was decreased in global DNA methylation in CBD-treated rats (5mg/Kg) in comparison to the vehicle group ($P<0.03$). However, higher doses of CBD caused an opposite results since an increase in DNA methylation was observed compared to CBD-5mg/Kg. This promising preliminary data suggest that CBD is able to promote epigenetical changes by an unknown

mechanism. Thus, further studies are needed to explore the epigenetic mechanism of action activated by this cannabinoid.
This study was supported by the Research Grant Program at Escuela de Medicina, Universidad Anáhuac Mayab given to E.M.-R.

Disclosures: D. Morales-Lara: None. **F. Duarte-Aké:** None. **J. Pastrana Trejo:** None. **C. De la Peña:** None. **R. Mechoulam:** None. **E. Murillo Rodriguez:** None.

Poster

847. Genetic Techniques

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 847.13/MMM32

Topic: I.01. Molecular, Biochemical, and Genetic Techniques

Support: NIA Grant AG032325

Title: Investigation of CRISPR-CAS9 system strategies for knockdown of the luteinizing hormone receptor

Authors: *S. BHATTA[1], J. A. BLAIR[1], G. CASADESUS[1,2];
[1]Sch. of Biomed. Sci., [2]Dept. of Biol. Sci., Kent State Univ., Kent, OH

Abstract: Luteinizing hormone (LH) and its receptor (LHR) are present in regions critical for learning and memory in the CNS. Previously, we have shown that ovariectomy (OVX) induced loss of LHR signaling in CNS is associated with cognitive deficits and importantly, reactivation of LHR signaling through intracerebroventricular (ICV) delivery of the ligand improves cognitive function *in vivo* and neuronal plasticity *in vitro.* In order to develop a fast and simple strategy to utilize knockdown of LHR to examine the effects of its absence *in vivo*, we explored the CRISPR/Cas9 system to knockdown the LHR in HEK cells overexpressing LHR. The simplicity of CRISPR/Cas9 technique is countered, however, by the inability to predict the specificity and efficiency of a guide RNA (sgRNA). Therefore, we selected two high scoring guides from three published predictive models and assessed the knockout efficiency of these guides in HEK cells overexpressing LHR *in vitro* by measuring the levels of LHR as well as signaling cascades associated with the activity of the receptor. Here we show that different sgRNAs resulted in differential decreases in protein levels as well as differential activation of signaling cascades.

Disclosures: S. Bhatta: None. **J.A. Blair:** None. **G. Casadesus:** None.

Poster

847. Genetic Techniques

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 847.14/MMM33

Topic: I.01. Molecular, Biochemical, and Genetic Techniques

Support: NIH Grant 5T32GM007491

Harold and Leila Y. Mathers Charitable Foundation

Title: Comparative connectomics of the adult male and hermaphrodite *C. elegans*

Authors: *S. J. COOK[1], T. JARRELL[2], Y. WANG[3], K. NGUYEN[1], C. BRITTIN[4], M. YAKOVLEV[5], L. TANG[3], E. BAYER[6], O. HOBERT[6], H. BUELOW[2], D. HALL[1], S. EMMONS[2];
[1]Neurosci., [2]Genet., [3]Albert Einstein Col. of Med., Bronx, NY; [4]Univ. of Leeds, Leeds, United Kingdom; [5]Penn State Univ., State College, PA; [6]Columbia Univ., New York, NY

Abstract: The ability of an organism to sense, integrate, and respond to environmental stimuli is dictated by the patterns of its synaptic connectivity. However, not all synaptic connections are conserved across different sexes, and can produce sexually dimorphic behaviors. Here we present the updated adult male and hermaphrodite connectomes of *C. elegans* based upon reconsturction and analysis of serial section electron micrographs. These results are based upon previously analyzed hermaphrodite data (White et al. 1986) and new electron micrograph series of the male that cover the complete nervous system of *C. elegans* and its endorgans (muscle, intestine, gonad). In a graph representation of synaptic connectivity, we visualize information flow through a multi-layered structure from sensory neurons to motor output. Through analysis of anatomical connections we have described different classes of inter- and motorneurons. Sensory information enters the worm through several modalities, and is separated into a four-layered, feedforward structure. Graphical layout algorithms based on connectivity reveal that neural network structure is conserved across the sexes. Correspondence of the layout to the worm's neuroanatomy is consistent with economical wiring. While most synaptic connections are conserved across sex, we find that sex-specific neurons target similar downstream partners to yield distinct behaviors. While the connectomes we have generated are static, we are using them to generate experimentally testable hypotheses. To incorporate the dynamics of development and inter-individual variability, we have developed a method called iBLINC (in vivo Biotin Labeling of INtercellular Contacts). This fluorescent system directionally labels individual synapses in the worm using neuron-specific promoters. By employing iBLINC we have verified sexually dimorphic synapses, as well as synaptic connections that break the left-right symmetry of the nervous system. By comparing complete connectomes mathematically and experimentally it is

possible to consider how diverse sensory cues are combined and processed by the nervous system to produce a coherent and adaptive behavioral output.

Disclosures: **S.J. Cook:** None. **T. Jarrell:** None. **Y. Wang:** None. **K. Nguyen:** None. **C. Brittin:** None. **M. Yakovlev:** None. **L. Tang:** None. **E. Bayer:** None. **O. Hobert:** None. **H. Buelow:** None. **D. Hall:** None. **S. Emmons:** None.

Poster

847. Genetic Techniques

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 847.15/MMM34

Topic: I.01. Molecular, Biochemical, and Genetic Techniques

Support: R01DC013070

Title: Upgrading transgenic DNA components by inducible gene replacement

Authors: *C.-C. LIN, C. POTTER;
Johns Hopkins Univ. Sch. of Med., Baltimore, MD

Abstract: Gene conversions occur when genomic double strand DNA breaks (DSBs) results in unidirectional transfer of genetic material from a homologous template sequence. Exogenous or mutated sequence can be introduced through this homology directed repair (HDR). We leveraged HDR and gene conversion to develop a method for in vivo genomic editing of existing transgenic insertions. Homology Assisted CRISPR Knockin (HACK) utilizes the CRISPR/Cas9 system to induce DSBs in a *GAL4* transgene, which is repaired by a single genomic transgenic construct containing *GAL4* homologous sequence flanking a *T2A-QF2* cassette. With two crosses, this technique converts existing *GAL4* lines, including enhancer traps, into functional *QF2* expressing lines. We used HACK to convert the most commonly used *GAL4* lines (labelling tissues such as neuronal, fat, glia, muscle, hemocytes) to *QF2* lines. We also identified 'hot' and 'cold' spots of HDR in the genome. The technique is robust and readily adaptable for targeting and replacement of other genomic sequences.

Disclosures: **C. Lin:** None. **C. Potter:** None.

Poster

847. Genetic Techniques

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 847.16/MMM35

Topic: I.01. Molecular, Biochemical, and Genetic Techniques

Support: GVSU Presidential Research Grant to GW

Title: Identification of deletions in the Hdc gene of *Drosophila melanogaster* generated through transposon-excision mutagenesis

Authors: G. WESSELING[1], J. VELDMAN[1], *M. G. BURG[2];
[1]Biomed. Sci., [2]Biomed. Sciences/Cell and Mol. Biol., Grand Valley State Univ., Allendale, MI

Abstract: Histamine is a biogenic amine that functions as a neurotransmitter in a number of vertebrate and invertebrate systems and is synthesized from its precursor histidine by histidine decarboxylase (HDC). In Drosophila, histamine has been shown to have function in photoreceptors, mechanoreceptor cells, as well as centrally located neurons. Mutations of the *Hdc* gene, such as Hdc^{JK910}, exhibit defects in histamine synthesis and display altered behaviors such as blindness, inability to groom, impaired thermal tolerance, and sleep. However, all *Hdc* mutants obtained thus far demonstrate residual histidine decarboxylase expression, leaving open the question: What would a complete elimination of *Hdc* function cause phenotypically in the fly?
To determine the true *Hdc* null phenotype, the *Hdc* gene was removed via *Minos* transposon-excision mutagenesis using a fly bearing a *Minos* transposon that is located within the *Hdc* gene, $Mi\{ET1\}Hdc^{MB07212}$. *Minos* excision mutagenesis of *Hdc* was achieved by mating the $Hdc^{MB07212}$ fly with another fly carrying the *Minos*-specific transposase gene. When the *Minos* transposase is activated, the existing $Mi\{ET1\}Hdc^{MB07212}$ element can transpose in the progeny's genome. The *Mi*{ET1} transposon used also contains a gene encoding green fluorescent protein (GFP) under the control of a promoter that induces GFP expression in the eye. The presence or absence of GFP in the $Hdc^{MB07212}$ fly can be used to visually identify a potential *Minos* excision. Once a GFP^- progeny fly was identified, a breeding line was established and flies from each line were examined using histamine immunostaining to determine the presence or absence of histamine. Progeny are expected to represent the following categories: (1) flies with wild-type levels of histamine, indicating a precise *Minos* excision from *Hdc*; (2) flies with trace levels of histamine, indicating a disrupted transposon left at the excision site; (3) flies having no histamine, indicating an imprecise excision event and consequent disruption of the *Hdc* gene. All strains with no detectable histamine were crossed with the Hdc^{JK910} mutant strain and their progeny examined for the presence of histamine to genetically confirm whether a deletion of *Hdc* occurred in that fly line.

Results indicate that >75 GFP$^-$ strains thus far established fall into one of the 3 expected categories, with a number of strains (>24) eliminating *Hdc* gene expression. At least 24 new *Hdc* deletion mutants have therefore been isolated, which lead to lack of *Hdc* function but do not cause lethality in the fly. The molecular nature of these genetic disruptions of the *Hdc gene* are currently being explored.

Disclosures: G. Wesseling: None. **J. Veldman:** None. **M.G. Burg:** None.

Poster

847. Genetic Techniques

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 847.17/MMM36

Topic: I.01. Molecular, Biochemical, and Genetic Techniques

Support: Support given by Escuela de Medicina- Universidad Anáhuac Mayab given to E.M.-R.

Title: Hypothamic cells show increased methylation to the administration of CBD in rats.

Authors: *J. C. PASTRANA TREJO[1], F. DUARTE-ÁKE[2], D. MORALES LARA[1], C. DE-LA-PEÑA[2], R. MECHOULAM[3], E. MURILLO-RODRIGUEZ[1];
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Abstract: Cannabis plants have been used long ago as it is known to have a potential effect on the human nervous system. Recently used in neurological treatments showing great efficiency. Here, we describe an experiment using Male Wistar rats (n=9) where they were administered intraperitoneally at doses of 10 mg / kg .Next, rats were sacrificed after one hour of administration and three different brain regions were collected (Pons , hypotalamus , Cortex.) The samples were examined with HPLC and methylation of these brain regiones were compared. Statistical analysis was performed by using ANOVA (Post Hoc Test) showing the difference is not statistically significant between Pons and Cortex (P = < 0.61) But they are statistically significant with hypotalamus showing a statisticall difference of pons (P = <0.0094) and Cortex with a (P = < 0.0047) difference. .In this very first study, we evidence the potencial activity of metilation and the vulnerability of the hypotalamic cells to the administration of CBD in rats. We think that this phenomenon is due to the activation of two possible mechanisms of activation such as ionotropic or metabotropic Associated activation of the G protein cells in the hypothalamus . Receptors as CB1 may be possibly involved in methylation processes since this receptor has neuronal and hormonal activity.

Disclosures: **J.C. Pastrana Trejo:** None. **F. Duarte-Áke:** None. **D. Morales Lara:** None. **C. De-La-Peña:** None. **R. Mechoulam:** None. **E. Murillo-Rodriguez:** None.

Poster

847. Genetic Techniques

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 847.18/MMM37

Topic: I.01. Molecular, Biochemical, and Genetic Techniques

Support: RMH096202A

RMH100650A

Texas Biomedical Device

Title: The development of a viral mediated CRISPR/Cas9 system for doxycycline dependent inducible *In vitro* and *In vivo* genome editing

Authors: *C. A. DE SOLIS[1], A. HO[2], R. HOLEHONNUR[1], J. PLOSKI[3];
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Abstract: The RNA-guided Cas9 nuclease, from the type II prokaryotic Clustered Regularly Interspersed Short Palindromic Repeats (CRISPR) adaptive immune system, has been adapted and utilized by scientists to edit the genomes of eukaryotic cells. Here we report the development of a viral mediated CRISPR/Cas9 system that can be rendered inducible utilizing doxycycline (Dox) and can be delivered to cells in vitro and in vivo utilizing adeno-associated virus (AAV). Specifically, we developed an inducible gRNA (gRNAi) AAV vector that is designed to express the gRNA from a H1/TO promoter. This AAV vector is also designed to express the Tet repressor (TetR) to regulate the expression of the gRNAi in a Dox dependent manner. We demonstrate that our inducible gRNAi vector can be used to edit the genomes of cells *in vitro* and neurons *in vivo* within the mouse brain in a Dox dependent manner. This system is cross compatible with many existing *S. pyogenes* Cas9 systems (i.e. Cas9 mouse, CRISPRi, etc.), and therefore it can be used to render these systems inducible as well.

Disclosures: **C.A. de Solis:** None. **A. Ho:** None. **R. Holehonnur:** None. **J. Ploski:** None.

Poster

847. Genetic Techniques

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 847.19/MMM38

Topic: I.01. Molecular, Biochemical, and Genetic Techniques

Support: NEI

Postdoctoral fellowship award 15POST22430003 supported by the American Heart Association (AHA), 2014-2016

Title: MitoTev-TALEs: a new generation of monomeric nucleases to reduce mutant mtDNA

Authors: *C. V. PEREIRA, S. R. BACMAN, S. L. WILLIAMS, C. T. MORAES;
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Abstract: Mutations in the mitochondrial DNA (mtDNA) induce severe phenotypes affecting different organs, including the central and peripheral nervous system. When pathogenic mutations occur in the mtDNA, most often mutant and wild-type (WT) mtDNA co-exist within the same cell (mtDNA heteroplasmy). Since there are multiple copies of mtDNA in a cell, the percentage of mutant mtDNA can vary and above a certain threshold, disease occurs. Our lab showed that mtDNA heteroplasmy can be manipulated by the use of mitochondrial-targeted transcription activator-like effector nucleases (MitoTALENs), which are site-specific dimeric nucleases. Previously, it was demonstrated that MitoTALENs generate double strand breaks in the mtDNA, eliminating the mutant genomes, by the rapid replication of residual WT mtDNA molecules. Although they could provide a potential cure for affected tissues, they are relatively large, making it difficult to package into viral vectors, limiting its clinical application. Recently, the GIY-YIG homing monomeric nuclease from T4 phage (I-TevI) provided an alternative to solve the size constraint imposed by the mitoTALENs. Our hypothesis is that mitoTev-TALEs can cleave mutated mtDNA specifically, and, because of their compact size, they can facilitate *in vivo* delivery. Different architectures of monomeric mitoTev-TALES were designed either to target the m.14459G>A, or the m.8344A>G mtDNA point mutations. This novel methodology was first optimized in yeast and then tested in patient-derived heteroplasmic cybrids, harboring the respective point mutations. Briefly, the mitochondrial localization of the mitoTev-TALEs was confirmed by immunocytochemistry. Next, cells were sorted by the presence of a GFP marker and the percentage of WT versus mutant mtDNA was determined by restriction digestion followed by PAGE. Preliminary data suggest that one out of the two tested mitoTev-TALEs targeting the m.8344A>G mutation, was capable of shifting the mtDNA ratio towards the wild type. To conclude, mitoTev-TALES provide a new architecture for mtDNA editing that may facilitate delivery to affected tissues.

Disclosures: **C.V. Pereira:** None. **S.R. Bacman:** None. **S.L. Williams:** None. **C.T. Moraes:** None.

Poster

847. Genetic Techniques

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 847.20/MMM39

Topic: I.01. Molecular, Biochemical, and Genetic Techniques

Support: Takeda Science Foundation

The Uehara Memorial Foundation

The Naito Foundation

KAKENHI (25702053)

Title: Comparative study of gene transduction efficiency for retrograde gene transfer lentiviral vector with novel fusion envelope glycoproteins.

Authors: *S. KATO[1], K. KOBAYASHI[1,2];
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Abstract: The frameworks of brain function are based on the neural complex circuitry. To understand the mechanism for the information processing and its regulation, we developed a novel technology for gene transfer and expression through retrograde axonal transport of the viral vectors. It enables us to introduce the transgene into neuronal populations that innervate the brain regions where the vectors are injected. Pseudotyping of a HIV-1-based lentiviral vector with fusion chimeric envelope glycoprotein composed of rabies virus glycoprotein and vesicular stomatitis virus glycoprotein domains confers a high efficiency of retrograde gene transfer. Recently, we established new type of fusion glycoproteins; termed type B2 (highly efficient retrograde gene transfer (HiRet)), type C and E (neuron-specific retrograde gene transfer (NeuRet)), which showed improved efficiency of retrograde gene transfer activity. In the present study, we tested gene transfer of HIV-1 lentiviral vectors pseudotyped with these types of fusion glycoproteins and compared each feature not only retrograde gene transduction efficacy but also the tropism around the vector injection site. These vectors were used for functional elimination of thalamostraital pathways (originating from parafascicular nucleus) in basal ganglia circuit to study the behavioral roles of the visual discrimination task in rodent (Kato et al., 2011), reversible blockade of motor cortex to spinal motoneurons in mid-cervical propriospinal neurons (PNs) to clarify the controls of dexterous hand movements in Macaque monkey (Kinoshita et al.,

2012). Another application is available to combine an optogenetics-mediated photoactivation, chemogenetic-mediated pharmacological treatment and so on. Also, to increase the expression level of gene, Cre- or Flp-mediated recombination is used. HiRet or NeuRet vector encoding Cre is injected into the neural terminal region and then AAV vector encoding double-floxed, inverted gene is injected into the innervating of the terminal. These strategies enable us to activate or inactivate specific neural circuitry functions. In addition, a trial for application to gene therapy, we investigated the efficiency of retrograde gene transfer of the HiRet and NeuRet vectors into motor neurons in the spinal cord and medulla oblongata in mice by injecting into gastrocnemius muscle and lingual muscle. As a result, our viral vector system with these fusion glycoproteins will provide a powerful tool for gene therapeutic trials of neurological and neurodegenerative diseases and for the study of the mechanisms of neural networks underlying a variety of brain functions.

Disclosures: **S. Kato:** None. **K. Kobayashi:** None.

Poster

847. Genetic Techniques

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 847.21/MMM40

Topic: I.01. Molecular, Biochemical, and Genetic Techniques

Title: Targeted sequencing powered by long read smrt sequencing in neurological disorders

Authors: *S. KUJAWA, A. SETHURAMAN, K. ENG, 94025;
Pacific Biosci., Menlo Park, CA

Abstract: Over the past decades neurological disorders have been extensively studied using positional cloning and association studies, which have produced a large number of candidate genomic regions and candidate genes. However, the SNPs identified in these studies rarely represent the true disease-related functional variants. Even using next-generation short-read sequencing technologies, the causative variants linked to the underlying association signals have not been uncovered. Over the past few years there has been some new breakthroughs that look beyond just SNPs and focus more on the larger structural variations present. In fact, germline structural variation events in the human genome account for a greater number of variable bases than single nucleotide variants. However, these structural variants have beendifficult to study using short-read sequencing approaches due to their short read length and mapability limitations. Here we have developed several different candidate screening methods for neurological diseases that combine enrichment of long DNA fragments (5kb-9kb) with long-read sequencing that is optimized for structural variation discovery. Single Molecule, Real-Time (SMRT)

Sequencing combines single-molecule observation, long read lengths, and the lowest degree of bias to fully characterize genetic complexity — including structural variation, rare SNPs, indels, copy number variation, microsatellites, haplotypes, and phasing. SMRT sequencing enabled us to move beyond simply cataloging SNPs and instead allowed us to target all types of variants across relevant genomic regions. These include low complexity regions like repeat expansions, promoters, and flanking regions of transposable elements in a wide range of neurological disorders like Alzheimer's disease (TOMM40, APOE, APP, PSEN1), Amyotrophic lateral sclerosis (C9orf72,), Schizophrenia (C4), Huntington's disease (HTT) and Fragile X disease (FMR1). For the TOMM40 gene we successfully detected and haplotyped the different lengths of the poly-T structural variation that are associated with age of onset in Alzheimer's disease. We are also accurately counted the repeats in several repeat expansion disorders (HTT, FMR1, C9orf72) in addition to detecting the interruption sequences and epigenetic information. For the C4 gene associated with psychosis in schizophrenia, we successfully differentiatedthe C4A and C4B isoforms, as well as the presence and absence of the endogenous retroviral (HERV) insertion in intron 9 of these isoforms.

Disclosures: **S. Kujawa:** A. Employment/Salary (full or part-time): Pacific Biosciences. **A. Sethuraman:** A. Employment/Salary (full or part-time): Pacific Biosciences. **K. Eng:** A. Employment/Salary (full or part-time): Pacific Biosciences.

Poster

847. Genetic Techniques

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 847.22/MMM41

Topic: I.01. Molecular, Biochemical, and Genetic Techniques

Title: Genetic labeling strategies for functional analysis of human neocortical cell types and microcircuits in *Ex vivo* brain slice cultures

Authors: *J. T. TING[1], P. CHONG[1], R. GWINN[3], C. COBBS[4], J. G. OJEMANN[5,7], A. KO[5,7], C. D. KEENE[6], C. KOCH[2], E. LEIN[1,5];
[1]Human Cell Types, [2]Allen Inst. For Brain Sci., Seattle, WA; [3]Epilepsy Surgery and Functional Neurosurg., [4]The Ben and Catherine Ivy Ctr. for Advanced Brain Tumor Treatment, Swedish Neurosci. Inst., Seattle, WA; [5]Neurolog. Surgery, [6]Dept. of Pathology, Div. of Neuropathology, Univ. of Washington Med. Ctr., Seattle, WA; [7]Regional Epilepsy Ctr., Harborview Med. Ctr., Seattle, WA

Abstract: What is the cellular and functional architecture of the human neocortex, and how does it differ from that of other mammals? It is a widely held belief that the remarkable evolutionary

expansion of the neocortex holds the key to our uniquely human abilities. Can the origins of our higher cognitive abilities be traced back to the functional contributions of distinctive neocortical cell types, or perhaps to structural divergence in neocortical wiring? To begin to address these longstanding questions necessitates access to living human brain tissue for functional studies, a daunting task with many logistical challenges. We have successfully established a local network of neurosurgeons providing routine access to vital human neocortical tissue resected during brain surgery. We have begun a program with the goal of cellular level dissection of the human neocortical circuit based on systematic analysis of intrinsic and synaptic properties, cellular morphology, and transcriptomics. In the course of this work we have observed that acute human brain slices prepared from neurosurgical specimens exhibit a remarkable viability that greatly exceeds the viability of rodent brain slices. This observation led us to establish a platform for human ex vivo brain slice culture and to explore rapid virus-mediated gene transfer into human neurons. With this approach we have achieved high density viral transgene expression in excitatory and inhibitory neuron populations. This has enabled targeted patch clamp recording of transgene expressing neurons for measurement of intrinsic and synaptic properties, as well as precise manipulation of neuron firing with light using Channelrhodopsin2. The feasibility we have demonstrated opens up many new avenues for applying modern molecular genetic tools to study the functional architecture of the human brain. We now describe progress in our efforts to achieve cell type specificity by restricting virus-mediated transgene expression to genetically defined neuronal populations. We hope to harness our emerging transcriptomic and epigenetic data to guide the rational design of novel vectors. Progress in this area is essential to gain access to the many diverse cell types of the human neocortex, an obligate step towards more precise cellular and circuit level investigations, as is currently possible in model organisms like rodent, fish, fly, and worm. Furthermore, the development of novel cell type-specific viral vectors will enable more rapid progress in a wide range of research areas, from human gene therapy for brain disorders to the functional manipulation and dissection of the neural circuitry basis of behavior in non-human primates.

Disclosures: **J.T. Ting:** None. **P. Chong:** None. **R. Gwinn:** None. **C. Cobbs:** None. **J.G. Ojemann:** None. **A. Ko:** None. **C.D. Keene:** None. **C. Koch:** None. **E. Lein:** None.

Poster

847. Genetic Techniques

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 847.23/MMM42

Topic: I.01. Molecular, Biochemical, and Genetic Techniques

Title: *In vivo* genome editing for single-cell labeling of endogenous proteins in the mammalian brain

Authors: *J. NISHIYAMA[1], T. MIKUNI[1], Y. SUN[1,2], N. KAMASAWA[1], R. YASUDA[1]; [1]Max Planck Florida Inst. For Neurosci., Jupiter, FL; [2]Integrative Program in Biol. and Neurosci., Florida Atlantic Univ., Jupiter, FL

Abstract: Imaging of endogenous proteins in single cells is essential for a better understanding of molecular processes in the brain. Inserting a tag sequence to a gene of interest by in vivo single-cell genome editing would allow a rapid, specific and sparse labeling of the endogenous proteins in the brain. However, targeted insertion of a sequence by genome editing has been a challenge in the brain due to the lack of homologous recombination activity in postmitotic neurons and the inefficient delivery of genome editing machinery into the brain. We recently succeeded in developing a technique based on in vivo genome editing to image endogenous proteins in single cells in the brain (Mikuni, Nishiyama et al., Cell, in press). The technique, termed SLENDR (single-cell labeling of endogenous proteins by CRISPR-Cas9-mediated homology-directed repair), allows inserting a tag sequence to a gene of interest by CRISPR-Cas9-mediated homology-directed repair (HDR). Single-cell, HDR-mediated genome editing was achieved by delivering the genome editing machinery to dividing neuronal progenitors in the embryonic mice brain through in utero electroporation. In this presentation, we show that SLENDR is a rapid, precise and effective technique to image endogenous proteins in brain tissue. In addition, we show that SLENDR can be used for simultaneous labeling of different proteins in single cells or for mosaic analysis by combining with CRISPR-mediated single-cell knockout. Furthermore, SLENDR is capable of inserting a long sequence such as that encoding mEGFP and thereby enables live imaging of endogenous proteins during biological processes in the brain tissue. Thus, SLENDR provides a versatile tool for assessing endogenous proteins in the brain.

Disclosures: J. Nishiyama: None. **T. Mikuni:** None. **Y. Sun:** None. **N. Kamasawa:** None. **R. Yasuda:** None.

Poster

847. Genetic Techniques

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 847.24/MMM43

Topic: I.01. Molecular, Biochemical, and Genetic Techniques

Title: Generation of transgenic mice with tightly regulated expression for cell type-specific studies

Authors: *T. L. DAIGLE[1], L. MADISEN[2], U. KNOBLICH[2], M. M. TAKENO[2], B. R. LEE[2], H. GU[1], M. MILLS[1], L. GRAY[1], J. T. TING[2], N. MACARICO DA COSTA[2], B. TASIC[1], H. ZENG[2];
[1]Mol. Genet., Allen Inst. For Brain Sci., Seattle, WA; [2]Allen Inst. for Brain Sci., Seattle, WA

Abstract: Modern genetic approaches have allowed for unprecedented access to diverse types of neurons within the mammalian brain and have greatly facilitated the study of their function. In parallel, the development of highly sensitive molecular sensors and optical tools has enabled the labeling of diverse cell types, the perturbation of neuronal activity with precise temporal control, and the visualization of distinct neural states. Over the last several years, we have developed multiple transgene expression platforms in mice using various molecular genetic approaches that achieve high levels of fluorescent proteins, sensors, and optogenetic tools within selective cell populations, defined largely by unique Cre driver lines. Here we report our newly developed Cre- and tTA-dependent reporter lines that were generated using our previously published strategy (Madisen L et al., Neuron, 2015), in which select transgenes are incorporated into the genomic locus known as TIGRE. We have also developed a new molecular strategy to create the next generation of reporter lines which builds upon the existing approach yet offers several key advantages such as a more simplified breeding strategy, robust transgene expression within different interneuron populations, and potentially greater genetic control. Anatomical and functional data for two of these next generation TIGRE reporter lines will be presented and the lines currently under development will be described. These novel transgenic lines will greatly expand the repertoire of high-precision genetic tools available to effectively identify, monitor, and manipulate distinct cell types within the mammalian brain.

Disclosures: **T.L. Daigle:** None. **L. Madisen:** None. **U. Knoblich:** None. **M.M. Takeno:** None. **B.R. Lee:** None. **H. Gu:** None. **M. Mills:** None. **L. Gray:** None. **J.T. Ting:** None. **N. Macarico da Costa:** None. **B. Tasic:** None. **H. Zeng:** None.

Poster

847. Genetic Techniques

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 847.25/MMM44

Topic: I.01. Molecular, Biochemical, and Genetic Techniques

Support: P50 MH096890

R01MH106056

Title: Exploring the 3D landscape of chromatin across neural differentiation

Authors: *P. RAJARAJAN[1], W. LIAO[2], S. E. GIL[3], N. ABE[2], S.-M. HO[4], J. TCW[4], K. BRENNAND[4], S. AKBARIAN[4];
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Abstract: Background: The human genome has traditionally been studied as a linear entity, ignoring how three-dimensional looping interactions that bring together distal non-coding regulatory elements and proximal promoters may modulate gene expression. Even with innovations in chromosome conformation capture techniques, the 3D neuroepigenome remains largely underexplored. Exploration of cell-type-specific chromosomal conformations will advance insight into hitherto unknown roles of non-coding sequences in the neurobiology of depression, schizophrenia, and other psychiatric disorders.
Methods: Genome-scale "agnostic" 3D genome mapping was done by *in situ* Hi-C on human induced pluripotent stem cell (iPSC)-derived neural progenitor cells (NPCs) and differentiated cell types, including Ngn2-induced glutamatergic neurons and astrocytes. *In situ* Hi-C involves a restriction-religation assay of fixed chromatin in intact nuclei, creating "chimeric" fragments, which were further analyzed by deep sequencing with >200M reads per libraries. Additional in situ Hi-C libraries were generated from FACS-sorted neuronal and non-neuronal nuclei of the human anterior cingulate cortex.
Results: Comparing an experimental sample to one that lacked the crucial ligation step, we show a drastically reduced number of chimeric reads and a contact-depleted map in the negative control. Contact domains (chromosomal portions with enriched interactions inside respective boundaries) in active (i.e., open) compartments versus inactive (i.e., closed) compartments showed strong evidence for cell-type specific regulation. However, domain boundaries remain largely fixed across cell types. Using the program diffHiC, we are currently exploring neuron-specific domains common to cultured neurons and neuronal nuclei extracted from postmortem brain.

Disclosures: P. Rajarajan: None. **W. Liao:** None. **S.E. Gil:** None. **N. Abe:** None. **S. Ho:** None. **J. Tcw:** None. **K. Brennand:** None. **S. Akbarian:** None.

Poster

847. Genetic Techniques

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 847.26/MMM45

Topic: I.01. Molecular, Biochemical, and Genetic Techniques

Support: Swedish Brain Foundation Research Fellowship (A.T.S.)

NIH Training Grant T32 GM007507 and NSF Graduate Research Fellowship DGE-1256259 (R.F.)

NIH Grant MH093412 (S.F.M)

NIH grants MH067774 and NS063245 (J.Y.)

the John Merck Scholar Program (Y.L.)

NIH MH091220 (Y.L.)

NIH NS088421 (Y.L.)

Title: A robust activity marking system for exploring active neuronal ensembles

Authors: ***Y. LIN**[1], A. SORENSEN[1], Y. COOPER[1], M. BARATTA[2], F.-J. WENG[1], Y. ZHANG[1], M. HEMBERG[3], R. FROPF[4], J. YIN[4], S. MAIER[2];
[1]MIT, Cambridge, MA; [2]Univ. of Colorado, Boulder, CO; [3]Wellcome Trust Sanger Inst., Cambridge, United Kingdom; [4]Univ. of Wisconsin-Madison, Madison, WI

Abstract: Understanding how the brain captures transient sensory experience and converts it into long lasting changes in neural circuits depends on the identification and investigation of the specific ensembles of neurons that are responsible for the encoding of each experience. We have developed a Robust Activity Marking (RAM) system that allows for the identification and interrogation of ensembles of neurons. The RAM system provides unprecedentedly high sensitivity and selectivity by the use of an optimized synthetic activity-regulated promoter that is strongly activated by neuronal activity and a modified Tet-Off system that achieves improved temporal control. Due to its compact design, RAM can be packaged into a single adeno-associated virus (AAV), providing great versatility and ease of use, including application to species other than the mouse. Cre-dependent RAM, CRAM, enables studying active ensembles of a specific cell type and anatomical connectivity, further expanding the versatility of the RAM system.

Disclosures: **Y. Lin:** None. **A. Sorensen:** None. **Y. Cooper:** None. **M. Baratta:** None. **F. Weng:** None. **Y. Zhang:** None. **M. Hemberg:** None. **R. Fropf:** None. **J. Yin:** None. **S. Maier:** None.

Poster

847. Genetic Techniques

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 847.27/MMM46

Topic: I.01. Molecular, Biochemical, and Genetic Techniques

Support: NIH Grant R01MH080047

NIH Grant DP1NS096787

HFSP Long-Term Fellowship LT000974/2014

Title: Scalable, high-resolution mapping of subcellular localization of endogenous proteins in the mammalian brain by SLENDR

Authors: *T. MIKUNI[1], J. NISHIYAMA[1], Y. SUN[1,2], N. KAMASAWA[1], R. YASUDA[1]; [1]Max Planck Florida Inst., Jupiter, FL; [2]Integrative Program in Biol. and Neurosci., Florida Atlantic Univ., Jupiter, FL

Abstract: A simple, rapid and generalizable method for mapping precise subcellular localization of endogenous proteins is essential for comprehensive understanding of a cell at the molecular level. Recently, we have developed SLENDR (single-cell labeling of endogenous proteins by CRISPR-Cas9-mediated homology-directed repair), which is based on *in vivo* genome editing to insert a short epitope or a fluorescent protein tag into a gene of interest in the mammalian brain (Mikuni, Nishiyama et al., *Cell*, 2016). Direct, single-cell genome editing enables rapid, specific and sparse labeling of the gene product. In this presentation, we show that SLENDR allows rapid determination of the subcellular localization of many endogenous proteins in various cell types, regions and ages in the brain. Furthermore, SLENDR can be easily applied to electron microscopic imaging for nanometer-resolution mapping of protein localization. Therefore, SLENDR provides a high-throughput platform to define the subcellular localization of endogenous proteins with the resolution of micro- to nanometers and thus may revolutionize the method for cellular and molecular neuroscience.

Disclosures: **T. Mikuni:** None. **J. Nishiyama:** None. **Y. Sun:** None. **N. Kamasawa:** None. **R. Yasuda:** None.

Poster

847. Genetic Techniques

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 847.28/MMM47

Topic: I.01. Molecular, Biochemical, and Genetic Techniques

Title: Molecular identification of active neurons defined by FOS expression or phosphorylation of ERK1/2

Authors: *D. LEIB, Z. A. KNIGHT;
UCSF, San Francisco, CA

Abstract: A central goal in neuroscience research is to uncover the organization of the neural circuits that control specific behaviors and physiological processes. For decades, neuroscientists have visualized populations of neurons linked to specific functions by staining for markers of neural activity, such as FOS expression and phosphorylation of ERK1/2, in response to experimental stimuli. However, the techniques have been lacking to identify molecular markers for these neurons that would permit genetic dissection of the associated neural circuits. Here we describe two new mouse genetic tools to profile gene expression of neurons defined by expression of FOS or phosphorylation of ERK1/2. In the first tool, an HA-tagged FOS fusion protein expressed from the endogenous *Fos* promoter dimerizes with the ribosome via the GFP/GFP-nanobody interaction, allowing for ribosome capture from FOS-expressing neurons by HA immunoprecipitation. In the second tool, direct fusion of ERK2 to the ribosome allows for capture of ribosomes based on phosphorylation of ERK1/2 by phospho-specific immunoprecipitation. In both cases, we then analyze mRNA associated with the captured ribosomes by qPCR or next generation sequencing to identify genes enriched in the neurons activated by the experimental stimulus. We have validated these tools by histology and immunoprecipitation from the mouse brain and find that we can reliably identify markers for known neural cell types activated by well characterized stimuli. Drawing on the vast published literature using FOS and phospho-ERK as histological markers for different stimuli, these tools will be easily applicable to determine the molecular identities of neural cell types involved with motivated behaviors, sensory and motor systems, psychiatric disease, and many other areas of ongoing research in neuroscience.

Disclosures: D. Leib: None. **Z.A. Knight:** None.

Poster

847. Genetic Techniques

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 847.29/MMM48

Topic: I.01. Molecular, Biochemical, and Genetic Techniques

Support: the Strategic Research Program for Brain, Japan

Title: Investigation of the gene-modification efficiency of CRISPR/Cas9 in the common marmoset

Authors: *W. KUMITA[1], K. SATO[1], E. SASAKI[1,2,3];
[1]Dept. of Applied Developmental Biol., Central Inst. For Exptl. Animals, Kawasaki-Shi, Japan; [2]Keio Univ., Shinjuku-Ku, Japan; [3]RIKEN, Wako-Shi, Japan

Abstract: Genetically modified non-human primates offer valuable models for understanding the brain's high cognitive function. Among several genetically modified models, embryonic-stem-cell-based target-gene knock out (KO)/in (KI) models are the most used models in mice. Although embryonic stem cells and induced pluripotent stem cells of the common marmoset (*Callithrix jacchus*) have been reported, these stem cells cannot be used to produce chimeric animals. This phenomenon occurs in many species and prevents the production of target gene KI and KO animals, with the exception of rodents. However, the recent development of innovative genome-editing technologies has helped to resolve this issue and will facilitate production of target-gene-modified animals of various species. We have successfully generated target-gene-KO marmoset using zinc-finger nucleases and transcription-activator-like- effector nucleases (TALENs). However, for genome editing in marmoset embryos, the effectiveness of the most recently developed genome-editing technology—clustered regularly interspaced short palindromic repeats (CRISPR)/CRISPR-associated (Cas) —in the production of target-gene-KO/KI animals has not been investigated extensively. The optimization of CRISPR/Cas9 for marmoset embryos was investigated in this study. To determine the optimum conditions, CRISPR/Cas9 targeted to the marmoset *c-kit* gene was injected into marmoset embryos. The concentration ranges of single-guide RNA mRNA and Cas9 mRNA were 5 to 100 ng/μl and 20 to 180 ng/μl, respectively. The concentration of single-guide RNA/humanized Cas9 mRNA was determined as 50 /100 ng/μl. Next, two humanized Cas9 mRNAs were injected into marmoset embryos. These showed different efficacies; one exhibited better cleavage activity and had little effect on embryo development. Furthermore, Cas9 nuclease was injected into marmoset embryos and its efficacy was compared with that of Cas9 mRNA. These results suggest that CRISPR/Cas9 is effective for genome editing in marmoset embryos. This finding will facilitate efficient production of KO and KI marmosets.

Disclosures: **W. Kumita:** A. Employment/Salary (full or part-time): Central Institute of Experimental Animals. **K. Sato:** A. Employment/Salary (full or part-time): Central Institute of Experimental Animals. **E. Sasaki:** None.

Poster

847. Genetic Techniques

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 847.30/MMM49

Topic: G.07. Other Psychiatric Disorders

Support: U54HG006332

Title: Integrated analysis of the Jackson Laboratory knockout mouse project 2 (KOMP2) data

Authors: ***V. KUMAR**[1], D. LEE[2], V. PHILIP[3], J. CLARK[3], K. SVENSON[3], S. RIZZO[3], R. E. BRAUN[3], E. J. CHESLER[3];
[1]Neurosci., Jackson Lab., Bar Harbor, ME; [2]Jackson Lab., Farmington, CT; [3]Jackson Lab., Bar Harbor, ME

Abstract: The Knockout Mouse Project at The Jackson Laboratory has characterized over 300 mouse knockout lines in 28 assays including 10 behavioral and 18 metabolic/physiology assays. This public dataset represents one of the largest using a classical rapid test battery approach. Here we present a comprehensive analysis of this data. We have statistically modeled the environmental and genetic contributions to phenotype variation using multiple statistical approaches. By modeling environmental variables captured in individual test metadata fields, we are able to increase the sensitivity and precision with which mutants can be detected. By modeling across behavioral, metabolic and physiological phenotypes we provide a rich phenotypic resource for the mouse genetics community. This data will be of interest to neuroscience community looking for novel models of mental illness. In addition this data allows correlations across behavioral traits and metabolism/physiology.

Disclosures: **V. Kumar:** None. **D. Lee:** None. **V. Philip:** None. **J. Clark:** None. **K. Svenson:** None. **S. Rizzo:** None. **R.E. Braun:** None. **E.J. Chesler:** None.

Poster

848. Electrode Arrays II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 848.01/MMM50

Topic: I.04. Physiological Methods

Support: DARPA HAPTIX

NSF IGERT

Title: Viability of a novel micro-electrocorticography electrode array design for intrasulcal implantation in macaca mulatta primary somatosensory cortex

Authors: *T. N. HEARN[1], J. C. TANNER[1], J. LACHAPELLE[2], J. BURNS, IV[2], J. GRAINGER[2], E. KEEFER[3], J. CHENG[3], S. HELMS TILLERY[1];
[1]Sch. of Biol. and Hlth. Systems Engin., Arizona State Univ., Tempe, AZ; [2]Draper, Cambridge, MA; [3]Nerves Inc., Dallas, TX

Abstract: The utility of micro-electrocorticography (μECoG) for recording neural activity is clear, but the rigid structure of traditional μECoG arrays has precluded access to cortical regions of the brain lying within sulci. The goal of this study was to design a μECoG array that could record from area 3b within the central sulcus of a *Macaca mulatta*.
Each array consisted of 16 polydimethylsiloxane electrodes with a nylon-like polymer overmold. Contact sites were 150 μm in diameter, arranged in a 4x8 pattern (eight contacts per 1 mm "finger"), and separated by 750 μm (center-to-center on a single "finger"). Arrays were implanted into two *Macaca mulatta* subjects. Arrays were cut into 4, 8x1 "fingers" to avoid vasculature traversing the central sulcus to minimize damage while maximizing insertion depth. Neural recordings were performed using a Ripple Grapevine Neural Interface System and custom MATLAB software. A custom vibration generator controlled by MATLAB provided vibratory stimulation. Somatosensory evoked potentials were elicited by stimulating the skin with an A-M Systems Isolated Pulse Generator. Post mortem, tissue surrounding the implant site was excised and examined for neuroimmune response to the implant.
Surgical implantation of the novel arrays proved to be no more difficult or time-consuming than those of the traditional μECoG design. The arrays provided stable, long-term neural recordings of activity from area 3b. While vibratory stimulation did not consistently elicit correlated neural activity, electrical stimulation did. We are awaiting the results of the post-mortem histological analysis.
Based on the results from electrical and mechanical stimulation, the novel μECoG array design was able to successfully resolve neural signals. Vibratory stimulation may not have elicited consistent neural activity due to unavoidable damage inherent to the implantation of the device into the sulcus. Histological analysis is expected to confirm neuronal damage in the more-apical

layers of the cortex due to separation of the pre- and postcentral gyri. While this surgery may prove to be damaging for this method of recording from within sulci, the novel electrode design may be applicable to other areas of the cortex where custom, irregular array geometries are desired.

Disclosures: **T.N. Hearn:** None. **J.C. Tanner:** None. **J. Lachapelle:** None. **J. Burns:** None. **J. Grainger:** None. **E. Keefer:** None. **J. Cheng:** None. **S. Helms Tillery:** None.

Poster

848. Electrode Arrays II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 848.02/MMM51

Topic: I.04. Physiological Methods

Support: R44 AA020676 to DJW.

Title: A new rotating tethered system with multiple, electrical, optical and fluid connections for many-channel electrical and chemical recording in behaving rodents.

Authors: *D. J. WOODWARD[1], J. CHANG[2];
[1]Neurosci. Res. Inst. of North Carolina, Winston Salem, NC; [2]Biographics Inc., Winston Salem, NC

Abstract: A goal to advance high throughput behavioral neurophysiology is to create new instrumentation that will allow high numbers of electrical, optical, and fluid connections to the CNS of animals during complex sensory, motor, and cognitive tasks. With freely behaving rodents an impediment has been the need to include multichannel swivels that allow a large number of separate rotating connections of all types. So far multimode swivels have not been constructed to allow such connections and to permit long duration recording and electrical and optical stimulation over many days. This project describes progress toward a new system with components to overcome multiple limitations of conventional swivels. A central new feature is a motor driven rotating platform, triggered by animal movement, located above the rodent that supports a small computer with a multifunction FPGA system including arrays of preamp/AD/DACs, multiple lasers or small fluid pumps, etc. Ring/brush sets provide power and an Ethernet link. A multifunction tethered connection system maintains continuous connections to the components above for many days. Novel electronics can potentially support continuous analog recording from up to 1000 neurons and/or 100 chemical fast scan carbon sensors when probes become available. Far larger configurations are possible. A novel real time software state machine coordinates many cpus on the network to achieve logic and timing control of behavioral

in multiple chambers, stimulus presentation and data acquisition. Initial applications include recording simultaneous EEG and oxygen transients during seizures, dopamine transients during tic movement, and long duration monitoring of water, 10% sucrose and/or ethanol intake from lick or nose poke/tone-activated fluid at spouts.

Disclosures: D.J. Woodward: E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); DJW owns IP, Biographics Inc. **J. Chang:** A. Employment/Salary (full or part-time): full, Biographics Inc.

Poster

848. Electrode Arrays II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 848.03/MMM52

Topic: I.04. Physiological Methods

Support: Simula-UCSD-University of Oslo Research and PhD training (SUURPh) funded by the Norwegian Ministry of Education and Research

Title: Spatial pattern optimization for neural stimulation with high-density multi-electrode arrays

Authors: *A. P. BUCCINO[1], G. CAUWENBERGHS[2], P. D. HÄFLIGER[1];
[1]Informatics, Univ. of Oslo, Oslo, Norway; [2]Bioengineering, Univ. of California San Diego, San Diego, CA

Abstract: Multi-Electrode Arrays (MEAs) have become one of the most promising tools for intracortical electrophysiology. In a recent prototype (Schröder et al. 2015) a matrix of CMOS-based MEA with 15 μm spacing allowed high-density (HD) imaging of Local Field Potentials *in-vivo*. Another advance is represented by the integration of recording and stimulation systems in implantable devices capable of performing closed-loop experiments based on real-time recordings. A successful example of such devices is ENIAC (Ha et al. 2015), which allows simultaneous recording and stimulation from the surface of the cortex. The effort in integrating stimulation capabilities on intracortical HD MEA will soon allow recording and stimulation with an electrode density down to tens of μm. While on the recording side, model-based techniques showed the possibility of triangulating the soma position of hundreds of neurons around the MEA *in-vivo* (Ruz et al. 2014) and of reconstructing the axonal arbor from HD *in-vitro* recordings (Müller et al. 2015), the exploitation of such HD devices for stimulation is still lacking, most likely because the technologies are still under development.
Here we developed a computational framework for the optimization of the spatial pattern of a square MEA. We assumed that the positions of the neurons' soma and directions of the axon

hillocks are available. Each neuron is modeled as a segment starting from the soma in the direction of the axon hillock. The modeling of neural excitation follows the cable equation, which predicts that for short pulses (hundreds of μs), the induction of a spike on a cylindrical axon is governed by the second derivative of the external potential along the axon, i.e. activation function (AF). MEA's electrodes are modeled as monopolar current sources with 15 μm pitch. Optimization of the spatial patterns is performed with genetic algorithms, which sort through viable solutions that excite a target neuron (AF above an activation threshold) and lightly hyperpolarize surrounding neurons (AF below a non-activation threshold), favoring solutions that maximize sparsity while limiting current values between ±50 μA in 5 μA steps. The results indicate that stimulation can be extremely selective. Two neurons whose soma is only 5 μm apart can be selectively stimulated when the axon hillock direction diverges more than 30°. Even when a target neuron is between two surrounding neurons 5 μm apart with 30° misalignment, it can be consistently excited while leaving the other neurons lightly hyperpolarized. Spatial pattern optimization for HD MEAs could yield precise *in-vivo* stimulation, allowing to target single neurons from extra-cellular probes.

Disclosures: **A.P. Buccino:** None. **G. Cauwenberghs:** None. **P.D. Häfliger:** None.

Poster

848. Electrode Arrays II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 848.04/MMM53

Topic: I.04. Physiological Methods

Support: NSF Award CCF-1422914

DARPA Award HR0011-14-C-0102

ARO Award W911NF-14-1-0173

Hirschl/Weill-Caulier Career Award

Sloan Research Fellowship

NYU Grand Challenge Award

NYU Postdoctoral and Transition Program for Academic Diversity Fellowship

Title: Multimodal validation of signal stability from chronically implanted micro-electrocorticographic arrays

Authors: *M. TRUMPIS[1], M. INSANALLY[2], C.-H. CHIANG[1], C. WANG[1], J. KING[2], R. C. FROEMKE[2], J. VIVENTI[1];
[1]Biomed. Engin., Duke Univ., Durham, NC; [2]Skirball Inst., Neurosci. Inst., Depts of Otolaryngology, Neurosci., and Physiol., New York Univ. Sch. of Med., New York, NY

Abstract: μECoG arrays are flexible microelectrodes that sense electrical potential fields from the surface of the brain at sampling distances of 10s-100s of microns. Recent and ongoing efforts will scale such surface arrays to incorporate 100s-1000s of channels while maintaining a minimally invasive form factor.
Investigating the lifetime recording ability of implanted μECoG arrays is complicated by the spatially distributed and state-dependent nature of the field potential in awake animals. In the present study, we developed multiple complementary metrics quantifying the spatial, temporal, and informative value of the μECoG signal. These metrics have been used to validate long-term recordings from a flexible-PCB electrode (Insanally, et al. 2016) and are presently being used to evaluate novel electrode designs.
The statistical divergence of evoked activity from background activity was measured using the Mahalanobis distance. The magnitude of this divergence defined an evoked-signal to noise ratio with a median value between 6.7-9.6 dB for acute preparations. Evoked-SNR was tracked over the lifetime of implants to ensure responses were significantly divergent with respect to baseline. Evoked-SNR averaged 1.1 dB across ten weeks of awake recordings.
The specificity of signals from multiple sites was inferred by modeling the spatial covariance of the potential field. The Matérn class of covariance function was fit to empirical spatial variograms by optimizing length-constant and process-regularity parameters. In a constrained model describing exponential decay of covariance, we found the length constant varied between 8-16 mm in a stable implant. The exponential length constant was also an effective indicator of electrode malfunction in another implant.
Stimulus decoding was used as an inclusive test of an array's sensitivity and specificity for distinct neural circuits. A linear classification scheme was used to predict tone pitch based on 50 ms of neural activity sampled over auditory cortex. The average prediction error in octaves was between 0.11-0.65 for various acute preparations. Prediction error was monitored during an implant's lifetime as the ultimate indicator recording utility. Implanted arrays were considered non-functional when the decoding error was consistent with uniform choice.
Due to the lack of action potentials in the typical μECoG signal, it is challenging to consistently evaluate the quality of recording from a μECoG array. The metrics presented here provide comprehensive feedback regarding recording quality over the implant lifetime and demonstrate the electrode's potential utility in neurophysiology studies.

Disclosures: **M. Trumpis:** None. **M. Insanally:** None. **C. Chiang:** None. **C. Wang:** None. **J. King:** None. **R.C. Froemke:** None. **J. Viventi:** None.

Poster

848. Electrode Arrays II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 848.05/MMM54

Topic: I.04. Physiological Methods

Support: NIH Grant U01NS090454

Title: Self-splaying silicon carbide electrode assemblies for stable recording and stimulation.

Authors: *Y. COHEN[1], B. PEARRE[1], J. SHEN[1], D. SEMU[1], F. DEKU[2], A. JOSHI-IMRE[2], S. F. COGAN[2], T. GARDNER[1];
[1]Biol., Boston Univ., Boston, MA; [2]Bioengineering, Univ. of Texas, Dallas, TX

Abstract: Single cells' action potentials are studied in relation to many cognitive functions. These 'neural correlates', in the form of firing rates, are measured with satisfactory precision in short recordings, lasting seconds to minutes. However, most biologically interesting processes occur in time scales of hours, days, and years. Furthermore, the study of neural correlates, or neural coding, in populations of cells requires sampling from the network activity state-space, whose size scales exponentially with the number of neurons and necessitates long recordings in order to be faithfully covered. Yet, stably recording from a population of neurons is limited by the ability to track single units and by the brain's reaction to the perturbing foreign object, leading to signal loss and reduced stimulation capabilities. Our recently developed carbon fiber ultramicroelectrodes (UME, Guitchounts et al, 2013), with <10um diameter, showed promising signal stability and reduction in immune response (see also Kozai et al, Nat. Materials 2012 and Patel et al, J. Neur. Eng. 2015) but their manual assembly process prevented design flexibility and scaling. Here we report the first in-vivo acute, and preliminary chronic, recording using novel self-splaying amorphous silicon carbide (a-SiC) electrode arrays. These UME are fabricated by depositing a thin film of biologically compatible a-SiC to encapsulate gold or platinum electrodes, creating shanks with 12um x 4um cross section exposed at the tip (Deku et al, in prep.). To test tissue response and recording and stimulation stability, we implanted 16 and 32-channel SIROF deposited a-SiC assemblies into various zebra finch song nuclei. We characterize the electrodes' capability to self-splay in the paths of minimal resistance and present preliminary histology results. We also quantified in-vivo electrochemical performance of these implants with impedance spectroscopy and cyclic voltammetry, in order to characterize the electrodes' capabilities in recording electric signals and in injecting stimulating currents over time. We believe that the design flexibility, scalability, and utility of these splaying electrodes surpass current standards of chronic electrophysiology, and open possibilities to study questions that are currently unaddressable.

Disclosures: **Y. Cohen:** None. **B. Pearre:** None. **J. Shen:** None. **D. Semu:** None. **F. Deku:** None. **A. Joshi-Imre:** None. **S.F. Cogan:** None. **T. Gardner:** None.

Poster

848. Electrode Arrays II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 848.06/MMM55

Topic: I.04. Physiological Methods

Support: NIH Grant 5R21NS084492

Title: Autonomous microelectrodes for intracellular neural recording

Authors: ***S. SAMPATH KUMAR**[1], M. S. BAKER[2], M. OKANDAN[2], J. MUTHUSWAMY[1]; [1]Arizona State Univ., Tempe, AZ; [2]Sandia Natl. Labs., Albuquerque, NM

Abstract: Technologies available to obtain intracellular neural recordings have three major limitations: 1) they are large and require cumbersome positioning systems for navigating their tips to targeted neurons; 2) their use requires extraordinary skill and training; 3) the size and weight of the system allows recording only from one neuron or a few neurons that belong to different neural circuits at a time. Our MEMS based, robotic intracellular recording system has 3 main features: 1) polysilicon microelectrodes integrated with glass micropipettes to impale neurons and record intracellular activity; 2) electrothermal microactuators to enable microscale navigation in brain and precise positioning of microelectrode inside neuron; 3) closed loop control algorithm to enable autonomous isolation and penetration of neurons. Previously, we had shown the ability of our microelectrodes to record intracellularly and validated the performance of our controller with conventional microelectrodes. Here, we demonstrate the ability of our MEMS system to autonomously isolate, penetrate and record from single neurons in abdominal ganglion of Aplysia Californica. The system was able to autonomously penetrate and obtain good quality recordings in n = 15 attempts in the Aplysia ganglion. Resting membrane potentials of -40 mV and action potentials of 60-70 mV were recorded in every attempt. Further, we also tested the ability of our glass-tipped polysilicon microelectrodes to record intracellularly from single neurons in-vivo. Our microelectrodes recorded good quality resting membrane potentials of 55-60 mV and action potentials of 80 mV from neurons in the rodent brain cortex. This system allows for significant reduction in form factor, autonomous isolation of neurons and an easily scalable approach to realize multi- channel intracellular recording systems. Further, it provides a mechanism to repeatedly seek new neurons in a circuit in the event of loss of intracellular signals.

Disclosures: **S. Sampath Kumar:** None. **M.S. Baker:** None. **M. Okandan:** None. **J. Muthuswamy:** None.

Poster

848. Electrode Arrays II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 848.07/MMM56

Topic: I.04. Physiological Methods

Support: NIH-1R01EB019804

Title: A multi-target 3D printed microdrive for simultaneous single-unit recordings in freely behaving rats

Authors: ***M. W. BILLARD**[1,2], F. BAHARI[1,2], C. TULYAGANOVA[1,2], K. D. ALLOWAY[1,3], B. J. GLUCKMAN[1,2,4,5];
[1]Ctr. for Neural Engin., [2]Engin. Sci. and Mechanics, Penn State, University Park, PA; [3]Neural and Behavioral Sci., [4]Neurosurg., Penn State, Hershey, PA; [5]Biomed. Engin., Penn State, University Park, PA

Abstract: Single-unit recordings for systems neuroscience approaches requires targeting neuronal
populations in multiple diverse brain structures. In many cases these cell groups are small and significantly separated, and thus reaching them requires high precision along different trajectories.
Here we present a 3D printed microdrive system which adapts existing drive technologies [Voigts,
2013] in combination with novel surgical techniques that leverages standard stereotaxic placement
but decouples the targeting from the placement of the drive mechanism. The body of the microdrive utilizes an open stadium structure that provides room for multi-site targeting of individually drivable microwire bundles as well as connections for other physiological measurements. The microwire bundles are integrated into a system of tight fitting tube-cannula combinations. The cannulas are implanted individually to provide stereotaxic alignment of trajectory with a set positioning and depth from the target. The tubes are fitted into the cannulas when the drive structure is secured to the animal's head. Our current design allows for ten drive positions with 3 mm drive stroke for each bundle. The bundles are distributed to upwards of three
distinct implant targets. Additionally, the design allows for up to 32 electrophysiological channel

connections, and is being tested for continuous recordings in freely behaving rats. A fully loaded microdrive with an electrode interface board together weigh less than 3 g; a complete system that includes an Intan amplifier board and animal head mount weigh approximately 11 g. This design is readily scalable to higher channel, drive, and target count. Currently, the microdrive is being used to study sleep-wake regulatory dynamics and to test the validity of existing mathematical models of the sleep-wake system [Sedigh-Sarvestani, 2012].
Voigts J et al. 2013. *Front. Syst. Neurosci*. 7:8. doi: 10.3389/fnsys.2013.00008
Sedigh-Sarvestani, M, et al. 2012. *PLoS Comput Biol*, *8*(11), e1002788.

Disclosures: M.W. Billard: None. **F. Bahari:** None. **C. Tulyaganova:** None. **K.D. Alloway:** None. **B.J. Gluckman:** None.

Poster

848. Electrode Arrays II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 848.08/MMM57

Topic: I.04. Physiological Methods

Support: This work was supported by an HFSP grant (RGP 00048/2013), an NIH BRAIN initiative grant (1U01NS094248-01), the Francis Crick Institute, and the Medical Research Council (MC_UP_1202/5).

Title: jULIEs - juxtaneuronal ultra-low impedance electrodes: nanostructured neural probes for highly-localized and minimally invasive extracellular recordings in the olfactory bulb

Authors: *R. R. RÁCZ, M. KÖLLő, W. WRAY, A. SCHAEFER;
Neurophysiol. of Behaviour, The Francis Crick Inst. - Mill Hill Lab., London, United Kingdom

Abstract: Highly orchestrated electrical and electrochemical events at cellular, tissue and neural systems level result in the behavior of the individual. Technical challenges in neural probe size, recording capability, lateral site density, channel count, and commercial availability have limited our understanding of brain function. To overcome these challenges, here, we introduce a modular, flexible, insulated metal microwire platform with ultra-low impedance recording sites compatible with standard read-out electronics.
At the center of this approach are glass-ensheathed microwires cast using the Taylor-Ulitovsky method with an outer diameter of 27µm ± 2µm and inner diameters of 1µm ± 0.2µm, resulting in minimal stray capacitance (<0.1 pF/mm length). These wires have been semi-automatically polished at an angle of <30° to facilitate brain insertion. Interfacial impedance was reduced by potentiostatic modification of the recording sites with nanostructured gold and subsequent

iridium oxide (IrOx) electrodeposition. Bundles containing 16 individual microwires have been assembled into Mill-Max connectors through a low-ohmic connection (100Ω±2Ω). Advantages of juxtaneuronal ultra-low impedance electrodes ("jULIEs") are their recording sites which are up to 50x smaller than in conventional electrodes ($1.3\mu m^2 \pm 0.05\mu m^2$) resulting in reduced tissue displacement and damage as well as in highly localized, high signal-to-noise recordings.
To test jULIEs we performed recordings in the olfactory bulb (OB) of anaesthetized mice (4-6 weeks old, Ketamine/Xylazine anesthesia) using a Tucker Davis RZ2 BioAmp with a PZ2 pre-amp and RA16AC-Z headstage. Extracellular spikes were reliably recorded with amplitudes of up to 1.6 mV. Conventional silicon probes result in tissue damage such as local vasculature damage as assessed by tail-vein injection of a fluorescent dye (Evans Blue) and post mortem imaging of the blood brain barrier (BBB) leakage around the penetration channel. In contrast, generally no detectable BBB leakage was observed with jULIE wire insertion. Consistent with this, when jULIEs were lowered several mm into the brain and returned to a superficial recording position, extracellular units were reliably recorded throughout the OB. Due to the small size of the recording site and minimal damage to the tissue, jULIEs were found to be exceptionally suited for recording large amplitude (500-1500 μV), well isolated signals from the close vicinity of neurons (20-30 μm).
Thus, the combination of insulated metal wires with nanostructured surface modifications provides a versatile platform for minimally invasive, highly localized neural recordings.

Disclosures: **R.R. Rácz:** None. **M. Köllő:** None. **W. Wray:** None. **A. Schaefer:** None.

Poster

848. Electrode Arrays II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 848.09/MMM58

Topic: I.04. Physiological Methods

Support: 101590/Z/13/Z

100154/Z/12/Z

Gatsby Charitable Foundation Grant

Title: Large-scale single unit activity recorded with high-density silicon probes in the hippocampus of freely behaving animals

Authors: **M. BAUZA**[1], J. KRUPIC[1], *S. BURTON[1], J. O'KEEFE[1], T. HARRIS[2];
[1]Univ. Col. London, London, United Kingdom; [2]HHMI Janelia Res. Ctr., Ashburn, VA

Abstract: Many brain processes depend on the collaborative activity of large numbers of single neurons. Optical imaging allows the recording of hundreds of neurons at the same time; however it works best in superficial layers of head fixed animals. Here we present data from a new generation of high-density silicon multi-electrode array (SMART probe) in which neural activity from up to 384 closely located contacts could be recorded simultaneously from freely-moving rats. Up to a hundred cells from CA1 and CA3 regions of the hippocampus were simultaneously recorded for more than 30 days including some which were reliably tracked over several weeks despite electrode drift.

Disclosures: **M. Bauza:** None. **J. Krupic:** None. **S. Burton:** None. **J. O'Keefe:** None. **T. Harris:** None.

Poster

848. Electrode Arrays II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 848.10/MMM59

Topic: I.04. Physiological Methods

Support: NIH Grant 1U18EB021760

Title: High-density extracellular recording from the buccal ganglia of *Aplysia* californica using a novel thin-film electrode array

Authors: Z. J. SPERRY[1,2], H. J. CHIEL[5,6,7], J. P. SEYMOUR[3,4], H. LU[5], C. E. KEHL[5], K. NA[3,4], E. YOON[3,4,1], *T. M. BRUNS[1,2];
[1]Biomed. Engin., [2]Biointerfaces Inst., [3]Electrical Engin. and Computer Sci., [4]Lurie Nanofabrication Facility, Univ. of Michigan, Ann Arbor, MI; [5]Biol., [6]Neurosciences, [7]Biomed. Engin., Case Western Reserve Univ., Cleveland, OH

Abstract: The ganglia of *Aplysia californica* are important models for study of neural physiology, especially in the fields of learning and memory. In order to better understand the neural networks underlying *Aplysia*'s function, it would be useful to record single-unit activity from many cell bodies simultaneously. Although it is possible to record multiple units simultaneously in *Aplysia* using voltage-sensitive dyes or rigid microelectrode arrays, the ability to record using a flexible array would allow recordings in semi-intact preparations and intact animals. As part of a project to optimize interfacing with vertebrate dorsal root ganglia, we have developed a flexible thin-film electrode array to provide a close fit to the surface of neural tissue. We propose that this array could also be used to record from *Aplysia* ganglia and have undertaken experiments to evaluate this approach. The 64-channel electrode array was

microfabricated on a 3.6 μm flexible polyimide substrate. Iridium electrode sites (410 sq. μm) have varying pitch (25-150 μm), with impedances of 530 ± 98 kΩ at 1 kHz. For neural recording, the buccal ganglia of *Aplysia* was resected and pinned in agar and immersed in isotonic saline. Buccal nerve 2 (BN2) was pulled into an Ag-AgCl suction electrode for electrical stimulation to induce a fictive feedling-like motor pattern in the ganglion. The thin-film array was pressed onto a hemiganglia. After 2 Hz stimulation, single-unit activity was observed on channels in contact with the ganglia, with at least 11 unique units. The mean signal-to-noise ratio of these signals, calculated as peak to peak amplitude over three times the noise standard deviation, was 2.5 with a maximum of 6.5. A variety of activity types were observed from multiple different cells, ranging in frequency from 1-4Hz. Some single units were observed simultaneously on closely spaced channels (25 μm pitch), with differing amplitudes depending on proximity to the firing cell. Analyses are underway to estimate distances from these closely-spaced electrode sites to neuron sources. These results demonstrate the utility of the thin-film array for recording extracellularly from many neurons simultaneously in the *Aplysia* ganglia and suggest that it may be a useful tool for spatial mapping of neural activity. Furthermore, this *Aplysia* testing provides us with an additional testbed towards our ultimate goal of an improved vertebrate dorsal root ganglia interface.

Disclosures: **Z.J. Sperry:** None. **H.J. Chiel:** None. **J.P. Seymour:** None. **H. Lu:** None. **C.E. Kehl:** None. **K. Na:** None. **E. Yoon:** None. **T.M. Bruns:** None.

Poster

848. Electrode Arrays II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 848.11/MMM60

Topic: D.08. Visual Sensory-motor Processing

Support: Focused Ultrasound Foundation

NIH R24 MH109105

NIH P30-EY08126

U54-HD083211

F32 EY023922

Robin and Richard Patton through the E. Bronson Ingram Chair of Neuroscience

Title: Focused ultrasound over frontal eye field of macaque monkeys: Modulation of visual search performance and EEG index of attention

Authors: *W. ZINKE[1], J. D. COSMAN[2], J. D. SHUMAN[3], J. D. SCHALL[2], C. F. CASKEY[3]; [1]Dept. of Psychology, [2]Dept Psychol, [3]Inst. Imaging Sci., Vanderbilt Univ., Nashville, TN

Abstract: Focused ultrasound (FUS) is a non-invasive, spatially precise method of neuromodulation. A previous study showed that low-intensity FUS over frontal eye field (FEF) influenced anti-saccade response times (Deffieux et al. 2013 Curr Biol). Here, FUS stimulation was applied through a craniotomy over FEF of two macaque monkeys (M. radiata) during simultaneous recording of cranial EEG over visual cortex while monkeys performed a T/L search task by shifting gaze to a target item. We alternated blocks of trials with or without FUS stimulation (300 ms of pulsed FUS starting 150 ms before search display onset, center frequency 500 kHz, repetition frequency 2 kHz, pulse duration 0.25 ms, peak negative pressures of 250 kPa or 425 kPa, warming of brain tissue < 1.5°C). In both monkeys, FUS stimulation at 250 and 425 kPa produced a marked attenuation of the N2pc index of attentional selection at electrode sites contralateral to FUS stimulation. Interestingly, this effect was not modulated by FUS trial-by-trial but instead through a sustained decrease in N2pc amplitude throughout the session. The monkey with the more dorsal craniotomy but not the monkey with the more ventral craniotomy showed a significant slowing of saccadic response times when the target was located in the upper visual hemifield contralateral to the FUS stimulation at 425 kPa. These findings demonstrate dose-dependent, spatially specific modulation of inter-areal circuit function and behavior by FUS, engendering more confidence in the feasibility of using FUS for experimental and therapeutic purposes.

Disclosures: W. Zinke: None. **J.D. Cosman:** None. **J.D. Shuman:** None. **J.D. Schall:** None. **C.F. Caskey:** None.

Poster

848. Electrode Arrays II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 848.12/MMM61

Topic: I.04. Physiological Methods

Support: DARPA Grant N66001-11-1-4010

NIH Grant R24NS086603

NIH Grant R01DC014044

Title: 3D tissue reconstruction provides accurate neuronal quantification near chronically-implanted hybrid microelectrode array

Authors: *M. HAN, H. DUONG;
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Abstract: Chronically-implanted microelectrode arrays are being investigated for restoring impaired sensory or motor functions in individuals suffering from a variety of neurological dysfunction. The long-term performance of these devices is largely dependent on chronic tissue response and the health of neurons proximal to the electrode-tissue interface for both long-term recording of neuronal activity and microstimulation. Assessment of neuronal viability at the interface region is commonly performed from histologically-processed tissue slices and corresponding two dimensional (2D) image analyses. In an effort to better visualize and more accurately quantify the tissue-electrode interface, we developed a method of combining three dimensional (3D) volumetric reconstruction of 2D confocal images with quantification methods measuring the distance between neurons and electrode surface. We analyzed cortical neurons near chronically-implanted microelectrode tips implanted in the cat cerebral cortex. A hybrid array containing Utah Intracortical arrays and microwire electrodes was used. We compared neuronal counting with distance segmentation in conventional single-slice counting and 3D volumetric counting. Results showed that, independent of device type, the average number of neurons counted in 2D was far fewer than those counted by 3D volume method. The disparity suggested that a significant percentage of neurons below the tip would not be counted without 3D volume reconstruction which is critical for functionality of recording and stimulating microelectrodes.

Disclosures: **M. Han:** None. **H. Duong:** None.

Poster

848. Electrode Arrays II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 848.13/MMM62

Topic: I.04. Physiological Methods

Title: A open-source system and interface standards for very high data rate neurophysiology and low latency closed-loop experiments

Authors: *J. VOIGTS[1], A. CUEVAS LOPEZ[2], J. P. NEWMAN[1], J. H. SIEGLE[3], G. C. LOPES[4], S. L. MONDRAGON[5], Y. A. PATEL[6], E. BURGUIÈRE[5], C. KEMERE[7], C. I. MOORE[8], A. S. WIDGE[9], A. KAMPFF[4], J. VIVENTI[10], M. WILSON[1];

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Abstract: Neuroscience is increasingly moving towards large numbers of simultaneously recorded neurons, via large multi-wire bundles, novel (CMOS) silicon probes, or optical methods. Simultaneously, testing increasingly specific hypotheses about neural computation will require closed-loop experiments that can react to neural activity on fast timescales. While many existing systems can cope with high data rates or low latencies, it is still technically challenging to develop and perform such experiments, and few standards exist that ensure interoperability of hardware and software components and that would allow researchers to share methods and replicate experiments. Existing systems capable of real-time feedback with sub-millisecond latency either do not scale well with channel count or are hardware specific and therefore not interoperable across preparations. We address these needs with set of standards for data acquisition and feedback methods, and have developed a working prototype system that implements many of these interfaces. The key specifications of the standard are full use of the PCIe bus which enables streaming and recording of over 1000 channels of electrophysiology, high speed microscopy, or similar data. The use of a standard PC platform and a DMA interface for low-latency data access by user-space programs gives researchers the ability to use high-level languages and libraries to unlock GPU, FPGA, or DSP co-processing to deliver computationally intensive closed-loop feedback with less than 1ms round-trip latency. The system is designed to be low-cost, extremely modular, and customizable. All interfaces are designed to adhere to existing and flexible standards, including a cross-platform API, a PCIe DMA interface, the use of commodity FPGA evaluation boards and industry standard connectors, external breakout board connectors, headstage connectors etc. Using these standards, we developed a prototype system using existing headstages based on neural amplifier chips from Intan Technologies, and plugins for the Open Ephys and Bonsai software packages. We hope this standard will provide a starting point for the development of other hardware and software components for data acquisition and online feedback algorithms that can be easily shared across many different types of experiments. Development of the standard, prototype hardware, host API, and software plugins has occurred completely in the open and has already benefited from input from a large number of neuroscientists. We encourage all members of the community to contribute to this projects development in order to ensure its general utility for many different research questions.

Disclosures: J. Voigts: None. **A. Cuevas Lopez:** None. **J.P. Newman:** None. **J.H. Siegle:** None. **G.C. Lopes:** None. **S.L. Mondragon:** None. **Y.A. Patel:** None. **E. Burguière:** None. **C. Kemere:** None. **C.I. Moore:** None. **A.S. Widge:** None. **A. Kampff:** None. **J. Viventi:** None. **M. Wilson:** None.

Poster

848. Electrode Arrays II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 848.14/NNN1

Topic: I.04. Physiological Methods

Support: NSF-CBET

Title: An all-carbon-based, transparent, flexible micro-electrocorticography device for large scale optical and electrical access to brain circuits

Authors: *J. LEE[1], N. DRISCOLL[1], I. OZDEN[1], Z. YU[1], A. KASKELA[2], E. KAUPPINEN[2], A. NURMIKKO[1];
[1]Sch. of Engin., Brown Univ., Providence, RI; [2]Dept. of Applied Physics, Aalto Univ., Aalto, Finland

Abstract: The range of neuroscience problems benefiting from optogenetic techniques is still partly limited by the capabilities of existing optoelectronic devices. For example, the ability to obtain electrophysiological recordings with simultaneous patterned optogenetic stimulation with high spatial and temporal resolution over large areas of the cortex has been a challenge. Here, we report a high-density carbon-nanotube-based transparent and flexible micro-electrocorticography (μECoG) array which allows optical and electrophysiological access to brain circuits over large areas of the cortex. The μECoG array demonstrated here employs a new class of aerosol synthesized flexible, stretchable, high-density single-walled carbon nanotube (HD-SWCNT) thin films which have demonstrated superior optoelectrical performance compared to that of conventional CNT- and indium tin oxide-based transparent conducting films. The HD-SWCNT films are optically highly transparent (> 90%) throughout the visible and near infrared spectra, enabling both optical stimulation and imaging of the cortex through the device. While the fabrication techniques we developed are scalable to arrays with hundreds of elements, here we introduce a 30 (5x6) element transparent microelectrode prototype arrays based on HD-SWCNT films formed through a simple yet powerful laser micro-patterning and transfer technique within a parylene-C insulation layer. The exposed electrodes are 100 μm in diameter (400 μm pitch), with an impedance of ~100 kΩ at 1 kHz. The μECoG device is 20 μm in its total thickness and exhibits optical transparency of greater than 70% in the visible spectrum. The thin and highly flexible nature of the device gives it the ability to achieve highly conformal contact with the surface of the brain as well as the potential to be folded and inserted into sulci, an area that has previously been very difficult to access for artifact-free electrophysiological recordings.The optical and electrical performance of our μECoG device was demonstrated in vivo in a transgenic mouse model (Thy1-ChR2-YFP). The transparent μECoG electrode array was placed over the parietal lobe and a laser beam (500 ms pulse duration, 473 nm, 70 μW) was focused

through the device to an area of cortex 100 μm in diameter. The device recorded optically-evoked neural activity without any observable light-induced artifacts, even when the stimulation was centered over the HD-SWCNT electrodes. We suggest that the SWCNT-based μECoG platform presents yet another alternative for the multimodal optical and electrical interrogation of cortical dynamics with capabilities that go beyond the currently available technologies.

Disclosures: **J. Lee:** None. **N. Driscoll:** None. **I. Ozden:** None. **Z. Yu:** None. **A. Kaskela:** None. **E. Kauppinen:** None. **A. Nurmikko:** None.

Poster

848. Electrode Arrays II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 848.15/NNN2

Topic: I.04. Physiological Methods

Support: Brain/MINDS from AMED, JAPAN

Title: Long-term implantable interface of high flexible multi-channel electrodes monitoring with wireless recording system

Authors: ***T. ARAKI**[1], F. YOSHIDA[2], S. YOSHIMOTO[1], T. UEMURA[1], T. KAIJYU[3], T. SUZUKI[3], M. HIRATA[2], T. SEKITANI[1];
[1]The Inst. of Scientific and Industrial Res., [2]Div. of Clin. Neuroengineering, Global Ctr. for Med. Engin. and Informatics, Osaka Univ., Osaka, Japan; [3]Ctr. for Information and Neural Networks, Natl. Inst. of Information and Communications Tec, Osaka, Japan

Abstract: Traditional biosensors have been fabricated with rigid materials, which Young's modulus values are MPa~GPa order and higher than biological body. That rigidness causes inflammation and damage to the cells, tissues, and organs [1,2]. In order to achieve less invasiveness and long lasting therapeutic benefits, soft materials such as thin polymers, rubbers, and gels can be applied. Recently, we developed silver nanowires-based electrodes , which have high aspect ratio, and also show excellence in optical transparency (~94%), electrical conductivity (~24 ohm/sheet), and mechanical stretchability (25% strain~) [3,4]. Here, we introduce silver nanowires-based multi-channel electrodes which successfully used to record electrocorticography (ECoG) with wireless recording system. We modified patterned 16 channels electrodes of silver nanowires on the 1 micron thickness parylene with biocompatible materials in order to achieve high electrical stability. After depositing encapsulation layer of total 3 micron thickness of parylene and making through-hall, the size of each electrode was ca. 150 micron meter square. To improve ease of handling, the sheet electrodes were coated with a

polymer which becomes hard at room temperature but soft near animal body temperature. With these developed sheet electrodes, rat brain activity was successfully monitored with wireless recording system. These neural signals was recorded until 7 weeks after implantation. The improved silver nanowires electrode has a feature of high biological compatibility and potential for long-term implantable passive sensor, realizing high spatial mapping of brain functions. Reference [1] I. R. Minev et al., Science, 347, 159, 2015. [2] S. Lee et al., Nature Comm., 5, 5898, 2014 [3] T. Araki et al., Nano Research, 7, 236, 2014. [4] Y. Yang et al., Nano Research, in press.

Disclosures: **T. Araki:** A. Employment/Salary (full or part-time): Osaka University. **F. Yoshida:** None. **S. Yoshimoto:** None. **T. Uemura:** None. **T. Kaijyu:** None. **T. Suzuki:** None. **M. Hirata:** None. **T. Sekitani:** None.

Poster

848. Electrode Arrays II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 848.16/NNN3

Topic: I.04. Physiological Methods

Title: Exploiting high content datasets recorded with high density Multi Electrode Array to investigate compounds functional effects with LTP protocols in cortico-hippocampal brain slices

Authors: *A. MACCIONE[1], S. ZORDAN[1], A. UGOLINI[2], C. VIRGINIO[2], M. CORSI[2], D. LONARDONI[1], M. GANDOLFO[3], L. BERDONDINI[1];
[1]Inst. Italiano Di Tecnologia, Genova, Italy; [2]Aptuit Ctr. for Drug Discovery & Development, Drug Design & Discovery, Verona, Italy; [3]3Brain GmbH, Wädenswil, Switzerland

Abstract: Brain slices are a widely used biological model in pharmacology to study the pathophysiology of brain diseases and for compound testing, in the pre-clinical study of the effects of drugs or neurotoxic compounds. High-resolution CMOS Multi Electrode Array devices (CMOS-MEA, 4096 electrodes, 42 um pitch, 7kHz/channel) allow to sense electrophysiological activity from thousands of sites, thus allowing to study the physiology of large neuronal assembly with an unprecedented level of details. As demonstrated in previously works [Ferrea et al. 2012], on brain slices these devices enable to perform functional electrophysiological imaging on large fields of view of several square millimetres at unprecedented resolution and allow to characterize both spontaneous or evoked spiking activity and LFPs in multiple and connected brain circuits. Here, we show how this capability can be exploited to develop targeted applications for preclinical in vitro screenings. The platform was used to perform Long Term Potentiation (LTP) protocols on cortico-hippocampal rat brain slices by inducing synaptic

facilitation in CA3-CA1 circuit. Computational tools developed in Python were developed for pre-processing the large datasets (>tens of GBytes), including filters and Local Field Potential detectors, as needed to reduce the dimensionality of the datasets and to optimize the computational performances. Furthermore, the software was optimized with real-time analysis routines for on-line monitoring of the experimental progress. Experiments were conducted under control conditions (no compounds) and by adding AP5 (50 μM) to validate the capabilities of detecting LTP alterations induced by compounds. Then, the platform has been used to assess the effect of d-Cycloserine (DCS, 100 μM) a potential candidate for alleviating the symptoms of schizophrenia. In addition to provide high statistically significant read-outs resulting from the large number of recording electrodes, we observed that DCS is able to induce a spatially heterogeneous effect on LTP. In particular, DCS showed an increased LTP in the CA1 area close to the stimulating electrode with respect to control slices, while it induced an opposite behaviour (i.e. a decreased LTP) in distal regions. Overall, our results show that CMOS-MEA based in-vitro screening can be a valuable tool for pre-clinical read-outs.

Disclosures: **A. Maccione:** None. **S. Zordan:** None. **A. Ugolini:** A. Employment/Salary (full or part-time): Aptuit. **C. Virginio:** A. Employment/Salary (full or part-time): Aptuit. **M. Corsi:** A. Employment/Salary (full or part-time): Aptuit. **D. Lonardoni:** None. **M. Gandolfo:** A. Employment/Salary (full or part-time): 3Brain GmbH. **L. Berdondini:** None.

Poster

848. Electrode Arrays II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 848.17/NNN4

Topic: I.04. Physiological Methods

Support: NIH Grant R03 NS095202-01

Title: Electrode materials affect the network formation and electrophysiological development of interfaced cortical neurons

Authors: C. H. THOMPSON[1], W. A. KHAN[2], W. LI[2], *E. K. PURCELL[3];
[1]Biomed. Engin., [2]Electrical and Computer Engin., [3]Michigan State Univ., East Lansing, MI

Abstract: The use of microelectrode arrays implanted into the brain has experienced rapid growth for both clinical and research applications. Understanding how neurons develop and react to specific biomaterial substrates used in the construction of these devices can inform the development of new and improved neural interfaces. This study observes the effects that different biomaterial substrates have on the maturation of embryonic rat primary cortical neurons

in regard to network formation and electrophysiological development. The materials chosen for this study are commercially available plastic cell culture coverslips ("control"), Indium Tin Oxide (ITO), Parylene-C, Silicon, Silicon Dioxide, and Polydimethylsiloxane (PDMS). Embryonic primary cortical neuron cultures were seeded on sterile biomaterials and evaluated at specific time points of 7, 14, and 21 days to monitor the development of network formation. Primary neurons were fixed at specific time points and stained for pre-synaptic and post-synaptic markers. Live neurons were evaluated at the same time points for responsiveness to stimulation using the whole cell configuration of a patch clamp electrophysiology set-up. Images of the fixed neurons were acquired using confocal microscopy and instances of co-localized synaptic puncta were quantified using ImageJ analysis software. The quantitative data suggest that cultured primary cortical neurons show preference to a particular material, ITO, in regard to neuron health, neurite outgrowth, and network formation. Likewise, early qualitative observations suggest a positive influence on the excitability of cells attached to this substrate. While the mechanism is currently unclear and data collection is on-going, these effects are hypothesized to be related to the conductivity and/or stiffness of the material substrate.

Disclosures: C.H. Thompson: None. **W.A. Khan:** None. **W. Li:** None. **E.K. Purcell:** None.

Poster

848. Electrode Arrays II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 848.18/NNN5

Topic: I.04. Physiological Methods

Support: NIH (NINDS) 2R01NS030853

The Ronald D. Deffenbaugh Family Foundation

DOD (CDMRP) W81XWH-10-1-0742

Title: Assessing the validity of extracellular recordings and variability of spike-triggered stimulation experiments

Authors: *E. RODRIGUEZ MANYARI[1,2], D. J. GUGGENMOS[3], G. VAN ACKER III[4], R. J. NUDO[2,3];
[1]Electrical Engin. and Computer Sci., Univ. of Kansas, Lawrence, KS; [2]Landon Ctr. on Aging, [3]Physical Med. and Rehabil., Univ. of Kansas Med. Ctr., Kansas City, KS; [4]Physical Med. and Rehabil., MetroHealth Systems, Cleveland, OH

Abstract: There is a demand for ever-increasing chronic electrode channel counts for neural recordings to enable a greater understanding of brain dynamics *in vivo*. The electrodes typically employed for extracellular recording consist of rigid substrates, which can induce a response within the brain tissue to encapsulate invasive foreign elements, causing individual or multiple channels to become compromised or unusable. As channel counts increase, it becomes unwieldy to manually assess the quality of neural recordings and subsequently detect and characterize neural activity across electrodes. This necessitates a way to validate and quantify the reliability of available extracellular signals and then perform accurate spike detection. Assurance of accurate and reliable recording data becomes essential in closed-loop architectures such as Activity Dependent Stimulation (ADS) experiments, where individual neuron activity is employed to trigger stimulation pulses. In current ADS paradigms, a trigger neuron is chosen through visual inspection and is thus subject to bias and experiment-to-experiment variability. In this study, we independently evaluated previous ADS recordings and developed performance metrics to find possibly damaged channels and to characterize single unit and multiunit neural activity. To compute the quality of the recordings across multiple sites, we examined the spatial information, and signal-to-noise ratio (SNR) metrics based on amplitude and power, taking into account the point process nature of spike trains and electrode geometry. Spike detection and sorting was performed with commonly employed online methods: median thresholding, k-means clustering, and corroborated with Fisher's Linear Discriminant Analysis. Identification of unitary events allowed us to quantify the variability of outcomes for "spike triggered" experiments or experiments based on single unit activity; e.g. stimulation rate in the case of ADS. We evaluated the local variation of inter-event intervals to observe the intrinsic dynamics of individual neurons as well as the network dynamics collected by the electrode array. Based on this metric, clusters of recorded neurons were identified and individual units were sorted according to their intrinsic similarity as possible trigger events. We propose a cost function to rank individual site performance and identify and sort single units as optimal trigger channels for ADS experiments. Our metric facilitates an acceptable assessment of signal quality and the unbiased selection of trigger neurons. Automation of these processes should optimize similar experiments and increase experimental reproducibility.

Disclosures: E. Rodriguez Manyari: None. **D.J. Guggenmos:** None. **G. Van Acker III:** None. **R.J. Nudo:** None.

Poster

848. Electrode Arrays II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 848.19/NNN6

Topic: I.04. Physiological Methods

Support: 1 R43 MH110287-01

Title: Recording and visualizing activity from thousands of single neurons.

Authors: *M. R. ANGLE[1], E. HUBER[1], D. POUZZNER[1], C. LAREAU, 95112[1], M. KOLLO[2]; [1]Paradromics, San Jose, CA; [2]The Francis Crick Inst., London, United Kingdom

Abstract: Here we describe a neural recording system that is capable of capturing over 300,000 independent channels sampled at 1.6 kHz, 30,000 channels at 16 kHz, or 10,000 channels at 32 kHz. The system is capable of continuous, multi-hour, lossless streaming to disk as well as real-time data processing for visualization. Using the browser-based GUI, researchers can monitor experiments from any web-connected computer in real time.
Hardware: our recording system is based on an off-the-shelf high speed image sensor with compact and purpose-built backing electronics. The image sensor is bonded to a bundle of 10,000-100,000 microwires, each of which is approximately 20 μm in diameter. The microwire electrodes detect extracellular potentials, which are amplified by the image sensor electronics and ingested by a framegrabber mounted in a commodity PC running our custom acquisition software.
Software: the Paradromics Input and Analysis ("PIA") suite provides a pipeline for acquiring neural data and processing the data in real time either conventionally on the CPU, or using GPU acceleration (CUDA). PIA is written in C, runs on Linux, and easily handles the present recording system's 1 GB/s workload on a 6-core Intel i7-5820K accessing a 7-HDD RAID array. At a low level, PIA achieves this performance by using a combination of core pinning, deep FIFOs in locked memory, realtime priority threads, lock-free central data structures, and lightweight and fine-grained locks when needed. At a higher level, PIA adopts a supervised multi-process model to achieve fault tolerance and recovery. Any number of concurrent users can access a web interface served by PIA, which allows control of acquisition parameters, and independently adjustable previewing of the data as it is being captured. The web interface uses WebSocket technology and WebGL to provide GPU-accelerated live visualizations of any number of recording channels.
Results: Here we show that the Paradromics neural recording system (Model P-1) can acquire and visualize simultaneous single unit recordings from thousands of independent channels.

Disclosures: **M.R. Angle:** A. Employment/Salary (full or part-time): Paradromics Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Paradromics Inc. **E. Huber:** A. Employment/Salary (full or part-time): Paradromics Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Paradromics Inc. **D. Pouzzner:** A. Employment/Salary (full or part-time): Paradromics Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Paradromics Inc. **C. LaReau:** A. Employment/Salary (full or part-time): Paradromics Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Paradromics Inc.. **M. Kollo:** None.

Poster

848. Electrode Arrays II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 848.20/NNN7

Topic: I.04. Physiological Methods

Support: UCSD Center for Brain Activity Mapping

UC MRPI

Title: Resonant inductive power harvesting in a mm-sized neural implant for brain activity mapping.

Authors: C. KIM, *G. CAUWENBERGHS;
Dept. of Bioengineering, UCSD, La Jolla, CA

Abstract: The Brain Research through Advancing Innovative Neurotechnologies (BRAIN) Initiative aims at accelerating our understanding of human brain function by developing technologies to register simultaneous activity over large numbers of neurons across the brain. We envision a minimally invasive means towards high-resolution mapping of electrocorticography (ECoG) activity spanning the human brain through distributing large numbers of wireless neural interface integrated circuits (ICs) across the cortical surface. To this end we developed a 3mm x 3mm sized fully integrated neural recording and stimulating IC with radio-frequency (RF) inductive power and data telemetry. In this talk I will present the on-chip fully integrated resonant regulating rectifier (IR3) for inductive power telemetry. Implemented in 180nm silicon-on-insulator (SOI) complementary metal-oxide semiconductor (CMOS), the IR3 circuit regulates a 0.1mW load from a 144MHz RF input at greater than 92% voltage conversion efficiency, and occupies just 0.078mm2 of silicon active area.

Disclosures: C. Kim: B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution; UCSD Center for Brain Activity Mapping, UC MRPI. **G. Cauwenberghs:** B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution; UCSD Center for Brain Activity Mapping, UC MRPI.

Poster

848. Electrode Arrays II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 848.21/NNN8

Topic: I.04. Physiological Methods

Support: NIH Grant 5R21NS084492

Title: Investigating neuronal cell types in the rat barrel cortex using a tunable microelectrode array

Authors: *V. VOZIYANOV, A. SRIDHARAN, S. PALANISWAMY, S. SAMPATH KUMAR, J. MUTHUSWAMY;
Bioengineering, Arizona State Univ., Tempe, AZ

Abstract: Here we report single and multi-unit responses to whisker stimulation in different layers of the whisker barrel cortex using a tunable microelectrode array. More specifically, we examined the response of different cell types within the different layers of the whisker barrel cortex in response to whisker stimulation. We used a movable microelectrode array, which consisted of microscale actuators and movable electrodes, to target and record from the individual neurons in anesthetized rats. Electronically activated microscale actuators enable reliable bidirectional displacement of microelectrodes in steps of 6.5 μm - a resolution being small enough to be able to target individual neurons. Furthermore, being able to move each electrode several millimeters independently allowed us to optimally position the microelectrodes for recording single neurons that specifically respond to whisker stimulation. Being able to individually move the electrodes also allowed us to simultaneously record neuronal responses across different cortical layers. Data from in vivo recordings in the barrel cortex will be presented.

Disclosures: V. Voziyanov: None. **A. Sridharan:** None. **S. Palaniswamy:** None. **S. Sampath Kumar:** None. **J. Muthuswamy:** None.

Poster

848. Electrode Arrays II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 848.22/NNN9

Topic: I.04. Physiological Methods

Support: DARPA N66001-09-C-2080

Title: Optimizing biomorphic microelectrode arrays for electrophysiological and neurochemical recordings

Authors: *P. HUETTL[1], A. LEDO[2], C. LOURENÇO[2], F. POMERLEAU[1], R. E. HAMPSON[3], S. A. DEADWYLER[3], J. LARANJINHA[2], R. BARBOSA[2], G. A. GERHARDT[1];
[1]Dept Anat & Neurobiol, Univ. Kentucky, Lexington, KY; [2]Univ. of Coimbra, Coimbra, Portugal; [3]Wake Forest Univ., Winston Salem, NC

Abstract: Our novel ceramic-based microelectrode arrays (MEA) have proven versatile and robust for in vivo recordings. Research using MEAs in electrophysiological recordings have contributed to our understanding and decryption of some memory patterns and their transfer to untrained, naïve animals. Neurochemical recordings combined with MEAs have proven to be an excellent tool to better understand neurotransmission and regulation in Parkinson, TBI, ADHD and epilepsy animal models. Preliminary data support that a polyimide-based MEA should provide improved chronic implantation (multiple weeks) and recording in rats and NHPs. The polyimide biomorphic arrays were fabricated based on data from prior ceramic-based MEAs and multi-wire microelectrode work [Hampson RE, et. al. (2004) PNAS 101, 9 3184-3189; Hascup ER, et. al. (2009) Brain Research, 1291].
Based on recording from in vivo models we have determined and established key criteria that biomorphic polyimide probes should possess: 1) Strong and durable probe that is reliable and long-lived. 2) It should have sufficient rigidity for stability during implantation to provide accuracy for deep brain targeting yet a certain degree of flexibility to limit damage by moving with brain. 3) It must be fabricated using biocompatible materials to reduce gliosis and encapsulation. 4) The desired probe design should be tailored to recording location creating dual-sided biomorphic arrays (bMEA) specific to target sites of interest and allow for self-referencing recordings. 5) A layered polyimide fabrication of the bMEA should also facilitate the incorporation of new components via micromachining to allow for variations in design. 6) An integrated connector to avoid wire bonding is also key in simplifying fabrication.
While the ceramic MEA provides most of these criteria it lacks in flexibility in moving with the brain. We are developing a robust, smaller profile (200 μm wide by 254 μm thick) bMEA designed to be implanted without need of a guide cannula or guide wire. The bMEA with identical recording sites on the front and back of the microelectrode has one side coated with

enzymes for detection of a specific analyte such as glutamate, glucose, lactate and a variety of other molecules, and the reverse side is coated as a control for self-referencing. A front-back design allows for optimum self-referencing subtraction of non-Faradaic background signals, elimination of noise and subtraction of unknown chemical interferents. The bMEA probe fabricated using our established criteria in concert with combined local field potential and electrochemical recordings should prove useful in advancing our understanding of neurotransmission.

Disclosures: **P. Huettl:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Quanteon LLC, BrainChem LLC. F. Consulting Fees (e.g., advisory boards); Quanteon LLC. **A. Ledo:** F. Consulting Fees (e.g., advisory boards); Quanteon LLC. **C. Lourenço:** None. **F. Pomerleau:** F. Consulting Fees (e.g., advisory boards); Quanteon LLC. **R.E. Hampson:** None. **S.A. Deadwyler:** None. **J. Laranjinha:** None. **R. Barbosa:** None. **G.A. Gerhardt:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Quanteon, LLC.

Poster

848. Electrode Arrays II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 848.23/NNN10

Topic: I.04. Physiological Methods

Title: Evaluating high-resolution frequency spectral estimation approaches to real-time frequency modulation neurofeedback

Authors: ***R. J. GOUGELET**[1], A. C. OUYANG[2], R. D. PATEL[8], X. WANG[3], B. VOYTEK[4,5,6,7];
[1]Dept. of Cognitive Sci., Univ. of California San Diego Dept. of Cognitive Sci., La Jolla, CA; [2]Dept. of Computer Sci. and Engin., [3]Dept. of Bioengineering, [4]Neurosciences Grad. Program, [5]Dept. of Cognitive Sci., [6]Inst. for Neural Computation, [7]Inst. for Brain and Mind, UCSD, La Jolla, CA; [8]Dept. of Cognitive Sci., Univ. of California San Diego, La Jolla, CA

Abstract: Traditional electroencephalography (EEG) neurofeedback training focuses on the user's real-time amplitude modulation (AM) of oscillatory sub-bands. This approach is based on ample evidence for the role of AM in cognition and behavior. However, there is mounting evidence for the potential mediation of oscillatory frequency dynamics on human brain function. Unfortunately, these dynamics occur at a frequency and temporal resolution too fine for traditional real-time spectral estimation methods, with a frequency resolution of around 0.02 Hz

and a temporal resolution at less than 100 ms (Samaha, J., Bauer, P., Cimaroli, S., & Postle, B. R. (2015). Top-down control of the phase of alpha-band oscillations as a mechanism for temporal prediction. Proceedings of the National Academy of Sciences of the United States of America, 112(27), 8439-8444.). Instead, traditional EEG spectral estimation methods tend to employ the Fast Fourier Transform (FFT) on seconds-long data windows to derive frequency spectra with resolutions rarely lower than 0.25 or 0.125 Hz. Speculatively, this may account for null findings on frequency dynamics that might have driven the focus on AM-based approaches. Post-hoc analyses benefit from complete datasets employing acausal filters and enough samples for FFT spectral estimation to provide sufficient frequency resolution. Real-time neurofeedback methods, however, are limited by causality and small time windows to provide timely high-resolution frequency dynamics to the user. Here, we examined multiple frequency spectral estimation methods run on simulated EEG data to assess their capacity to detect an FM alpha (8-12 Hz) oscillation embedded in 1/f noise under real-time constraints. These methods include: Welch's method, a median-based Welch's method, phase-locked loops, signal subspace methods such as MUSIC and eSPIRIT, maximum entropy and Burg spectra, and spectral envelope. These methods were implemented in both python and MATLAB. Our results show that maximum entropy and signal subspace methods outperform the other methods in silico, and attained time-frequency resolutions that could make feasible real-time alpha estimation in situ. These results suggest that FM-based neurofeedback training using these methods is plausible, allowing for the study of state- or trait-dependent neurofeedback effects in human subjects and their possible impact on cognition.

Disclosures: **R.J. Gougelet:** A. Employment/Salary (full or part-time): University of California, San Diego. **A.C. Ouyang:** None. **R.D. Patel:** None. **X. Wang:** None. **B. Voytek:** B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution; California Institute for Telecommunications and Information Technology, Strategic Research Opportunities Program, Sloan Research Fellowship.

Poster

848. Electrode Arrays II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 848.24/NNN11

Topic: I.04. Physiological Methods

Support: Internal Research and Development

Title: Utilization of multi-electrode array technology to investigate electrophysiological properties within human cerebral organoids

Authors: *M. E. HESTER;
The Res. Inst. At Nationwide Childrens Hos, Columbus, OH

Abstract: Human cerebral organoids represent a powerful *in vitro* tool to model human cortical development and can be utilized to gain mechanistic insight into brain disorders. These cerebral organoids are generated from pluripotent stem cells (PSCs) and are differentiated towards a neuroectodermal lineage within a spinning bioreactor over the course of several months. Using these conditions, regionalized brain structures form and stratification of cortical layers has been documented, however the functional, electrical properties of discrete structures within cerebral organoids has not been fully investigated using multi-electrode array technology. Here we analyzed the spontaneous electrophysiological properties of cerebral organoids using a planar MEA measurement system. We show multiple cortical regions within cerebral organoids exhibit robust spontaneous activity and can be electrically stimulated to increase the spike activities in neighboring regions. Furthermore, spontaneous bursts were observed in multiple electrodes throughout the cerebral organoid. These results show that multi-electrode array technology has the powerful potential of evaluating the effects of genetic and pharmacological manipulation and also for dissecting the functional properties of neural circuits within cerebral organoids.

Disclosures: M.E. Hester: None.

Poster

848. Electrode Arrays II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 848.25/NNN12

Topic: D.08. Visual Sensory-motor Processing

Support: Human Frontier Sciences Program Postdoctoral Fellowship to NAS

Marie Curie Postdoctoral Fellowship to NAS

Wellcome Trust 100154

Wellcome Trust 095669

Wellcome Trust 095668

Title: Recording large, distributed neuronal populations with next-generation electrode arrays in behaving mice

Authors: *N. A. STEINMETZ[1], M. PACHITARIU[1], C. P. BURGESS[1], C. ROSSANT[1], T. HARRIS[2], M. CARANDINI[1], K. D. HARRIS[1];
[1]Univ. Col. London, London, United Kingdom; [2]Janelia Res. Campus, Ashburn, VA

Abstract: To understand behavior and cognition, we require the ability to monitor the activity of large neuronal populations across multiple brain regions with millisecond temporal precision. The next-generation "Neuropixels" electrode arrays promise to deliver this ability, by recording from 384 high-density recording sites with low noise, on-probe amplification and digitization, and a small, lightweight package. Here we demonstrate the use of multiple Neuropixels arrays to record simultaneously from hundreds of neurons distributed across the brain of mice that perform a visual discrimination task.
We trained mice on a three-alternative visual discrimination task (Burgess et al., bioRxiv, 2016) and we used one or two "Neuropixels" electrode arrays to record simultaneously from multiple brain regions. In the task, mice viewed gratings of varying contrast located on the left and/or right of the screen. Mice earned a water reward by selecting the correct response by turning a wheel: turn left or right if the grating on the left or right had the higher contrast respectively, or refrain from turning if no grating was shown.
The arrays delivered high-quality data from multiple brain regions simultaneously, including motor and sensory neocortex, hippocampus, thalamus, and striatum. The size of the data produced presents a challenge to traditional spike sorting methods; by using new tools (the spike-sorting algorithm Kilosort and graphical interface phy), we were able to process the resulting data quickly and accurately, revealing the spike times of hundreds of well-isolated neurons. These data allowed us to quantify the task responsiveness of neurons across brain regions, showing a diversity of responses to task sensory and motor components.
These results illustrate the power of high-count electrode technologies to radically advance our measurement of brain activity, allowing multiple-region recordings of hundreds to thousands of neurons with single-neuron resolution and millisecond temporal precision.

Disclosures: **N.A. Steinmetz:** None. **M. Pachitariu:** None. **C.P. Burgess:** None. **C. Rossant:** None. **T. Harris:** None. **M. Carandini:** None. **K.D. Harris:** None.

Poster

849. Models of Excitability: Networks and Single Neurons II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 849.01/NNN13

Topic: I.06. Computation, Modeling, and Simulation

Support: JSPS Grants-in-Aid KAKENHI 16H03162 and 16K12870

JSPS Grant-in-Aid for JSPS Fellows 26-8435

Title: Developing an *In vitro* system for investigating neuronal linear system identification

Authors: *T. ISOMURA[1], T. TOYOIZUMI[3], K. KOTANI[2], Y. JIMBO[1];
[2]Res. Ctr. for Advanced Sci. and Technol., [1]The Univ. of Tokyo, Tokyo, Japan; [3]RIKEN Brain Sci. Inst., Saitama, Japan

Abstract: It is a mystery how people perceive the dynamics of the external world. One hypothesis is that people reconstruct in their brains the model of the external world generating sensory inputs -- the so-called internal model hypothesis. This hypothesis implies that such function is phenomenologically explained using machine-learning-like algorithms. However, it remains unclear whether and how living neural networks implement algorithms to identify dynamical systems. We previously showed that even cultured neural networks perform blind source separation (BSS) of mixed inputs, which is one of the requirements of linear system identification. Here, based on that result, we develop an in vitro system to investigate whether cultured neural networks can identify and reconstruct a linear system that generates inputs. Rat cortical cells were dissociated and cultured on microelectrode arrays (MEAs) that have 8×8 microelectrodes embedded in the bottom of the dishes. Electrical stimulations and recordings were performed using a custom MEA system. We designed a generative model that consists of two hidden sources and an infinite impulse response (IIR) filter. The sources were independent of each other and had no time correlation. The IIR filter is a composite of a convolution with an exponential filter and a spatial mixing matrix. Mixed inputs generated by the model were induced into cultured neural networks as sequential stimulations (100 ms interval, 25.6 s duration) of electrical pulses (1 V amplitude, 0.2 ms duration, biphasic). We first demonstrated that when inputs were not mixed but had time correlation, the neural responses corresponding to electrodes included in the most likely subsequent pattern increased after training. The result indicates that cultured neural networks can perform inference that is consistent with the maximum a posteriori (MAP) estimation of the input sequence. Then, we induced inputs with spatial mixing and time correlation into the networks and observed the neural response transitions during training, suggesting the occurrence of activity-dependent plasticity. Considering the previous results of neuronal BSS, these results suggest that this in vitro system will be a useful tool to examine whether cultured neural networks can simultaneously perform BSS of spatial mixing and the MAP-like estimation of the input sequence, both of which are requirements of neuronal linear system identification.

Disclosures: **T. Isomura:** None. **T. Toyoizumi:** None. **K. Kotani:** None. **Y. Jimbo:** None.

Poster

849. Models of Excitability: Networks and Single Neurons II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 849.02/NNN14

Topic: I.06. Computation, Modeling, and Simulation

Support: PAIFAC

Title: Neural networks closure

Authors: *J.-C. LETELIER[1], C. MAUREIRA[2];
[1]Univ. of Chile, Santiago, Chile; [2]Biol., Univ. de Chile, Santiago, Chile

Abstract: Since the work of Wilson, Cowan and Amari in the 70s it has been common to write equations describing the dynamics of neural activity in neural laminae as a a integro-differential equation. During the 80s and 90s this viewpoint was a peripheral member of all the work involved in theoretical/mathematical neuroscience. Since a decade ago this viewpoint, termed under the intriguing title of NEURAL FIELD EQUATION, has witnessed a strong resurgence specially under the work of S. Coombes and P. Bressloff that have expanded the original framework as well as providing new tools. Here we present a complementary viewpoint, based on the operational closure of the nervous system (Autopoiesis and Cognition, Maturana and Varela, (1980) ISBN 978-94-009-8947-4) where the activity of neural groups, which is defined by neural field equations, has a strong re-entry component that serves to continuously calibrate the internal activity of the network in relation with the external medium. In line with other applications of closure, we write a system of integro-differential equations that embody the core of closure as the self-referential equation $f(f)=f$. We present computer simulations that exhibit the basic properties of such system as the connectivity component changes according to various plasticity rules. Furthermore, we also discuss closure as a new paradigm relative to others principles and theories in neural functions.
References.
H.R. Wilson and J.D. Cowan. Excitatory and inhibitory interactions in localized populations of model neurons. Biophys. J., 12:1-24 (1972).H.R. Wilson and J.D. Cowan. A mathematical theory of the functional dynamics of cortical and thalamic nervous tissue. Kybernetik 13.2 (1973)S. Amari. Dynamics of pattern formation in lateral inhibition type neural fields. Biological Cybernetics, 27:77-87 (1977).S Amari. Homogeneous nets of neuron-like elements. Biological Cybernetics, 17:211-220 (1975).Sengupta B, Tozzi A, Cooray GK, Douglas PK, Friston KJ. Towards a Neuronal Gauge Theory. PLoS Biol 14(3) (2016)

Disclosures: J. Letelier: None. **C. Maureira:** None.

Poster

849. Models of Excitability: Networks and Single Neurons II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 849.03/NNN15

Topic: I.06. Computation, Modeling, and Simulation

Support: NIH Grant 5R01DC013906

Title: Characterization of a novel analysis method for single trial analysis of fluctuating neural responses

Authors: *J. T. MOHL, V. C. CARUSO, C. GLYNN, S. TOKDAR, J. M. GROH;
Duke Univ., Durham, NC

Abstract: Trial-to-trial variation in neural signals is known to be perceptually relevant, yet most analysis methods collapse data across many trials, obscuring the significance of this variability. Here, we characterize a novel analysis method for evaluating activity fluctuations at individual trial levels. The method was developed to test whether neural responses to combined stimuli reflect a mixture of the responses to the component stimuli, and was tested with both real neural data and synthetically-created spiking patterns drawn from representative response distributions. Responses to individual component stimuli were first fit with Poisson distributions. Then, a Bayesian model comparison was performed to determine whether combined responses were best explained by a mixture of these component Poisson distributions or several alternatives. These alternatives consisted of a winner take all model (a preference for one of the two component distributions), weighted averaging of components (a single distribution at an intermediate rate), or summation of component distributions. The model comparison was tested using synthetic data sets created to match each of these possibilities. That is, spike trains were generated as draws from a mixture of the two component distributions, a single component distribution, a single intermediate distribution, or distributions with higher mean rates than either component distribution. These data sets were correctly classified for more than 95% of cases when at least 20 trials worth of data were analyzed, demonstrating that the method is sensitive to each of these possibilities and has sufficient power for use with real data sets. Actual neural data from sound responses in the primate inferior colliculus were also analyzed using this method. Responses to combinations of sound spanned the range of models tested, but were often best described by the mixture model, a result obscured by across trial averaging methods. By characterizing neural response fluctuations on short timescales, the presented analysis reveals features which are not visible to methods that pool data across trials. This analysis is part of a growing family of short timescale analyses which provide a window into neural processing at biologically relevant timescales. Although here it is tested only on combinations of two components which are

assumed to have Poisson variance, the method can in principle be extended other types of distributions and to any number of components.

Disclosures: **J.T. Mohl:** None. **V.C. Caruso:** None. **C. Glynn:** None. **S. Tokdar:** None. **J.M. Groh:** None.

Poster

849. Models of Excitability: Networks and Single Neurons II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 849.04/NNN16

Topic: I.06. Computation, Modeling, and Simulation

Support: JSPS P15383 to RV

MEXT (26221003) to TI

JSPS KAKENHI (13350518) to TI

JST/DFG/BMBF collaborative project in Computational Neuroscience (12800297) to MY

JSPS KAKENHI Grant Number 15H01673 to MY

Title: Approximate Bayesian Computation to estimate parameters of spiking neural models of superior colliculus

Authors: ***R. VEALE**[1,2], T. ISA[1,2], M. YOSHIDA[1];
[1]Natl. Inst. for Physiological Sci., Okazaki, Aichi, Japan; [2]Dept. of Med., Kyoto Univ., Kyoto, Japan

Abstract: Estimating the parameters for complex neural circuit models is an area of intense research. Advances in experimental methods have made it possible to collect high-dimensional data about the physiologic and anatomical properties of the brain. However, we are still actively researching the issue of how to use these troves of data to produce better models and better functional predictions. We have previously applied differential evolution/Markov chain Monte Carlo (DE-MCMC) algorithms to estimate the parameters of a spiking neural circuit model of the superior colliculus (SC) (Veale, Isa, and Yoshida, 2015). However, using these statistical methods we encountered two methodological questions: 1) Does the structural model have sufficient degrees of freedom to fit the salient properties of the data? 2) How should one weight the contribution of each data point in the fitness/likelihood function? In order to address the

shortcomings of traditional likelihood-based approaches, we present our application of Approximate Bayesian Computation (ABC) within the DE-MCMC framework. Unlike traditional likelihood functions, ABC does not require weighting the contribution of each data point in the fitness function. We use the PSWEEP2 software package to execute large-scale paramter sweeps using GPU acceleration for each model run. Using this method, it is feasible to estimate hundreds of parameters in parallel.
We compare the DE-MCMC-ABC method to the likelihood based DE-MCMC method we used previously. As with our previous experiments, we use empirical data provided from in vitro slice experiments that revealed that the superficial and deeper layers of SC have different computational functions (Phongphanphanee et al, 2014). The slice experiments provide a large corpus of data, for example the membrane potential of neurons at different distances from applied electrical stimulation as a function of time. Previously, we constructed a spiking neural circuit model of the superior colliculus and used DE-MCMC to estimate the paramters of the spiking neural circuit to fit the slice data. However, the formulation of the likelihood function used in our previous research prevented us from using the time course data available in the slice data to obtain better parameter estimates for our superior colliculus model. Here, we present application of DE-MCMC-ABC to estimate the parameters using the time course data. Using the PSWEEP2 software, it is possible to fit our large-scale simulations while taking advantage of the high-dimensional data collected from modern neuroscience techniques.

Disclosures: **R. Veale:** None. **T. Isa:** None. **M. Yoshida:** None.

Poster

849. Models of Excitability: Networks and Single Neurons II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 849.05/NNN17

Topic: I.06. Computation, Modeling, and Simulation

Support: FP7-ICT-2011-9-601055

Title: Simplified models of interstitial flow and diffusion

Authors: ***K. HOLTER**[1], K. H. PETTERSEN[2], A. M. DALE[3], A. DEVOR[3], K.-A. MARDAL[1]; [1]Matematisk institutt, Universitetet I Oslo, Oslo, Norway; [2]Norwegian Univ. of Life Sci., Ås, Norway; [3]Sch. of Med., UCSD, San Diego, CA

Abstract: Clearance of waste products like amyloid-beta from the brain is crucial for a healthy central nervous system. For example, Alzheimer's disease has been linked to significant accumulation of amyloid-beta, which could be the result of a malfunctioning clearance process.

However, the mechanisms through which waste clearance occurs is not yet fully understood. Convection and diffusion have both been suggested as drivers of waste clearance, but no consensus has yet been reached.
In particular, there has been significant disagreement about whether convection can contribute to waste clearance, or indeed whether there is significant convective flow present in the brain at all, with different studies arriving at very different conclusions. [Bakker et al. 2016] To better understand waste clearance, a better understanding of interstitial fluid flow and diffusion is needed.
Due to the intricate micro-scale geometry of brain tissue, modeling of these phenomena is computationally expensive. In this work, we investigate idealized geometries approximating the shape of brain tissue and use them to model fluid flow and diffusion with the finite element method. Fluid flow is assumed to be viscous, and hence modeled by the Stokes equations. Diffusion is assumed to follow Fick's law, and modeled as a Poisson problem. Simulations are performed with FEniCS [Logg et al., 2012].
Two geometrical parameters of importance are the ratio between the volume of the intracellular and the extracellular space (ECS), and the ratio between the volume of tunnels (wider gaps of extracellular volume, about 40-80 nm in diameter, at the junctions of three or more cellular processes) to the volume of the ECS.
We find that the tunnel volume fraction strongly affects the permeability. Keeping the volume fraction at 20% and applying a pressure gradient of 1 mmHg/mm, we vary the tunnel volume fraction from 50% to 80%. This nearly doubles the average velocity and permeability from 0.42 micron/s and 5.71 * 10^{-15} m^2 to 0.74 micron/s and 9.93 * 10^{-15} m^2. This shows that convective flow is affected not only by the size of the ECS, but also by its shape.

Disclosures: **K. Holter:** None. **K.H. Pettersen:** None. **A.M. Dale:** None. **A. Devor:** None. **K. Mardal:** None.

Poster

849. Models of Excitability: Networks and Single Neurons II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 849.06/NNN18

Topic: I.06. Computation, Modeling, and Simulation

Title: Rivalry with irregular spiking: resolving mutual inhibition and the balanced state

Authors: B. COHEN, *C. C. CHOW, S. VATTIKUTI;
Lab. of Biol. Modeling, NIH/NIDDK, Bethesda, MD

Abstract: Perceptual rivalry is the subjective experience of alternations between competing percepts when an individual is presented with an ambiguous stimulus. Current neural models of rivalry rely on mutual inhibition, a network architecture in which competing pools of neurons inhibit one another. However, cortical models employing such an asymmetry between excitation and inhibition appear to be at odds with the balanced state theory, where excitatory and inhibitory inputs to a given neuron approximately balance leaving the net input close to zero, and the neuron sensitive to input fluctuations. The balanced state theory has been used to explain why neurons paradoxically output Poisson-like spike trains rather than regular spiking which would represent the expectation value for their Gaussian input. Here we present a mutual inhibition model of rivalry with irregular spiking, and characterize parameter regimes for which rivalry and such spike statistics are possible.

Disclosures: **B. Cohen:** None. **C.C. Chow:** None. **S. Vattikuti:** None.

Poster

849. Models of Excitability: Networks and Single Neurons II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 849.07/NNN19

Topic: I.06. Computation, Modeling, and Simulation

Support: NIH Grant T15 LM007056

NIH Grant R01 MH086638

Title: Expanding NEURON support for reaction-diffusion models

Authors: ***R. A. MCDOUGAL**[1], C. TROPPER[2], M. L. HINES[1], W. W. LYTTON[3];
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[3]SUNY Downstate, New York, NY

Abstract: The NEURON simulator provides support for simulating neurons and networks of neurons across multiple spatial and temporal scales. Historically, much of the focus was on neuronal electrophysiology; in 2012, we introduced a reaction-diffusion specification to facilitate studies of how the cell biology of neurons interacts with the electrophysiology. We describe recent improvements in NEURON's support for this field of research.
In small spatial domains, such as spines, volume is low and the total number of molecules present is correspondingly low. At this spatial scale, stochastic effects play key roles in the dynamics. Numerous strategies exist in the literature for simulating these dynamics. We have added a "plugins" submodule to NEURON to connect to external stochastic solvers; this

submodule has been tested with NTW (Neuron Time Warp), which performs parallel 3D stochastic simulations. External solvers that work with the plugins submodule receive the morphology, diffusion, and reaction dynamics from NEURON. The user can switch between the built-in deterministic simulations and external solvers by activating the external solver; specification of reaction kinetics is thus made simulator independent.
In some cases, such as after ischemic shock, neurons and glia affect each other by altering extracellular concentrations. Although the extracellular space is inhomogeneously tortuous, molecular dynamics there is also governed by reaction-diffusion kinetics. We describe our progress toward supporting these dynamics: molecules may react and diffuse anisotropically in the extracellular space, concentrations in the extracellular space are modulated by ion channel and pump activity and themselves modulate electrical activity by altering the Nernst potentials. Concentrations may be further modulated by extracellular sources such as blood vessels. Ongoing work seeks to improve the performance of reaction-diffusion simulations to reduce the time cost of studying the effects of these dynamics on neural activity by moving central loops into compiled code.

Disclosures: **R.A. McDougal:** None. **C. Tropper:** None. **M.L. Hines:** None. **W.W. Lytton:** None.

Poster

849. Models of Excitability: Networks and Single Neurons II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 849.08/NNN20

Topic: I.06. Computation, Modeling, and Simulation

Support: University of Oslo

Research Council of Norway Grant No. 216699

Title: UncertainPy: a Python toolbox for uncertainty quantification in neural and neural-network models.

Authors: ***S. TENNØE**[1], G. HALNES[4], M. LEPPERØD[2], J. FEINBERG[1], G. T. EINEVOLL[4,3], H. P. LANGTANGEN[1,5];
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Abstract: Computational models in neuroscience typically contain a number of parameters that are poorly constrained by experimental data. The sources of parameter uncertainty may be many, including measurement uncertainty and variability in the parameter values within a population of cells or dynamically within a single cell. By quantifying the uncertainties in features of the model output we can determine the effects of measurement uncertainty as well as the uncertainty arising from the intrinsic variability. The standard method of accounting for this uncertainty/variability is to assign a probability distribution instead of a single value to the parameter value, and then to compute the corresponding uncertainty in the model output with Monte Carlo methods. A more recent mathematical framework for estimating uncertainties is that of Polynomial Chaos expansions (Xiu & Hesthaven, SIAM J. Sci. Comput., 2005). Polynomial Chaos is much faster than the standard Monte Carlo methods used for uncertainty quantification as long as the number of uncertain parameters is relatively low, typically smaller than about twenty. This is the case for many, if not most, neuroscience models.Here we present UncertainPy, a novel Python toolbox, tailored to perform uncertainty quantification in neuroscience models. UncertainPy bases its uncertainty analysis on quasi-Monte Carlo methods or Polynomial Chaos, depending on the number of uncertain model parameters. Polynomial Chaos expansions are obtained from the previously developed package Chaospy (Feinberg & Langtangen, Journal of Computational Science, 2015). UncertainPy is feature based, i.e., if applicable, it recognizes and calculates the uncertainty in salient model response features such as spike timing, action potential shape and similar. UncertainPy is parallelized, has support for a wide range of different models, and can easily be customized to new models and features. To demonstrate UncertainPy, we perform uncertainty analysis of (i) the standard Hodgkin-Huxley point-neuron model for action-potential generation, (ii) a comprehensive multi-compartmental model for interneurons in the dorsal lateral geniculate nucleus (Halnes et al, PLoS Comp Biol, 2011) and (iii) a sparsely connected recurrent network model (Brunel, J Comp Neurosci, 2000).

Disclosures: **S. Tennøe:** None. **G. Halnes:** None. **M. Lepperød:** None. **J. Feinberg:** None. **G.T. Einevoll:** None. **H.P. Langtangen:** None.

Poster

849. Models of Excitability: Networks and Single Neurons II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 849.09/NNN21

Topic: I.06. Computation, Modeling, and Simulation

Support: ANR-BALAV1

ANR-BASCO

France-Israel Laboratory of Neuroscience Show original message

Title: The correlated state in cortical circuits

Authors: *R. DARSHAN[1], C. VAN VREESWIJK[2], D. HANSEL[2];
[1]ELSC, Hebrew Univ., Jerusalem, Israel; [2]Ctr. for Neurophysics, Physiol. and Pathology; Cerebral Dynamics, Learning and Memory Lab; CNRS-UMR8119 and Univ. Paris Descartes, Paris, France

Abstract: Cross-correlations (CCs) of neuronal activity in cortical networks are commonly used to characterize their dynamical states and their anatomical or functional organizations. Yet, how these latter network features affect the spatio-temporal structure of the CCs in strongly recurrent networks is not fully understood. Recent theoretical works showed that in unstructured networks, CCs are on average extremely small, even when the fraction of recurrent inputs that neurons share is large (Renart et al., 2010; Hertz, 2010; Helias et al., 2014). On the other hand, in a previous work (Darshan et al., SFN Abstract, 2015) we demonstrated that the interplay between a topographic organization in feedforward projections to a network and its recurrent dynamics can result in significant and spatially modulated CCs, when the footprint of the recurrent connectivity is wider than the footprint of the feedforward projections. Here, we develop a general theory for the emergence of correlations in strongly recurrent structured networks, in which the recurrent connectivity, as well as the external feedforward projections to the network, depend on the distance or on the functional properties of the neurons. We establish the conditions under which such networks settle into a dynamical state where CCs are highly robust and spatially modulated. In local cortical circuits the footprint is in general narrower for inhibition than for excitation. We demonstrate that when the feedforward projections are broad: 1) Excitatory (E) neurons can be substantially correlated, but this requires the interactions between the inhibitory (I) cells to have a footprint wider than the inhibition to the E cells; 2) The spatial profile of the CCs of the E neurons is then a high-pass filtered version of the profile of the I-to-E connectivity. In particular, CCs are in general negative for E neurons far apart 3) The CCs of I neurons are on average extremely small. For the activity to be correlated in both E and I populations, the feedforward projections to the I neurons have to have a narrower footprint than the recurrent interactions.

Disclosures: R. Darshan: None. **C. van Vreeswijk:** None. **D. Hansel:** None.

Poster

849. Models of Excitability: Networks and Single Neurons II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 849.10/NNN22

Topic: I.06. Computation, Modeling, and Simulation

Title: Applying uncertainty quantification and sensitivity analysis to spiking neural network models of asynchronous irregular firing activity

Authors: *K. D. CARLSON, J. B. AIMONE;
Sandia Natl. Labs., Albuquerque, NM

Abstract: Advances in experimental neuroscience have resulted in the production of heterogeneous, multiscale brain data at an unprecedented rate. Many neuroscientists are focused on integrating this data into large-scale, biologically, realistic, computational neural models with parsimonious descriptions and well-constrained predictions. However, as models have grown in both size and complexity, it has become difficult to quantitatively judge the efficiency of description, robustness, reliability, and overall accuracy of these computational models. The inability of modelers to convincingly verify and validate computational neural models remains a major a hurdle in computational neuroscience as it casts doubt on both the efficacy and predictive power of their models. A solution may lie in the engineering community which has long been performing verification and validation on complex computational models by using uncertainty quantification (UQ) and sensitivity analysis (SA) techniques. UQ techniques focus on characterizing and reducing uncertainty in models while SA techniques focus on attributing variance in model outputs to uncertainties in the inputs. Although UQ and SA offer both quantitative and qualitative methods for model analysis, we focus on quantitative model verification and validation in this study. We perform model reduction and characterize the robustness, reliability, and overall accuracy of multiple spiking neural network (SNN) models by applying sampling-based Bayesian probabilistic UQ and SA. Specifically, we evaluate SNN models capable of producing asynchronous irregular (AI) firing activity which resembles the discharge activity recorded in the cerebral cortex of awake animals. We examine how uncertainty in the neuronal parameters and network connectivity affect uncertainty in the measured outputs of the neural model such as the duration of the sustained AI activity, average firing rate of the network, the coefficient of variation for interspike interval distributions, and the averaged cross-correlation between neurons in the network. We then apportion the uncertainty in the model outputs to specific model parameters in a quantitative fashion. Results show that UQ/SA is often more computationally efficient and informative than brute force parameter space characterization and can be viewed as a complimentary technique. The UQ/SA techniques we introduce in this study are well-studied and we believe they can provide the computational neuroscience community with an important tool for building and evaluating complex computational neural models.

Disclosures: **K.D. Carlson:** None. **J.B. Aimone:** None.

Poster

849. Models of Excitability: Networks and Single Neurons II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 849.11/NNN23

Topic: I.06. Computation, Modeling, and Simulation

Title: A novel method for simulating stochastic reaction and diffusion of complex biomolecules

Authors: *X. LI, W. HOLMES;
Ohio Univ., Athens, OH

Abstract: Simulation of intracellular chemical reactions is an important way to understand cell signaling. There are well-built and widely used simulation tools such as COPASI, BioNetGen, MCell, and Smoldyn. These tools address different aspects of reactions and are not without limitations. COPASI and BioNetGen are concentration based and are designed for reactions that happen in a homogenous environment. MCell and Smoldyn can simulate stochastic reaction-diffusion. However, it is still difficult to model interactions between macromolecules when one molecule consists of multiple subunits with multiple binding sites, as this usually gives rise to the problem of "combinatorial explosion".
We introduce a novel method to simulate biomolecular interactions for stochastic models. Beginning with the source code of Smoldyn, we added new data structures to describe molecule species in three hierarchical levels: macromolecule complex, subunits, and binding sites. Binding and unbinding reactions are all defined at the binding sites level, which reduces the total number of reaction rules to describe a given reaction network. This approach is similar to the "rule-based" idea in BioNetGen, which can expand a full-size network based on a set of given reaction rules.
The current version of Smoldyn reads in the network file generated from BioNetGen before a simulation starts. However, the full-size network usually takes a long time to load. Instead, our customized Smoldyn can load the reaction rules and expand the network "online" during the simulation by choosing reaction paths dynamically at each time step. Complex molecules are modeled using linked-lists that allow the subunits to diffuse together but to react independently. The reaction network is implemented as a hash table to allow fast search during the simulation. Defining reactions on binding sites enables us to keep reactants after binding or unbinding, instead of removing and replacing them with newly generated product molecules as in the default Smoldyn. Therefore, we can track the reaction history of each molecule.
We have tested this customized simulator with a biophysically realistic Ca2+ signaling cascade model. The cascade includes Ca2+ influx from the cell surface membrane, interacting with CaM, and CaM reacting with 6-subunit rings of beta- and gamma- CaMKII, CaMKIV, and CaMKK, leading eventually to CREB phosphorylation in the nucleus.

Disclosures: **X. Li:** None. **W. Holmes:** None.

Poster

849. Models of Excitability: Networks and Single Neurons II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 849.12/NNN24

Topic: I.06. Computation, Modeling, and Simulation

Support: Office of Naval Research MURI

Title: Dataassimilation of membrane dynamics and channel kinetics with a neuromorphicintegrated circuit

Authors: ***J. WANG**[1], D. BREEN[2], R. KUBENDRAN[3], S. SHIRMAN[2], F. BROCCARD[4], H. D. I. ABARBANEL[2], G. CAUWENBERGHS[5];
[1]Bioengineering, UCSD, LA Jolla, CA; [2]Physics, [3]Electrical and Computer Engin., [4]Inst. for Neural Computation, [5]Bioengineering, Univ. of California San Diego, San Diego, CA

Abstract: Techniques of data assimilation (DA) for parameter identification and forecasting in complex dynamical systems offer promising tools for the analysis of neural data and inference of neural function. Here we present experiments using DA to characterize the dynamics of a neuromorphic very large-scale integrated (VLSI) circuit emulating membrane dynamics and channel kinetics in a network of 4 generalized Hodgkin-Huxley neurons coupled through 12 conductance-based chemical synapses. The analog VLSI chip, NeuroDyn, features 384 digitally programmable parameters specifying for all neurons and synapses reversal potentials, conductances, and spline-regressed voltage dependence profile of opening and closing rates of the gating variables. In a set of twin experiments, we conducted DA on the membrane potentials of neurons recorded on the chip under current injection according to the model structure upon which the chip was designed and the known current input sequence, to arrive at the programmed parameters save for model errors due to analog imperfections in the chip fabrication. In a related set of experiments we extended the DA procedure to map songbird neural dynamics onto the chip by identifying and programming parameters extracted using DA from intracellular neural recordings. These experiments illustrate the power of neuromorphic systems in modeling function of simple neurobiological systems enabled through DA. Unlike software emulation, the neuromorphic chip runs in real-time and consumes only 1.29 mW of power. Application of the chip to neurological data may help to understand the effects of neuromodulators or neurodegenerative diseases on ion channel kinetics, and may further provide insights into the relationship between molecular properties of neurons and the emergence of different spike patterns or different brain behaviors.

Disclosures: **J. Wang:** None. **D. Breen:** None. **R. Kubendran:** None. **S. Shirman:** None. **F. Broccard:** None. **H.D.I. Abarbanel:** None. **G. Cauwenberghs:** None.

Poster

849. Models of Excitability: Networks and Single Neurons II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 849.13/NNN25

Topic: I.06. Computation, Modeling, and Simulation

Title: Serial spike time correlations affect probability distribution of joint spike events

Authors: ***M. SHAHI**[1], G. PIPA[1], C. VAN VREESWIJK[2];
[1]Univ. of Osnabrueck, Osnabrueck, Germany; [2]Paris Descartes Univ., Paris, France

Abstract: Detecting the existence of temporally coordinated spiking activity and its role in information processing in the cortex has remained a major challenge for neuroscience research. Different methods and approaches have been suggested to test whether the observed synchronized events are significantly different from those expected by chance(Truccolo, Eden, Fellows, Donoghue, & Brown, 2005; Pipa & Grun, 2003). To analyze the simultaneous spike trains for precise spike correlation, many of these methods model the spike trains as a stochastic Poisson process.However, studies have shown that neural spike trains can show a substantial deviation from Poisson distribution and exhibit dependencies among spike sequences, such as the absolute and relative refractory periods or bursting behavior(Krahe & Gabbiani, 2004,Farkhooi, StrubeBloss, & Nawrot, 2009).
Follow up the previous study (Pipa, Gruen, van Vreeswijk, 2013), this study offers a non-renewal inter-spike interval distribution model that incorporates spike-history dependence in the autostructure of the spiking activity of individual neurons. Moreover, this study uses Monte Carlo estimation to examine the effect of the model's parameters on the full shape of the coincidence count distribution and on the generation of false positives. The results shows that compared to distributions based on homogeneous Poisson processes, and non-Poisson processes, the width of the distribution of joint spike events changes. Non-renewal process, can lead to both heavy tailed or narrow coincidence distribution. We conclude that small differences in the exact autostructure of the point process can cause large differences in the width of a coincidence distribution. Therefore manipulations of such structure for the estimation of significance of joint spike events seem to be inadequate.

Disclosures: **M. Shahi:** None. **G. Pipa:** None. **C. van Vreeswijk:** None.

Poster

849. Models of Excitability: Networks and Single Neurons II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 849.14/NNN26

Topic: I.06. Computation, Modeling, and Simulation

Support: BBSRC BB/K001817/1

Susanna Mitolo was funded by the MRC

Title: An unsupervised complex spike detection algorithm relying on two signal feature selectors: Time Frequency Manifold and Power

Authors: *S. BATIR[1], S. MITOLO[1], T. MUZZU[1], S. SCHULTZ[1,2];
[1]Dept of Bioengineering, Imperial Col. of London, London, United Kingdom; [2]Ctr. for Neurotechnology, Imperial Col. London, London, United Kingdom

Abstract: Action potentials (spikes) are widely accepted to act as the "currency" of the brain, transmitting information that is encoded in distinct frequency and temporal states. These frequently observed action potentials, lasting for about 2ms with an extended refractory period, are known as simple spikes. However, the mammalian cerebellum also produces a less frequent spiking pattern known as a complex spike characterized by continuous, oscillatory activity that persists for 5-6 ms. Attempts to isolate complex spikes have proven more difficult due to variation in the oscillatory activity following the initial action potential of a complex spike. Moreover, successful signal classification requires the optimal subset of signal features to be chosen amongst a melange of signal feature candidates. Through post-hoc analysis of electrophysiological recordings from the lateral cerebellum of fourteen female C57/BL6 mice trained in a motor task, we developed an algorithm that examines two features of a signal and invokes a Gaussian mixture model to cluster putative spikes into either 1. Simple or 2. Complex classes.
By performing a continuous wavelet transform of the putative spike's voltage trace (real valued Morlet wavelet), we can construct the energy manifold with high spectrotemporal resolution for each putative signal. We discovered a frequency-temporal segment of the energy landscape unique only to complex spikes. For each signal, the energy landscape segment feature was compared against the corresponding power and clustered using a gaussian mixture model. We validated this algorithm in an additional six, post-hoc cerebellar datasets. The Receiver Operating Characteristic produced from the algorithm's clustering performance suggests that our approach of feature selection and unsupervised gaussian mixture clustering yields an accuracy rate of roughly 90%. These results provide new insight into the unique spectrotemporal structure of individual cell-specific signals and lay the groundwork for tools that may be used by

neuroscientists hoping to analyze the contribution of complex spikes produced by cerebellar Purkinje cells to whole-brain networks.

Disclosures: **S. Batir:** None. **S. Mitolo:** None. **T. Muzzu:** None. **S. Schultz:** None.

Poster

849. Models of Excitability: Networks and Single Neurons II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 849.15/NNN27

Topic: I.06. Computation, Modeling, and Simulation

Title: Translational regulation of re1 silencing transcription factor (rest) using a synthetic rna binding protein approach

Authors: ***M. GATTI IOU**[1], S. CRISCUOLO[1], L. MARAGLIANO[1], F. CESCA[1], F. BENFENATI[1,2];
[1]Ctr. for Synaptic Neurosci. (NSYN), Italian Inst. of Technol. (IIT), Genova, Italy; [2]Exptl. Med., Univ. of Genova Med. Sch., Genova, Italy

Abstract: The RE1-silencing transcription factor (REST) is a transcriptional repressor controlling several neuronal genes and regulating nervous system development and lineage specification. The importance of maintaining physiological levels of REST is reflected by the consequences of its dysregulation. Indeed, either increments or decrements of REST protein levels have been identified in several neuropathologies such as cerebral ischemia, Down syndrome, epilepsy, Huntington's disease and Alzheimer's disease. Using the *A. sativa* light, oxygen, voltage (LOV) domain we engineered an optogenetic probe able to decrease REST activity by interfering with the formation and activation of the REST complex (Paonessa et al., *PNAS* 2016), providing a tool for studying neuronal physiology and correcting gene expression changes taking place in brain diseases. In an attempt to create an alternative probe able to increase REST expression/activity, we used a synthetic approach based on the RNA binding Pumilio PUF domain, belonging to a class of proteins that regulate gene expression by binding to sequences in the 3' untranslated region (3'UTR) of target mRNAs. PUF proteins bind RNA following a known recognition code, whereby each ribonucleotide is recognized by a protein motif containing five variable residues. According to this code we modified the Pumilio homology domain PUM1 to make it specific for binding the sequence of 3' UTR of REST mRNA. To investigate the interaction between engineered PUF variants and the target REST mRNA, we used Electrophoretic Mobility Shift (EMSA) RNA assay and RNA immunoprecipitation, and we are planning to use Surface Plasmon Resonance (SPR) to measure binding affinity and kinetics. Moreover, we employed computational tools to investigate the

molecular structure of the new complexes and how the recognition code specifically affects the binding interface. Furthermore, we used Free Energy calculation methods to determine the most probable conformation of the protein-RNA complexes and to quantify the effect of mutations on the binding strength. Based on this information and to increase REST translation, we fused the synthetic PUF domain to the poly(A) polymerase PAP protein, able to increase mRNA stability by adding adenines to polyA.

Disclosures: M. Gatti Iou: None. **S. Criscuolo:** None. **L. Maragliano:** None. **F. Cesca:** None. **F. Benfenati:** None.

Poster

849. Models of Excitability: Networks and Single Neurons II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 849.16/NNN28

Topic: I.06. Computation, Modeling, and Simulation

Support: MAGNET program of the Israeli OCS at the ministry of economy

The Russell Berrie Nanotechnology Institute

Israel Science Foundation Grant No. 1725/13

Title: Ultrasonic neuromodulation biophysics predicts intrinsic capacity for cell-type-selective stimulation

Authors: *M. PLAKSIN[1], E. KIMMEL[2], S. SHOHAM[2];
[1]Biomed. Engin., Technion - Israel Inst. of Technol., Nesher, Israel; [2]Fac. of Biomed. Engin. & Russell Berrie Nanotechnology Inst., Technion - Israel Inst. of Technol., Haifa, Israel

Abstract: Diverse translational and research applications could benefit from the non-invasive ability to reversibly modulate (excite or suppress) activity using ultrasound pulses - essentially anywhere in the CNS. However, without clarifying the underlying mechanism, advanced design-based ultrasonic neuromodulation remains elusive. Recently, intramembrane cavitation within the bilayer membrane was proposed to underlie both the *biomechanics* and the *biophysics* of acoustic bio-effects through a Neuronal Intramembrane Cavitation Excitation (NICE) model, which was shown to quantitatively explain *in vivo* motor-cortical stimulation results. Here, NICE theory is shown to provide a detailed predictive explanation for the ability of ultrasonic pulses to also suppress neural circuits through a *cell-type selective* mechanisms: according to the predicted mechanism T-type calcium channels boost charge accumulation between short US pulses selectively in Low Threshold Spiking (LTS) interneurons, promoting net cortical network

inhibition. The theoretical results fit and clarify a wide array of earlier empirical observations in both the cortex and thalamus regarding the dependence of ultrasonic neuromodulation outcomes (excitation-suppression) on stimulation and network parameters. These results further support a unifying hypothesis for ultrasonic neuromodulation, highlighting the potential of advanced waveform design for obtaining cell-type selective network control without requiring genetic transduction.

Disclosures: **M. Plaksin:** None. **E. Kimmel:** None. **S. Shoham:** None.

Poster

849. Models of Excitability: Networks and Single Neurons II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 849.17/NNN29

Topic: I.06. Computation, Modeling, and Simulation

Support: NSF grant SMA 1041755

Title: Measuring encoding efficiency in networks of correlated poisson neurons.

Authors: ***V. H. MINCES**, A. A. CHIBA;
UCSD, La Jolla, CA

Abstract: The development of powerful recording techniques emphasizes a need for understanding how information is represented in large neural populations. Elucidating the role of correlated activity in network encoding lies at the heart of this understanding. Although recent years have seen a great advancement in our comprehension of the problem, major questions remain. Specifically, the amount of information encoded in a network composed of realistic neurons has been very difficult to measure. This is a concern given that the literature suggests that information can be severely underestimated by employing the commonly used Gaussian models. We extend a technique used to generate correlated activity in neurons with Poisson statistics, for the purpose of applying it to large networks. We further use Bayesian methods to quantify the encoding efficiency of the network. We compare this real encoding efficiency to the estimation that can be found by using a less realistic, but more manageable, Gaussian model. Our technique allows for a systematic exploration of the role of neuronal correlations in network encoding and holds the potential to be extended to very large networks.

Disclosures: **V.H. minces:** None. **A.A. Chiba:** None.

Poster

850. Algorithms and Network Models for Cognition and Behavior

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 850.01/NNN30

Topic: I.06. Computation, Modeling, and Simulation

Support: NIH-MH60163

T32 NS058280-04S1

Title: Understanding the mechanisms of motor temporal scaling using a recurrent neural network model.

Authors: *N. HARDY[1,2], J. L. ROMERO-SOSA[2], D. V. BUONOMANO[2,1,3];
[1]Neurobio., [2]Neurosci. Interdepartmental Program, [3]Psychology, UCLA, Los Angeles, CA

Abstract: Humans can perform the same action at multiple speeds with little conscious effort. For example, people can dynamically adjust how quickly they write in order to meet the demands of a particular task, and trained musicians can play the same piece at different tempos. The motor cortex of primates consists of a recurrent network that represents muscles and movements in specific groups of neurons (Capaday et al., 2013), thus to temporally scale a movement the same set of neurons in the motor cortex must be activated in the same order, but at different speeds. To examine the mechanisms underlying temporal scaling we turned to a recurrent neural network (RNN) model. Previous work has shown that by training the recurrent weights, RNNs can learn to autonomously (i.e. without external feedback) produce complex, stable spatiotemporal motor patterns such as handwriting (Laje and Buonomano, 2013). We asked whether this model could also account for temporal scaling. We trained RNNs to produce an activity pattern at different speeds in response to a tonic "speed cue". When a network was trained on only one speed and tested with different speed cues performance was poor: the patterns generated were not temporally scaled versions of the trained pattern. However, when an RNN was trained to produce the same activity pattern at different speeds it was not only able to reproduce the trained speeds, but also to generalize its activity to untrained speeds. Analysis of the recurrent activity at different speeds revealed that networks generated parallel neural trajectories in state space—accounting for temporal scaling.
Based on these results, we predicted that training to produce the same pattern of motor activity at different speeds should improve temporal scaling in humans. To test this prediction we trained human subjects on a temporal scaling task that consisted of reproducing a pattern of auditory tones by tapping a keyboard. One group of subjects was trained only at an intermediary speed, while a second group was trained at two speeds. Both groups were tested on their ability to produce the learned pattern over a fourfold range of speeds (ranging from 0.5x to 2x). Despite having the same overall amount of training, subjects trained at two speeds exhibited better

temporal scaling.
Our psychophysical results suggest that temporal scaling is itself learned—i.e., being able to produce a motor pattern does not automatically translate into the ability to produce that same pattern at different speeds. Our computational results suggest that by encoding temporal patterns as neural trajectories the brain may naturally resolve the problem of temporal scaling.

Disclosures: **N. Hardy:** None. **J.L. Romero-Sosa:** None. **D.V. Buonomano:** None.

Poster

850. Algorithms and Network Models for Cognition and Behavior

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 850.02/NNN31

Topic: I.06. Computation, Modeling, and Simulation

Support: Marie Curie - NETT 289146

Title: Optimal pixel-wise reconstruction of visual scenes from two photon imaging of mouse V1

Authors: ***S. GARASTO**, M. GO, A. A. BHARATH, S. R. SCHULTZ;
Dept. of Bioengineering, Imperial Col. London, London, United Kingdom

Abstract: How the brain processes sensory information is a question fundamental to cognitive processing and the control of behaviour. Despite an increasing body of work, how neurons encode and decode information remains an open question. We address this issue from a decoding perspective: we aim to develop a model-based algorithm for reconstructing visual scenes from two photon calcium imaging of the visual cortex, and analyse its performance under different model assumptions. Instead of an implicit natural image prior based on a weighted average of images, we focus on optimal reconstruction in the pixel space. The proposed algorithm is suitable for decoding neural data at the level of individual cells, e.g. two-photon imaging data. The proposed method involves a parametric forward model based on adapting a mixture model of linear and non linear Gabor-based receptive fields (Nishimoto et al. Current Biology 21.19: 1641-46, 2011), and is trained to predict neural response patterns to given inputs. The mixture model approach adopted allows our algorithm to exploit both somatic and neuropil signals for decoding. We then use principles of Bayesian inference to invert the model and reconstruct the visual scenes on a separate set of test data. The optimal reconstruction is the one that maximizes a posterior probability with a Gaussian regularization prior. We also extend the model to include a divisive normalization step. The training set consists of natural images; we test the algorithm using letters of the alphabet, to assess how well it generalizes to different types of images.
We study how the algorithm performs under two different conditions. First, we evaluate

performance using a computationally efficient approximation of Gabor receptive fields, the Berkeley Wavelet Transform (Willmore et al. Neural Comp. 20.6:1537-1564, 2008). We find that this reduces computational time, while still providing similar results when the Gaussian prior is applied. The inclusion of a simple divisive normalization step was found to be consistently helpful in estimating the mixture weights for the receptive fields. However, it resulted in slightly decreased performance when kept for decoding. Our results suggest that sensory reconstruction from two photon imaging of neural circuit activity may prove to be a powerful tool for revealing information processing principles in the brain.

Disclosures: **S. Garasto:** None. **M. Go:** None. **A.A. Bharath:** None. **S.R. Schultz:** None.

Poster

850. Algorithms and Network Models for Cognition and Behavior

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 850.03/DP10 (Dynamic Poster)

Topic: I.06. Computation, Modeling, and Simulation

Support: Inserm

Title: The virtual mouse brain

Authors: ***C. BERNARD**, F. MELOZZI, M. WOODMAN, V. JIRSA;
INSERM U1106, Marseille cedex 05, France

Abstract: The Virtual Brain (TVB) is an open source software that offers many possibilities to simulate human whole brain dynamics with several models and neuroimaging signals such as functional magnetic resonance, electroencephalography and magnetoencephalography. It allows investigating the relationship between the structure (the connectome) and function (e.g. resting state dynamics). This is particularly relevant for brain disorders, since they are characterised by altered connectivity patterns and altered dynamics. Here we present The Virtual Mouse Brain (TVMB) that builds upon TVB and that allows to simulate whole brain dynamics in mice. We present two models. The first one is based on the full connectome of the mouse brain, using the anterograde tracer data from the Allen Institute for Brain Science (Oh et al., Nature, 2014). The second model is based on imaging data (anatomical MRI and Diffusion Tensor Imaging, DTI) as in Calabrese et al., PNAS 2015). A set of mathematical models allows the genesis of different types of activities, including resting state dynamics and seizure genesis/propagation. Using the enhanced non-linearity Mean-Field Model, we could reproduce the dynamics of functional connectivity as observed in humans. Functional connectivity patterns were stable during short time periods before switching to another pattern. The switching behaviour and the resting state

networks identified in silico were in good agreement with empirical ones. The dynamic repertoire was richer when using the "true" connectome as compared to DTI. Mimicking the reorganisation of the connectome found in epilepsy, we found a dramatic reduction in the dynamical repertoire as compared to the control situation. Finally, we could reproduce the propagation pattern of epileptic seizures in TVMB, as found experimentally in Toyoda et al., J Neurosc 2013. This work validates TVMB as a platform to explore mouse whole brain dynamics in control and pathological conditions.TVMB is fully integrated into the TVB open source neuro informatics platform and freely available (http://www.thevirtualbrain.org).

Disclosures: **C. Bernard:** None. **F. Melozzi:** None. **M. Woodman:** None. **V. Jirsa:** None.

Poster

850. Algorithms and Network Models for Cognition and Behavior

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 850.04/NNN32

Topic: I.06. Computation, Modeling, and Simulation

Support: NIDCD Intramural Research Program

Title: Using a large-scale neural model of cortical object processing to investigate the neural substrate for holding multiple items in short-term memory and for performing a paired associate task

Authors: Q. LIU[1,2], A. ULLOA[1,3], *B. HORWITZ[1];
[1]Brain Imaging & Modeling Sect., Natl. Inst. on Deafness and Other Communication Disorders, Bethesda, MD; [2]Physics, Univ. of Maryland, College Park, MD; [3]Neural Bytes, LLC, Washington, D.C., DC

Abstract: Previously, a pair of large-scale, neurobiologically realistic, multi-region computational models were constructed for simulating cortical processing of visual and auditory objects during a short-term memory task (Tagamets & Horwitz, 1998; Husain et al., 2004; Ulloa et al., 2008). The models successfully simulated cortical neuronal activities and fMRI data that generally agreed with experimental results.
We have modified the structural design and connectivity of the visual model to incorporate a gating mechanism and a long-term memory component. The original visual model consisted of arrays of Wilson-Cowan-like neuronal populations representing primary and secondary visual cortices, inferior temporal cortex and PFC. We added a module representing parahippocampal cortex, which functions as a gating module, and a module representing medial temporal cortex that functions as a long-term memory store. With the gating mechanism, the model is able to

hold multiple items in short-term memory and accomplish related cognitive tasks. During simulations of memorizing a list of objects, the first and the last item in the sequence were recalled best with certain combinations of attention levels and connectivity weights, which may implicate the neural basis behind this important psychological effect (i.e., the primacy and recency effects). We also show that the model is able to perform a paired associate task with visual objects stored and associated in long-term memory. We find neuronal units that exhibit memory encoding and retrieval types of behaviors during the simulations of the paired associate task that generally match previous monkey electrophysiological experimental findings (Miyashita, 1988). Our results suggest a specific cortical architecture that reflects the neural bases by which the brain performs particular short and long term memory tasks.

Disclosures: **Q. Liu:** None. **A. Ulloa:** None. **B. Horwitz:** None.

Poster

850. Algorithms and Network Models for Cognition and Behavior

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 850.05/NNN33

Topic: I.06. Computation, Modeling, and Simulation

Title: Efficient and scalable massively parallel neural networks with hodgkin-huxley neurons for human-level simulations

Authors: *L. N. LONG;
Pennsylvania State Univ., University Pk, PA

Abstract: This paper describes neural network algorithms and software that scale up to massively parallel computers. The Hodgkin-Huxley neuron model, with simple point-based synapses, are used. Most massively parallel simulations use very simplified neuron models, which cannot accurately simulate biological neurons and the wide variety of neuron types. For many years now researchers have stated that the Hodgkin-Huxley model was far too expensive to use due to its computational cost and complexity. This is simply not the case. The H-H model can be programmed efficiently, and it can model many types of neurons. Sixty years after the first AI conference we have supercomputers on the order of the human brain. Supercomputers such as the 3,120,000-processor Chinese TianHe computer are capable of human level neural networks. The software developed here is written in C++ and uses the Message Passing Interface (MPI). C++ was used due to its wide acceptance, high performance, efficient memory usage, and powerful modern syntax. MPI was used since it is essentially the only possible approach for massively parallel computers. One of the difficult aspects of using distributed memory computers, especially when there might be millions of processors, is how to distribute the

problem across the processors while minimizing communication costs. This is especially difficult for neural networks, since we have to simulate neurons and synapses and they are connected in very complicated networks. In the approach used here, the neurons are evenly distributed across the processors using MPI in a single program multiple data (SPMD) approach. Each neuron also has a list of synapses that it is connected to, and each synapse has information on its post-synaptic neuron and its processor number. The H-H neuron model requires roughly 184 bytes for each neuron plus an integer list of synapses. While biologically a synapse might store roughly a byte of data, in the computer program used here each synapse requires roughly 5 bytes. So any of the top five computers in the list above could store roughly as many of these synapses as the human brain (1014). Human-brain-scale simulations are now feasible on massively parallel supercomputers. With careful attention to efficient event-driven programming, table lookups, and memory minimization these simulations can be performed. The next phase of this research will be incorporating learning. We have implemented back propagation and spike time dependent plasticity (STDP) in the past, and could use that for these networks also. The code can also simulate neuro- and synapto-genesis.

Disclosures: L.N. Long: None.

Poster

850. Algorithms and Network Models for Cognition and Behavior

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 850.06/NNN34

Topic: I.06. Computation, Modeling, and Simulation

Title: Measuring causality in simulations of large scale brain networks

Authors: *M. MANNINO[1], S. L. BRESSLER, 33431[2];
[1]Florida Atlantic Univ., Doral, FL; [2]Florida Atlantic Univ., Boca Raton, FL

Abstract: Inferring causal relations between the nodes of large-scale brain networks is important to reveal network topology, connectivity, and function, and help uncover the neurobiological basis of cognition. Yet appropriate methodologies for measuring causal relations in brain networks remain varied and elusive. The application of directed functional connectivity analysis to simulated neural data can recover neural connectivity patterns and validate inferences from causality analysis of veridical neural data (Tang et al, 2012). However, simulated data has not previously been widely used because it has failed to capture important aspects of neural function. Here, we performed computational simulation and mathematical analysis on a neuroinformatics platform called The Virtual Brain (TVB) that simulates biologically realistic neural population data generated by a large-scale distributed brain network model. TVB is unique in the field of

neural simulation in that it is organized at the mesoscopic level of large-scale brain networks with nodes that are neural populations. TVB provides a framework for evaluating various methodologies on biologically plausible simulated data (Wang et al, 2014). The overall objective of this project is to use a nonlinear dynamical system, specifically a neural mass model to generate time series simulations of local field potentials (LFPs), and use linear autoregressive modeling to analyze the data, thereby inferring causal relations in large-scale brain networks. Data are generated from coupled oscillatory neural populations, with the Stefanescu-Jirsa 3D model in the TVB simulator governing the intrinsic dynamics of each population.

Disclosures: M. Mannino: None. **S.L. Bressler:** None.

Poster

850. Algorithms and Network Models for Cognition and Behavior

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 850.07/NNN35

Topic: I.06. Computation, Modeling, and Simulation

Support: EPFL Blue Brain Project Fund

ETH Board Funding to the Blue Brain Project

Title: Computational characteristics of large scale brain simulations

Authors: *F. CREMONESI, J. PLANAS, F. DELALONDRE, F. SCHÜRMANN;
Blue Brain Project, Ecole Polytechnique Fédérale De Lausanne, Geneve, Switzerland

Abstract: Large-scale simulations of brain models are grand challenge problems that are being actively tackled by many different research groups in the computational neuroscience community. At the same time a systematic analysis of the computational characteristics of brain simulations has not yet been carried out in the community. Such an analysis, however, is useful in determining the technical feasibility of large-scale brain simulations as well as their computational requirements on the underlying hardware. The analysis is made difficult by the wide variety of methods and techniques being used to model brain tissue and brain components, stemming from an on-going debate on what constitutes a meaningful approximation of brain activity. For a selected set of published brain models, namely network models of neurons of leaky integrate-and-fire to morphologically detailed type, we present a framework for a quantitative analysis of their computational characteristics. We define a set of metrics based solely on information from the model and the underlying algorithm, in order to capture intrinsic differences among in silico neuroscience models rather than extrinsic ones due to variations of

the implementation or the underlying hardware architectures. We analyze in detail the algorithms and workflows pertinent to each model, and show how to extract the relevant quantitative information to compute the proposed metrics in a systematic way. In order to make a concrete performance prediction, we conduct a fine-grained investigation of the communication characteristics of the network models, where we analyze the different underlying spike exchange routines and create quantitative performance models based on the available hardware. This low level analysis shows that the proposed metrics are good indicator of the overall performance of the in silico models.

Disclosures: **F. Cremonesi:** None. **J. Planas:** None. **F. Delalondre:** None. **F. Schürmann:** None.

Poster

850. Algorithms and Network Models for Cognition and Behavior

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 850.08/NNN36

Topic: I.06. Computation, Modeling, and Simulation

Support: BBSRC UK BB/L000814/1

BBSRC UK BB/L002353/1

Title: A computational model of interacting neuronal populations for decision making and behaviour selection in Xenopus tadpole

Authors: ***R. BORISYUK**[1], R. MERRISON-HORT[1], S. KOUTSIKOU[2], A. ROBERTS[2], S. R. SOFFE[2];
[1]Plymouth Univ., Plymouth, United Kingdom; [2]Univ. of Bristol, Bristol, United Kingdom

Abstract: A general approach to decision making postulates that signals from different sensory modalities are integrated to select from amongst multiple options. This integration process is important due to the noisy nature of sensory signals. We implement the integration of noisy sensory signals in a simple computational model that can describe the behavioural switching observed in hatchling *Xenopus* tadpoles (Roberts et al., 2010, Front Behav Neurosci 4:16). This animal provides a good place to study decision making because its repertoire of behaviours and sensory signals is small, and many biological details are known from experimental work. Despite its simplicity, the computational model can clarify the universal neurobiological mechanisms and theoretical principles of decision making, as well as provide new ideas and hypotheses for experimental testing.

The model has two parts. The first relates to the central pattern generator (CPG) that generates locomotor behaviour. Possible actions include: swimming start, stop and acceleration, and struggling start and stop. To model these we consider populations of excitatory and inhibitory neurons on both sides of the body. Each population is represented by the Wilson-Cowan equations, which describe the average population dynamics. Bifurcation analysis of coupled excitatory and inhibitory populations can determine the parameter values for which oscillations exist. We studied two coupled neural oscillators and found a many possible dynamical regimes: steady-state, in-phase and anti-phase oscillations, quasiperiodic (modulated) activity, and chaos. These studies allow us to select parameter values that mimic swimming (anti-phase oscillations) with a range of frequencies, acceleration and slowing. Struggling is modelled by bursting activity, where fast in-phase oscillations on opposite body sides are modulated in an envelope by slow anti-phase oscillations. Bifurcation analysis also highlights how the parameters can be used to control dynamics and switch from one mode to another.
The second part of the model describes sensory pathways and signal integration. This modelling is based on recent neurobiological findings on neuronal coordination of the initiation of locomotion. The model includes four sensory signals: (1) touch trunk skin (TS); (2) touch head (TH); (3) dimming light (DL) and (4) press head or cement gland (inhibitory signal). These signals arrive at an integrating population, which selects an action from the repertoire of CPG. We demonstrate how arbitrary external environmental inputs in the form of noisy sensory signals are integrated to control locomotor behaviour.

Disclosures: R. Borisyuk: None. **R. Merrison-Hort:** None. **S. Koutsikou:** None. **A. Roberts:** None. **S.R. Soffe:** None.

Poster

850. Algorithms and Network Models for Cognition and Behavior

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 850.09/NNN37

Topic: I.06. Computation, Modeling, and Simulation

Support: UNAM-DGAPA-PAPIIT IA207316

Title: Modeling tritocerebrum by using artificial spiking neural networks. effects of temperature and social status

Authors: *K. MENDOZA-ANGELES[1], S. ARELLANO-TIRADO[2], A. ESPINOZA-GARCÍA[3], I. CHAIREZ[2], J. HERNÁNDEZ-FALCÓN[3];
[1]Univ. Nacional Autónoma De México, México, Mexico; [2]Inst. Politécnico Nacional, México, Mexico; [3]Univ. Nacional Autónoma de México, México, Mexico

Abstract: Crayfish cardiorespiratory activity seems to have a central control, located in tritocerebrum. Electrical oscillations of this area parallel those recorded from scaphognathites. Many stimuli induce changes in heart or respiratory frequency. There are no data on a particular region in charge of cardiac or respiratory regulation or on the involved mechanisms.
The main purpose of this work was to build a computational model capable to correlate tritocerebral electrical activity and cardiorespiratory responses to temperature and social hierarchical status. Our model should be able to predict the neural elements involved in cardiorespiratory adjustments. We used pulsed artificial neural networks.
We used *Procambarus clarkii* crayfish and recorded tritocerebral electrical activity via implanted electrodes on the brain surface, cardiac electrical activity via an electrode inserted over the cardiac sinus, and respiratory activity through a couple of electrodes inserted in the branchial cavity. Electrodes were implanted in cold anesthetized crayfish. After recovery, we obtained simultaneous recordings of these variables from control animals and from animals under different temperatures or before, during and after agonistic encounters.
We developed a massive, parallel neural network model with pulsated Izhikevich neurons. They were interconnected with relative weights representing interaction among neural layers. Weights were adjusted using differential algorithms. The model reproduced the recorded tritocerebral signals. After training the model under control conditions we reproduced the signals obtained in experimental conditions.
Therefore, from the correlation among the weights from the artificial network, we propose a correlation between the tritocerebral electrical activity and the cardiorespiratory response under different experimental conditions.

Disclosures: K. Mendoza-Angeles: None. **S. Arellano-Tirado:** None. **A. Espinoza-García:** None. **I. Chairez:** None. **J. Hernández-Falcón:** None.

Poster

850. Algorithms and Network Models for Cognition and Behavior

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 850.10/NNN38

Topic: I.06. Computation, Modeling, and Simulation

Support: HHMI

Title: A model for zebrafish adaptive optomotor behavior

Authors: S. ROMANI, H. ROUAULT, M. B. AHRENS, *N. VLADIMIROV;
Janelia Res. Campus / HHMI, Ashburn, VA

Abstract: The optomotor response (OMR) and motor adaptation are well-established visually driven behaviors in zebrafish. In the OMR, animals turn and move along with the direction of visual flow, thus stabilizing their heading direction and body position relative to visual cues present in a water stream. In head-restrained zebrafish, the OMR can be studied in two distinct settings. In open-loop, a constantly drifting visual scene is presented, and zebrafish swim vigorously in the direction of motion. In closed-loop, locomotion of the restrained animal is emulated by motion of the visual scene, such that fictive swim bouts of the fish generate corresponding backward accelerations of the stimulus. In the latter setting, fish perform the OMR and additionally motor adaptation, i.e. they adjust the intensity and frequency of swim bouts to the motosensory gain of the closed-loop system.
We propose a minimal population-based neural network model that accounts for the open-loop OMR. The flow of the visual scene is decomposed into forward and backward components, and these drive and inhibit premotor centers, respectively. Predictions of the model - specifically, a long-term effect of backward motion on OMR - are confirmed in real fish at the behavioral level. This basic model can further be placed in the closed-loop setting, where simulated motor activity drives the motion of the visual stimulus. We show that this joint system reproduces periodic swimming and gain adaptation, in a good qualitative agreement with experimental data. These results show that the OMR and gain adaptation can be accounted for by a shared circuit mechanism. Future work will be aimed at identifying the model components in functional brain data, extending the model to account for additional aspects of adaptive behavior, as well as comparing this model to other models capable of explaining adaptive visual behaviors.

Disclosures: S. Romani: None. **H. Rouault:** None. **M.B. Ahrens:** None. **N. Vladimirov:** None.

Poster

850. Algorithms and Network Models for Cognition and Behavior

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 850.11/NNN39

Topic: I.06. Computation, Modeling, and Simulation

Support: SNI fellowship

Title: Examination of large-scale functional brain networks in *Drosophila*

Authors: *K. MANN, IV[1], C. GALLEN[3], T. CLANDININ[2];
[1]Neurosci., [2]Neurobio., Stanford, Stanford, CA; [3]Helen Wills Neurosci., Univ. of California, Berkeley, Berkeley, CA

Abstract: Recent advances in neuroscience have demonstrated that the brain can be conceptualized as a complex network. Work in both humans and other organisms suggests that there are common organizational properties of brain networks that are critical for supporting efficient information transfer across the brain, such as the presence of highly connected network hubs, long-range connections, and densely interconnected sub-networks. Thus far, studies of brain networks in non-human animals have been primarily limited to the analysis of structural data, such as through clonal analysis in Drosophila or EM reconstruction in C. elegans. Drosophila is an excellent model organism to investigate functional brain networks in non-human animals, both at rest and during behavior. Whole brain calcium imaging can be performed at a sufficient rate to examine a range of fluctuations in functional network connections. Further, there is a highly developed set of tools for genetic manipulation and the control of neurons in vivo. Here, we developed novel analysis tools to characterize the resting brain network organization in Drosophila. Adult Drosophila expressing GCaMP6M pan-neuronally were head fixed and dissected, exposing the central brain. Whole brains were imaged using a two-photon laser at 2Hz. Following functional scans, high-resolution anatomical scans of the brains were acquired for alignment. Brains were aligned to a standard fly brain and were parcellated into 68 regions of interest (ROIs). Time series from the voxels in each ROI were averaged and correlations between each ROI-pair were computed to generate correlation matrices representing the functional connectivity between ROIs.Brain regions known to support similar functions in Drosophila showed high functional correlations. For example, regions important for olfactory processing, such as the antennal lobes, mushroom bodies, and lateral horns, exhibited high connectivity, suggesting that resting state connectivity reflects canonical circuit function. Further, the correlation matrices were characterized by high interhemispheric connectivity and the presence of long-range (i.e., physically distant) connections. Future experiments will aim to quantify the reconfiguration of resting brain architecture during behavior and to examine longitudinal changes in brain network structure in early development, focusing on critical network alterations that occur with the emergence of behavioral abilities. By using a model organism that is amenable to many causal manipulations of brain function, these analysis tools will provide important advances in our understanding the network architecture of the brain.

Disclosures: **K. Mann:** A. Employment/Salary (full or part-time): stanford. **C. Gallen:** A. Employment/Salary (full or part-time): uc berkeley. **T. Clandinin:** A. Employment/Salary (full or part-time): STANFORD.

Poster

850. Algorithms and Network Models for Cognition and Behavior

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 850.12/NNN40

Topic: I.06. Computation, Modeling, and Simulation

Title: The computational role of dopamine, basal ganglia, and hippocampus in extinction and spontaneous recovery.

Authors: J. RODNY, *D. C. NOELLE;
Cognitive and Information Sci., Univ. of California, Merced, Merced, CA

Abstract: The effects of dopamine (DA) on synaptic plasticity have been broadly implicated in associational learning. Computational neuroscience models of the basal ganglia (BG), including the striatum and the DA nucleus of the substantia nigra pars compacta (SNc), have captured an extensive array of learning phenomena by incorporating the temporal difference (TD) learning method. These models view DA as encoding changes in expected future reward, and the DA signal modifies synapses so as to both improve predictions of reinforcement and increase the likelihood of taking actions leading to reward (Montague, Dayan, & Sejnowski, 1996). We note that TD learning is symmetric with regard to the acquisition of an association and its extinction, and we view this symmetry as a weakness. Studies of both non-human animals and patient populations have found a critical dependence on the hippocampus for extinguishing an association but not for its initial acquisition (Kimble & Kimble, 1970; Weikart & Berger, 1986; Shohamy et al., 2009). In response to this observation, we have explored alternative computational accounts of DA-mediated learning in the BG, focusing on approaches that incorporate biologically plausible, yet computationally efficient, models of neural spiking dynamics (Izhikevich, 2007). Specifically, we have replicated the spiking neural network model of the BG proposed by Chorley & Seth (2011), and we have performed analyses showing that this model, while producing observed DA spiking patterns, is not symmetric with regard to the acquisition and extinction of an association. Inspired by the abstract reinforcement learning account of Redish et al. (2007), we have explored augmenting the Chorley & Seth (2011) BG model with a spiking model of the hippocampus. The hippocampus is seen as producing sparse conjunctive representations (McClelland, McNaughton, & O'Reilly, 1995) of the animal's current state, and, critically, this state incorporates internal variables, such as hunger and satiation. In our account, hippocampus supports extinction by changing the representation of the animal's current state, rather than removing an association with the state present during initial conditioning. This mechanism leaves in place synaptic changes that can produce spontaneous recovery. The augmented model also provides an explanation for the relative lack of spontaneous recovery when an association undergoes gradual extinction (Gershman et al., 2013). In this presentation, the resulting spiking neural network model of interactions between the BG and the hippocampus is compared to TD learning accounts, and computational simulation results are discussed.

Disclosures: J. Rodny: None. **D.C. Noelle:** None.

Poster

851. Computational Tools for Human Data II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 851.01/NNN41

Topic: I.06. Computation, Modeling, and Simulation

Support: MEXT Grant-in-Aid for Scientific Research on Innovative Areas 15H05877

ImPACT Program of Council for Science, Technology and Innovation (Cabinet Office, Government of Japan)

Title: EEG metastable states in the resting human brain

Authors: *T. SASE, K. KITAJO;
RIKEN Brain Sci. Inst., Saitama, Japan

Abstract: It has been reported that electroencephalography (EEG) signals exhibit rapid transitions among four representative topographical patterns or states called microstates in a resting condition. These four EEG microstates are extracted based on a cluster analysis and therefore, it has not been well known how to associate such microstates with metastable and multistable states from a dynamical systems point of view. Accordingly, the relationship between the microstates and the underlying mathematical structure remains unclear. We report novel states named mesostates, exhibiting slow transitions compared to the conventional microstates. In contrast to the microstates extracted directly from raw EEG signals, the mesostates are derived from the instantaneous amplitude of the signals. Here we provide experimental evidence that EEG mesostates are associated with the metastable and multistable states in the resting-state brain networks, by using dimensionality reduction methods to investigate whether multiple mesostates coexist separately with each other in the state space. We recorded scalp EEG signals of 63 electrodes from 80 subjects during 180 s in an eyes-closed resting condition. The subjects gave informed consent before participating in this study. We extracted 63-dimensional time series of the 10 Hz alpha-band instantaneous amplitude, derived an optimal number of mesostates for each individual, and identified a trajectory moving in the multistable potential. In addition, we have found that intrinsic noise in the brain causes transitions among the mesostates, by applying the recently developed novel dimension called time series dimension (TSD), to raw EEG signals (Sase, et al. Physics Letters A, 2016). Based on this TSD analysis, the negative correlation between the estimated noise level and the alpha power has been verified. This relationship suggests a possibility that the power is associated with the potential energy of metastable states since if the power is high, then the brain dynamics is robust to intrinsic noise. To validate the aforementioned EEG results, a toy model comprising multistable states was tested. We discuss functional significance of the mesostates from a dynamical systems point of view.

Disclosures: **T. Sase:** None. **K. Kitajo:** None.

Poster

851. Computational Tools for Human Data II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 851.02/NNN42

Topic: I.06. Computation, Modeling, and Simulation

Support: ImPACT Program of Council for Science, Technology and Innovation (Cabinet Office, Government of Japan)

KAKENHI No. 25120011 (MEXT, Japan)

KAKENHI No. 16H01617(MEXT, Japan)

Title: Discovering consistency in human brain activities with noisy visual inputs using reservoir kernel machines

Authors: *H. SUETANI[1], Y. MIZUNO[2], K. KITAJO[2];
[1]Oita Univ., Oita, Japan; [2]RIKEN Brain Sci. Inst., Wako, Japan

Abstract: Neural activity in the brain is composed of the combination of spontaneous activities as an autonomous nonlinear dynamical system and responses to the external sensory inputs. As known in the seminal paper by Mainen and Sejnowski (Mainen and Sejnowski 1995), at the single cell level, spike timings are consistent (or reliable) against the fluctuating inputs i.e., a neuron driven by the common fluctuating inputs exhibits the precise timing of firings over different trials starting from different initial conditions. In general, however, circuits in central nervous systems exhibit irregular spontaneous activities which seem not directly related to sensory information from the outside. It has not been clarified whether neural dynamics at the global network level is also consistent or not against the external inputs. In our preliminary study (Kitajo and Suetani 2014), we have shown that human brain activities include consistent components against the visual inputs by analyzing 63-ch electroencephalography (EEG) time series while subjects were watching a randomly flickering checkerboard movie using canonical correlation analysis (CCA). It is not, however, enough to clarify the dynamical mechanism behind these observations only using descriptive statistical methods such as CCA. We, therefore, propose a reservoir computing approach (Jaeger 2001, Maas et al. 2002) in the situation where "reservoirs" (large and recurrent artificial neural networks) are considered as spatiotemporal kernel functions as the system size goes to infinity (Hermans and Schrauwen 2012). We apply the reservoir kernel machines to the both problems of encoding (prediction of EEGs from noisy

stimuli) and decoding (prediction of noisy stimuli from EEGs). We focus on how EEG consistency is reflected in the structure of the synaptic weights from the reservoir neurons to the output neurons. We also discuss the features of the reservoir kernel machines after learning as nonlinear dynamical systems.

Disclosures: **H. Suetani:** None. **Y. Mizuno:** None. **K. Kitajo:** None.

Poster

851. Computational Tools for Human Data II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 851.03/NNN43

Topic: I.06. Computation, Modeling, and Simulation

Support: ImPACT Program of Council for Science, Technology and Innovation (Cabinet Office, Government of Japan)

Title: Individual differences in noise-induced human brain dynamics

Authors: ***K. KITAJO**[1], T. SASE[1], Y. MIZUNO[1], H. SUETANI[2];
[1]RIKEN Brain Sci. Inst., Wako, Saitama, Japan; [2]Fac. of Engin., Oita Univ., Oita, Japan

Abstract: It is known that spikes of a single neuron responding to a repeatedly presented noisy input show highly consistent temporal patterns across trials (Mainen and Sejnowski, 1995). From a nonlinear dynamical systems viewpoint, this phenomenon is called “consistency”, which is defined as the reproducibility of response waveforms of a nonlinear dynamical system driven by the same input signal, starting from different initial conditions of the system, as has been observed in laser systems (Uchida et al. 2004). It remains an open question whether macroscopic neural signals such as electroencephalography (EEG) shows such a temporally consistent nature to noisy sensory inputs. To this end, we investigated if human EEG responses to noisy visual inputs show a signature of consistency. We also tested if there exist individual differences in response waveforms. Ninety subjects participated in the study after giving informed consent. We measured 63-ch EEG signals at a sampling rate of 1000 Hz while subjects were watching a noisy flickering checkerboard. Subjects were presented with two different temporal realizations of Gaussian white noise for 5.5 seconds. Fourteen trials were given for each realization. To estimate the degree of consistency of brain responses, we applied a canonical correlation analysis (CCA)-based method between pairwise EEG trials within and across individuals. We observed that intra-individual correlations between pairs of EEG trials for an identical realization of noisy inputs were significantly higher than the intra-individual correlations between pairs of EEG trials for two different realizations of noisy inputs. Notably, FFT analyses revealed that the first

canonical components showed a prominent peak in the 4-8 Hz theta band, suggesting that this EEG consistency is related to macroscopic common noise-induced synchronization. We also found that inter-individual correlations were significantly lower than the intra-individual correlations for pairs of EEG trials for the same visual inputs. We also tested if a support vector machine (SVM) with CCA could classify single-trial EEGs from different individuals by the leave-one-out cross-validation method. Crucially, the SVM classifier showed the averaged accuracy of 98.5%. Together, macroscopic human brain responses exhibit a signature of consistency to identical noisy visual inputs. We speculated differences of nonlinear dynamical systems (i.e. individual brains) should be associated with distinct patterns of noise-induced neural responses across individuals. We also discuss trait-like and state-like features of EEG consistency.

Disclosures: **K. Kitajo:** None. **T. Sase:** None. **Y. Mizuno:** None. **H. Suetani:** None.

Poster

851. Computational Tools for Human Data II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 851.04/NNN44

Topic: I.06. Computation, Modeling, and Simulation

Support: Ruby Fellowship

NIH CoBRE P20GM109098

Research was sponsored by the U.S. Army Research Office and the Defense Advanced Research Projects Agency (DARPA) was accomplished under Cooperative Agreement Number W911NF-15-2-0016.

Title: Optimal solutions of human hand movements using inverse musculoskeletal model

Authors: ***M. BOOTS**[1], R. HARDESTY[1], A. SOBINOV[1], V. GRITSENKO[1], M. MANSOURI[2], R. A. GAUNT[2], S. YAKOVENKO[1];
[1]West Virginia Univ., Morgantown, WV; [2]Univ. of Pittsburgh, Pittsburgh, PA

Abstract: With advances in restorative robotics, complex limb prosthetics are becoming ever more realistic and can restore the functionality of an able-bodied human or even surpass it. However, a major bottleneck to widespread adoption and associated improvements in activities of daily living is that controlling these devices is neither intuitive nor robust. Muscle activation signals, measured with electromyography (EMG), are often noisy and have a non-linear relationship with the desired motion. The nonlinearities are partly due to muscle dynamics,

which is dependent on muscle length and velocity. This poses a barrier to utilizing EMG signals in prosthetic control. One intriguing solution is to take a biomimetic approach that uses musculoskeletal dynamics to resolve the relationship between muscle activation and intended movement. In practice, we can use intended kinematics to calculate biomimetic control signals and match them to recorded EMGs. Our hypothesis is that the optimal inverse solution of arm and hand movement produces simulated activation signals related to the intramuscular EMG in human volunteers.
To create simulated activation signals, we designed a feedforward dynamic model of a human hand in a real-time physics engine (MuJoCo) where joint torques were generated by simulated muscle forces using appropriate musculoskeletal dynamics. Able-bodied subjects were instrumented with up to 16 fine-wire intramuscular EMG electrodes in wrist and finger muscles and were asked to perform a variety of movements ranging from single-joint flexion and extension to ensemble finger and wrist movements. Detailed hand and arm kinematics included all hand degrees of freedom (DOF), and it was used within error minimization algorithm to calculate muscle activation inputs. We assumed that these inputs had Gaussian characteristics. Altogether, the optimization used 3 parameters per muscle: the first two were μ and σ that defined Gaussian temporal profile and the third lumped parameter that scaled muscle model. The optimization algorithm converged on solutions within expected muscle force levels. The overall kinematic errors were below 0.2 rad per DOF, and the spatiotemporal profiles of simulated and recorded activity were generally correlated across different movements. These results support our hypothesis and open opportunities for the development of robust biomimetic controller for hand prosthesis.

Disclosures: **M. Boots:** None. **R. Hardesty:** None. **A. Sobinov:** None. **V. Gritsenko:** None. **M. Mansouri:** None. **R.A. Gaunt:** None. **S. Yakovenko:** None.

Poster

851. Computational Tools for Human Data II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 851.05/NNN45

Topic: I.06. Computation, Modeling, and Simulation

Support: NIH/NIGMS U54GM104942

NIH CoBRE P20GM109098

the U.S. Army Research Office and the Defense Advanced Research Projects Agency (DARPA) under Cooperative Agreement Number W911NF-15-2-0016

Title: 'Good-enough' approximation of musculoskeletal dynamics

Authors: ***A. SOBINOV**, M. BOOTS, R. HARDESTY, V. GRITSENKO, S. YAKOVENKO; West Virginia Univ., Morgantown, WV

Abstract: Real-time control of artificial limbs and exoskeletons requires a fast and efficient way to compute and predict musculoskeletal dynamics. These computations are complex because most muscles span multiple degrees of freedom (DOF) with complex geometrical constraints. The common accurate, but costly approach to this problem is a detailed numerical simulation of physical interactions, for example dynamical modeling of musculoskeletal anatomy and physiology in OpenSim (Delp et al., 2007). The speed of simulations could be significantly improved with approximations. The global approximations in the form of inverse solutions have been successfully implemented to estimate muscle forces for problems that do not require a muscle model (Menegaldo et al., 2006). More recently, B-splines were used as an approximation method to calculate musculotendon length and moment arms as functions of joint angles (Sartori et al., 2012). This method improved precision of these calculations and enabled the implementation of muscle modeling, but the number of best-fit parameters increased exponentially with the number of vertices and DOFs required for different muscles. We developed a novel approximation using a phenomenological multivariate polynomial that contains different power and interacting terms to describe the musculotendon parameters. The polynomial was expanded from a constant to multivariate form that included significant terms and contracted from a complex polynomial form. This procedure quantified the contribution of each term to the overall precision of approximation. Our implementation approximated moment arms and muscle lengths with 'good-enough' precision (<5% error in length and moment arm), high evaluation speed (<1 ms for 26 arm muscles with 5 DOFs on average), and low memory demands (~40 KB). This 'good-enough' implementation is appropriate for systems with low computational power that need biomimetic signal representations for either control or system estimation.

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Menegaldo, L. L., de Toledo Fleury, A., & Weber, H. I. (2006). A "cheap" optimal control approach to estimate muscle forces in musculoskeletal systems. Journal of Biomechanics, 39(10), 1787-1795.

Sartori, M., Reggiani, M., van den Bogert, A. J., & Lloyd, D. G. (2012). Estimation of musculotendon kinematics in large musculoskeletal models using multidimensional B-splines. Journal of Biomechanics, 45(3), 595-601.

Disclosures: A. Sobinov: None. **M. Boots:** None. **R. Hardesty:** None. **V. Gritsenko:** None. **S. Yakovenko:** None.

Poster

851. Computational Tools for Human Data II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 851.06/NNN46

Topic: I.06. Computation, Modeling, and Simulation

Support: NSF: IIS-1420897

Google Faculty Research Award

Title: Encoding spoken and written digits as continuous trajectories in recurrent neural networks

Authors: *V. GOUDAR[1], D. BUONOMANO[1,2];
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Abstract: Many, if not most, of the tasks the brain performs are inherently temporal in nature: from recognizing and generating complex spatiotemporal patterns, such as speech and music, to creating temporal expectations of when an event will occur. Sensory and motor processing require the recognition and generation of complex time-varying patterns, respectively. However, the mechanisms that underlie the brain's ability to perform such spatiotemporal tasks are not known. A highly influential theory in computational neuroscience has long held that memories can be stored in the dynamics of RNNs—it argues that they are encoded as fixed-point attractors. A limitation of this theory is that the spatiotemporal "objects" processed and stored by the brain—e.g., a spoken word or the motor pattern used to sign your name—are defined as much by how they unfold in time as by their spatial structure at any given moment in time. To cope with this fact traditional models treat time-varying patterns as a sequence of transitions between discrete steady-state patterns. Consistent with mounting theoretical and experimental evidence, however, we show how the same RNN model can naturally encode both sensory and motor patterns as *continuous* neural trajectories. Representing a time-varying pattern as a continuous neural trajectory addresses a long-standing computational problem pertaining to temporal processing: temporal warping. Specifically, much like the brain, the RNN can recognize a stimulus played at different speeds as the same.
We demonstrate these results with an RNN trained to perform a complex sensory-motor task: transcribing spoken digits to "handwritten" digits. The network is composed of nonlinear continuous-time firing rate units with sparse recurrent connections. Its dynamics are initially chaotic; however, tuning its recurrent weights with the "innate-trajectory" learning rule (Laje and Buonomano, 2013), sculpts these dynamics to improve the RNN's ability to encode related sensory and motor spatiotemporal patterns as locally stable *continuous* trajectories. Consequently, trained networks are able to generalize to novel utterances and speakers, despite wide variations in the spatiotemporal structure and speed of these utterances. This framework predicts that computations on time-varying sensory and motor objects emerge from the voyage

through neural phase space—as opposed to the destination—and naturally captures how the brain represents time.

Disclosures: V. Goudar: None. **D. Buonomano:** None.

Poster

851. Computational Tools for Human Data II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 851.07/NNN47

Topic: I.06. Computation, Modeling, and Simulation

Support: NINDS Grant NS0802069

NIMH Grant MH063901

Title: Forward modeling in fMRI: efficacy and limits

Authors: *D. E. NEE, A. R. E. VANDENBROUCKE, E. S. LORENC, M. D'ESPOSITO; Univ. of California, Berkeley, Berkeley, CA

Abstract: fMRI data are increasingly being used to understand the representational basis of cognition. One useful technique is to train a forward model by projecting the fMRI data onto a lower dimensional basis set that is presumed to reflect underlying neural computations. The forward model can then be used to reconstruct representations in new data. A simple forward model where the basis set consists of a series of sinusoidal channels emulating the tuning properties of visual neurons (Brouwer and Heeger, 2009) has been increasingly used in the domains of perception, attention, and memory (hereafter, forward sinusoidal modeling or FSM). An advantage of FSM over multi-variate classification approaches is the ability to reconstruct representations that the model has never been trained upon. Such reconstruction enables the systematic examination of how representations are modulated or transformed by cognitive processes (e.g. Brouwer and Heeger, 2011; Kok et al., 2013). Additional uses of FSM include visualizing representations through the construction of tuning curves and examining properties such as the tuning curve amplitude, width, and center to infer details about the precision or accuracy of the underlying representations (Kok et al., 2013; Ester et al., 2013). FSM has also been implied to be more sensitive than multi-variate classification techniques, potentially revealing brain areas involved in representation that other techniques might miss (Ester et al., 2015). Here, we use simulations to assess the efficacy and limits of FSM. First, we find that tuning curves can be constructed using FSM even when the underlying representations are categorical (i.e. not tuned) rather than continuous in nature. This suggests that additional

measures must be taken to demonstrate continuous representational coding prior to performing inferences on constructed tuning curves. Second, we find that when the underlying data are tuned in the manner presumed by FSM, FSM is no more sensitive than categorical forward modeling under a range of signal-to-noise ratios (SNRs). This suggests that FSM may not be a more sensitive approach than categorical based multi-variate analysis. Third, we find that inferences based on properties of constructed tuning curves require high levels of SNR and/or very large numbers of samples. We conjecture that such SNR levels may be achievable in studies of perception, but difficult to achieve in studies of memory. Collectively, we conclude that while FSM can be useful to detail how representations are modulated or transformed by cognitive processes, several checks must be performed to ensure that inferences based on reconstructed representations are valid.

Disclosures: D.E. Nee: None. **A.R.E. Vandenbroucke:** None. **E.S. Lorenc:** None. **M. D'Esposito:** None.

Poster

851. Computational Tools for Human Data II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 851.08/NNN48

Topic: I.06. Computation, Modeling, and Simulation

Support: HP2020-PHC-2014 63454 / CDS-QUAMR

Title: Resolving large-scale networks in ultra-high field fMRI (9.4T) of the human brain

Authors: *J. STELZER[1,3], P. EHSES[3,4], J. BAUSE[4], K. SCHEFFLER[2,4], G. LOHMANN[2,4]; [1]Max Planck Inst. for Biol. Cybernetics, [2]Universitaetsklinik Tuebingen, Neuroimaging, Tuebingen, Germany; [3]Dept. of Biomed. Magnetic Resonance, Univ. of Tübingen, Tuebingen, Germany; [4]Max Planck Inst. for Biol. Cybernetics, MRC dept, Tuebingen, Germany

Abstract: The combination of ultra-high field fMRI with state-of-the art network approaches offers a unique window for studying human brain function at the mesoscopic level. In this study, we used a 9.4T MRI system to acquire functional data at submillimetre resolution, covering more than 500000 voxels in fronto-parietal areas. As experimental manipulation we tested a simple 2-back against an 0-back memory task, as in the human connectome project. We analysed the data with a network-based method which we specifically tailored for ultra-high-resolution data on the single subject level, named “task-induced edge density” or “TED”. Our method aims to detect task-dependent changes in synchronization across the entire brain. The algorithm operates on the voxel level and does not require any presegmentation or spatial smoothing of the data.

Our method reveals widespread changes in the network configuration across the two memory tasks. A large proportion of grey matter voxels changes its connectivity to the rest of the brain between the two tasks. Thus our findings suggest that vast parts of the cortex might subserve the underlying brain functions. Interestingly, a distributed subset of areas appears to change its connectivity to an especially large number of voxels, possibly indicating key areas or super-hubs within the network. We further discuss the fine structure of the connectivity patterns, such as the formation of subnetworks on smaller spatial scales and the relation to the underlying anatomical structure.
The present results distinctively favour a more integrative rather than segregative view of brain function, which appears to be wide-spread instead of sparse. However, our results also raise other issues of interpretability due to the sheer extent of the involved brain areas.

Disclosures: J. Stelzer: None. **P. Ehses:** None. **J. bause:** None. **K. Scheffler:** None. **G. Lohmann:** None.

Poster

851. Computational Tools for Human Data II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 851.09/NNN49

Topic: I.06. Computation, Modeling, and Simulation

Title: Transcranial magnetic stimulation (tms) coil designing for high electromagnetic field gradient generation

Authors: *Q. MENG[1], E. HONG[2], Y. YANG[3], H. LU[3], F.-S. CHOA[1];
[1]Univ. of Maryland, Baltimore County, Baltimore, MD; [2]Univ. of Maryland, Baltimore, Baltimore, MD; [3]Natl. Inst. on Drug Abuse, Baltimore, MD

Abstract: Transcranial magnetic stimulation (TMS) is currently the primary non-invasive brain stimulation methods. It relies on magnetic induced current to stimulate brain tissues. Cable equation is usually used to describe the stimulation bio-physics. Interestingly if we look carefully into the cable equation we will find that it is not the strength of the magnetic field, neither the strength of the induced electrical field that is used to charge the membrane potential and generate action potential. It is the spatial gradient of the induced electrical filed, **grad(E)**, which decides where the action potential will take place. Recently we and other reported experimental results have shown this is the case. As a result, many of the existing TMS tools, which designed to obtain highest magnetic field at desired relative location to the stimulator, are not working in optimized condition. Since they were designed to produce highest magnetic field instead of producing highest **grad(E)**. A well designed TMS tool with optimized **grad(E)** in mind can

achieve better focused stimulation spots at lower driving power. In this work, we propose a new TMS stimulator designs. Using two coils each with current flow running in opposite directions we can first achieve high magnetic field gradient. Since the induced E field is proportional to dB/dt, we expect the spatial derivative can be transferred to the induced E-field and achieve high grad(E). Two-dimensional calculation was completed by FEMM, a finite element analysis tool. A coil with larger radius was selectively located over several different relative positions to another coil with smaller radius. Their directions are in parallel and their size ratio is about 2 to 1. Current excitations in the stimulator were 150A for the big coil and 100A for the smaller one. By shifting the smaller coil along its horizontal level and change the two coils' relative positions, we can identify the optimized relative location. We found that the highest magnetic field gradient was able to be achieved when the inner diameter of big coil wiring is aligned with the outside diameter of the smaller coil. By adjusting the current excitation in both coils, it was found that the optimized current ratio (big coil current to smaller coil current) was from 1.5:1 to 1.7:1 in this case. With the two coil in antiphase operations we can achieve the same grad(E) amplitude at a lower total current compared with the conventional structure, like the figure-8 structure case. We expect new types of coil structure with optimized grad(E) design will replace these conventional design in the near future.

Disclosures: **Q. Meng:** None. **E. Hong:** None. **Y. Yang:** None. **H. Lu:** None. **F. Choa:** None.

Poster

851. Computational Tools for Human Data II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 851.10/NNN50

Topic: I.06. Computation, Modeling, and Simulation

Support: John D. and Catherine T. MacArthur Foundation

Alfred P. Sloan Foundation

Army Research Laboratory and the Army Research Office through contract numbers W911NF-10-2-0022 and W911NF-14-1-0679

National Institute of Mental Health (2-R01-DC-009209-11)

National Institute of Child Health and Human Development (1R01HD086888-01)

Office of Naval Research

National Science Foundation (BCS-1441502 and BCS-1430087)

Title: Using algebraic topology to characterize mesoscale structure in resting state fMRI

Authors: *C. GIUSTI[1], G. HENSELMAN[2], R. GHRIST[2], R. C. GUR[3], R. E. GUR[3], T. D. SATTERTHWAITE[3], D. S. BASSETT[1];
[1]Bioengineering, [2]Mathematics, [3]Psychiatry, Univ. of Pennsylvania, Philadelphia, PA

Abstract: The intricate way in which groups of brain regions dynamically interact provides a window into the brain's underlying computational organization. The language of networks, while well suited for describing structural connectivity between brain regions, is limited in its ability to express the inherently non-dyadic nature of observations of function. To investigate this higher-order structure, we apply a collection of tools called *clique topology*, recently adapted from the field of algebraic topology, to provide quantitative characterization of mesoscale structures in observations of neural population activity [1]. Specifically, we consider any collection of brain regions with strong pairwise coherence in activity time series to be a *clique*; certain cohesive motifs of cliques called *cycles* then detect interesting system-scale structure in the observed coherence patterns. Considering resting state fMRI in normative neurodevelopment, acquired from 780 healthy subjects aged 8 to 22, we find a consistent cycle structure that indicates geometric organizational principles underlying the population coherence [2]. This suggests that an organizational model for resting state activity based on a geometric “computation space” may be suitable for understanding human brain resting state dynamics during development.
[1] Chad Giusti, Eva Pastalkova, Carina Curto, and Vladimir Itskov. Clique topology reveals intrinsic geometric structure in neural correlations. Proc. Nat. Acad. Sci. USA, 112(44):13455{13460, 2015.
[2] Ann Sizemore, Chad Giusti, and Danielle S Bassett. Classification of weighted networks through mesoscale homological features. Journal of Complex Networks (to appear), 2016.

Disclosures: C. Giusti: None. **G. Henselman:** None. **R. Ghrist:** None. **R.C. Gur:** None. **R.E. Gur:** None. **T.D. Satterthwaite:** None. **D.S. Bassett:** None.

Poster

851. Computational Tools for Human Data II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 851.11/NNN51

Topic: I.06. Computation, Modeling, and Simulation

Title: Space-independent community structure of the human connectome

Authors: *R. BETZEL[1], J. MEDAGLIA[2], L. PAPADOPOULOS[3], D. BASSETT[4];
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Abstract: The *human connectome* is the complete set of brain regions linked by white-matter fascicles. As a network the human connectome is modular, meaning that it can be partitioned into internally dense modules. Modules take on practical significance as they are often interpreted as estimates of the brain's "functional systems". Accordingly, the methodology used to detect modules has a profound effect on their interpretation.The most popular algorithm for doing so is *modularity maximization*, which seeks a partition that maximizes a modularity quality function, *Q*. The optimal partition is composed of modules whose internal densities are maximally dense compared to some null model. In this framework, the form of the null model is left unspecified. The *de facto* null model is preserves certain aspects of the real network but otherwise assumes that connections are made uniformly at random. For spatial networks like the human connectome, however, where geometric constraints penalize the formation of long connections, such a model may be inappropriate. Consequently, the null model should be informed by these geometric constraints. Here, we propose modifying the modularity quality function to include a spatially-informed null model. Specifically, our null model supposes that the probability of connection formation between brain regions decays monotonically as a function of distance. We subsequently maximize this modularity for connectomes reconstructed using spectrum imaging and tractography. We show that the resulting modules (1) exhibit distinct geometric profiles, distinguishing them from communities detected using standard null models. In particular, the modules detected using the modified quality function tend to be spatially-distributed, oftentimes spanning both left and right cerebral hemispheres. This is in stark contrast to modules detected using the standard quality function, which tend to be spatially-compact. (2) Moreover, the topographic profiles of the communities detected using the spatially-informed null model better agree with the topography of canonical cognitive systems (e.g. subnetworks for cognitive control and attention). Finally, modular structure can be used to assess brain regions' functional roles, an intuition quantified by the participation coefficient. With the standard null model, influential hub regions are located in posterior cingulate and precuneus, possibly reflecting their positions near the geometric center of the brain. We show that (3) using the spatially-informed null model, influential regions move laterally and include portions of the posterior parietal and lateral prefrontal cortices.

Disclosures: R. Betzel: None. **J. Medaglia:** None. **L. Papadopoulos:** None. **D. Bassett:** None.

Poster

851. Computational Tools for Human Data II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 851.12/NNN52

Topic: I.06. Computation, Modeling, and Simulation

Title: A method for the automatic quantification of the first response of the corticocortical evoked potential measured with ECoG

Authors: *D. HERMES[1,3], A. VASSILEVA[4], K. J. MILLER[2], N. F. RAMSEY[4], F. S. S. LEIJTEN[4], G. HUISKAMP[4];
[2]Dept. of Neurosurg., [1]Stanford Univ., Stanford, CA; [3]Dept Neurol. & Neurosurg., UMC Brain Ctr. Rudolf Magnus, Univ. Med. Ctr. Utrecht, Utrecht, Netherlands; [4]Dept Neurol. & Neurosurg., Brain Ctr. Rudolf Magnus, Univ. Med. Ctr. Utrecht, Utrecht, Netherlands

Abstract: Electrical stimulation has been used to characterize the directional connectivity between brain regions. It has been hypothesized that structural connections between areas decrease the variability (latency and occurrence) in the evoked responses in connected regions. When electrodes are implanted on the human brain for electrocorticography (ECoG) recordings and epilepsy monitoring, electrodes can be stimulated with a brief pulse. This type of stimulation elicits cortico-cortical evoked potentials (CCEPs) in connected areas throughout the brain. The first negative deflection in the CCEP, typically peaking between 15 and 60 ms, (the N1) is thought to specifically reflect cortico-cortical connections. In order to capture the variability of the N1, we developed a method that automatically detects this feature and characterizes its amplitude, latency and variability. CCEPs were measured during ECoG recordings in 4 patients with electrodes covering anterior and posterior regions involved in speech and in 3 patients with electrodes covering ventral and dorsal visual pathways. These areas have known anatomical connections (the arcuate fasciculus and vertical occipital fasciculus respectively). Electrode pairs were stimulated with 10 monophasic pulses for 1 ms (8mA). CCEP data were corrected for offset and drift in individual trials, and a single Gaussian function was fitted to the evoked potential up to 100 ms, thus capturing the latency, width and amplitude of the N1. The function was fitted on half the trials, and described the other half of the trials well, explaining over 30% of the variance in the response on connected regions. The latency and width of the CCEP showed large variations across subjects and electrodes, but could be captured well with this simple model. Fast, narrow responses, were found adjacent to the stimulated electrodes and on regions with known connectivity. A simple function could characterize a large variability in the evoked potentials elicited by stimulating connected brain regions. The robust and reliable characterization of these features is important to understand connectivity in the human brain for both clinicians and basic scientists.

Disclosures: **D. Hermes:** None. **A. Vassileva:** None. **K.J. Miller:** None. **N.F. Ramsey:** None. **F.S.S. Leijten:** None. **G. Huiskamp:** None.

Poster

851. Computational Tools for Human Data II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 851.13/OOO1

Topic: I.06. Computation, Modeling, and Simulation

Support: NIDCD Intramural Research Program

Title: Using a large-scale neural model to simulate laminar fmri activity for a visual delayed match-to-sample task.

Authors: *P. T. CORBITT[1], A. ULLOA[2], B. HORWITZ[3];
[1]NIDCD, NIH, Westminster, MD; [2]Neural Bytes LLC, Washington DC, DC; [3]Natl. Inst. on Deafness and Other Communication Disorders, Bethesda, MD

Abstract: Electrophysiological and neuroanatomical studies in nonhuman mammalian preparations have begun to elucidate the role of neurons in different cerebral cortical laminae. Functional neuroimaging can, in principle, resolve cortical lamina, potentially providing insight into laminar computation and interregional laminar connectivity in human subjects. However, limited spatial and temporal resolution of human neuroimaging results are difficult to interpret. Biologically realistic simulations can aid the experimental interpretation by relating the neuroimaging data to the activity of the underlying neural substrate. Previously, we have constructed a large-scale, multiregion neural model that simulates neural activity for a visual delayed match-to-sample (vDMS) task (Tagamets & Horwitz, Cerebral Cortex, 1998; Ulloa & Horwitz, submitted). Each region of the model consists of multiple neural mass models representing a cortical column. Here, we employ a modified Wang-Knösche unit (PloS One, 2013), representing a simplified cortical column. This basic unit has supragranular, granular, and infragranular layers representing different types of neurons: spiny stellate, pyramidal, and inhibitory. We simulated layer specific neural activity which is translated into local field potential-like integrated synaptic activity and then converted into simulated fMRI activity. The Wang-Knösche units allows for detailed connectivity schemes, e.g. Felleman and van Essen (Cerebral Cortex, 1991), between regions that produce different response patterns. Differences in the magnitude of laminar synaptic activities are the prominent finding. We show differences between conditions (DMS and passive viewing) in the fMRI signal and in the functional connectivity. The model provides proof that in principle laminar specific fMRI can provide insights into laminar processing. These results suggest that overcoming technical challenges of

laminar specific fMRI will create a potent tool that will provide fundamental insights to human neuroscience.

Disclosures: **P.T. Corbitt:** None. **A. Ulloa:** None. **B. Horwitz:** None.

Poster

851. Computational Tools for Human Data II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 851.14/OOO2

Topic: I.06. Computation, Modeling, and Simulation

Support: John D. and Catherine T. MacArthur Foundation

Alfred P. Sloan Foundation

Army Research Laboratory W911NF-10-2-0022

Army Research Office W911NF-14-1-0679

National Institute of Mental Health (2-R01-DC-009209-11)

National Institute of Child Health and Human Development (1R01HD086888-01)

Office of Naval Research (Young Investigator)

Title: White matter connectivity supports increasing diversity of neural dynamics across normative neurodevelopment

Authors: ***E. TANG**[1], C. GIUSTI[1], G. BAUM[2], S. GU[1], A. E. KAHN[1], D. ROALF[2], R. C. GUR[2], R. E. GUR[2], T. D. SATTERTHWAITE[2], D. S. BASSETT[1];
[1]Bioengineering, [2]Psychiatry, Univ. of Pennsylvania, Philadelphia, PA

Abstract: The human brain is able to support a wide range of cognitive functions via the coordinated activity of multiple regions. Such coordination is vital in many processes, including the synchronization[1] of two or more brain regions, and the control of activity patterns[2, 3] across length scales. The role of white matter connectivity in supporting these different coordination types is not well understood, nor is it easy to quantify how such structure emerges across development. Here we use a network representation of diffusion imaging data to show that the pattern of white matter connectivity changes appreciably with age, displaying a global increase in controllability and associated decrease in global synchronizability. These trends emerged from an ensemble of networks[4] obtained from diffusion tensor imaging of 882

healthy individuals from ages 8 to 22. In addition to these global trends, we also observed pronounced regional differentiation in which regions of high control become super-controllers whose influence only extends locally to short length-scale synchronization. Conversely, regions of low control in executive areas become even less influential, but whose influence extends broadly to long length-scale synchronization. Our results quantify the range of supported dynamics and regional specialization in the brain, which significantly increase with age. These analytical methods allow the relating of disparate cognitive systems to different types of controllability and oscillatory patterns -- indicating how structure can facilitate rhythms and more general dynamics in the human brain.

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Disclosures: **E. Tang:** None. **C. Giusti:** None. **G. Baum:** None. **S. Gu:** None. **A.E. Kahn:** None. **D. Roalf:** None. **R.C. Gur:** None. **R.E. Gur:** None. **T.D. Satterthwaite:** None. **D.S. Bassett:** None.

Poster

851. Computational Tools for Human Data II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 851.15/OOO3

Topic: I.06. Computation, Modeling, and Simulation

Support: John D. and Catherine T. MacArthur Foundation

the Alfred P. Sloan Foundation

Army Research Laboratory W911NF-10-2-0022

the National Institute of Mental Health (2-R01-DC-009209-11),

the National Institute of Child Health and Human Development (1R01HD086888-01)

Office of Naval Research (Young Investigator)

the National Science Foundation (BCS-1441502, BCS-1430087 and PHY-1554488))

Title: Energy landscape underpinning module dynamics in the human connectome

Authors: *A. ASHOURVAN[1,6,2], S. GU[2,3], M. G. MATTAR[2,4], J. M. VETTEL[6], D. BASSETT[2,5];
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Abstract: Human brain dynamics can be viewed fruitfully through the lens of statistical mechanics, where neurophysiological activity evolves around and between local attractor basins. Traditionally these models define the state of the brain or a set of neurons based on instantaneous measurements of regional or neuronal activity, respectively (Tang et al., 2008; Watanabe, Masuda, Megumi, Kanai, & Rees, 2014). Yet, recent work in the emerging field of *network neuroscience* has provided initial evidence that the human brain might also be characterized by time-varying states of locally coherent activity forming functional modules (e.g. (Bassett et al., 2011)). Here we study this network-based notion of brain state to understand how functional modules dynamically interact with one another to perform cognitive functions. Specifically, we estimate the functional relationships between regions of interest (ROIs) by fitting a pair-wise maximum entropy (Watanabe, Hirose, et al., 2014) model to each ROI's pattern of module allegiance. Local minima in this model represent attractor states characterized by specific patterns of modular structure. Hierarchical clustering of these local minima highlight three classes of ROIs with similar patterns of allegiance to community states. Visual, attention, sensorimotor, and subcortical ROIs tend to form a single functional community (Class-I). The remaining ROIs tend to form a putative executive control community (Class-II) or a putative default mode and salience community (Class-III). We simulate the brain's dynamic transitions between these community states using a Markov Chain Monte Carlo random walk (Zhou, 2011). We observe that simulated transition probabilities between basins strongly resemble empirically observed transitions between community allegiance states in resting state fMRI data. The accuracy of our predictions is strongest for the transitions probabilities of Class-I ROIs (primary sensorimotor, attention, subcortical), followed by Class-III ROIs (default mode), but to a lesser extent Class-II ROIs (executive), highlighting the transient fluctuations characteristic of cognitive control systems. Together, these results offer a view of the brain as a dynamical system that transitions between basins of attraction characterized by coherent activity in small groups of brain regions, and that the strength of these attractors depends on the cognitive computation being performed.

Disclosures: **A. Ashourvan:** None. **S. Gu:** None. **M.G. Mattar:** None. **J.M. Vettel:** None. **D. Bassett:** None.

Poster

851. Computational Tools for Human Data II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 851.16/OOO4

Topic: I.06. Computation, Modeling, and Simulation

Support: NIH-R44NS092144

Title: Direct experimental validation of transcranial electric stimulation models with intracranial recordings in human

Authors: *Y. HUANG[1], A. LIU[2], B. LAFON[1], D. FRIEDMAN[2], M. DAYAN[3], X. WANG[2], O. DEVINSKY[2], L. PARRA[1];
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Abstract: Transcranial electric stimulation (TES) aims to stimulate the brain by applying weak electric currents at the scalp surface. However, there is significant debate as to the magnitude and spatial distribution of the resulting electric fields achieved in the human brain. Sophisticated computational models of current flow have been used to predict these electric fields, but none of these models have been validated in humans. Here we measure electric potentials intracranially in ten (10) patients undergoing invasive monitoring for epilepsy surgery. The voltage distribution across the cortical surface and depth electrodes are well predicted by models which capture individual head anatomy at a 1 mm^3 resolution. However, electric field magnitude is systematically overestimated when using tissue conductivity values reported in the literature. When calibrating scalp and skull conductivities to provide accurate prediction of field magnitudes, we find fields of up to 0.5 V/m at the cortical surface for 2 mA of TES. We identify a single set of conductivity values which provide good predictions across individuals. While modeling cerebro-spinal fluid is important, more sophisticated modelling approaches, such as differential conductivity between skull spongiosa and compacta, and white matter anisotropy, do not improve model predictions. These findings provide prescriptive guidelines for future modeling efforts and a solid foundation for human experimentation.

Disclosures: **Y. Huang:** None. **A. Liu:** None. **B. Lafon:** None. **D. Friedman:** None. **M. Dayan:** None. **X. Wang:** None. **O. Devinsky:** None. **L. Parra:** None.

Poster

851. Computational Tools for Human Data II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 851.17/OOO5

Topic: I.06. Computation, Modeling, and Simulation

Support: NIH Grant EB009666

Title: Network changes between task- and resting- state functional connectivity predict behavior across datasets

Authors: *M. SALEHI[1], D. SCHEINOST[5], E. S. FINN[2], M. D. ROSENBERG[3], M. M. CHUN[2,3,4], R. CONSTABLE[2,5,6];
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Abstract: Differences in functional connectivity patterns are observed between task and resting-state. Despite the widespread use of task-based fMRI to study brain function, studies have yet to address fundamental questions regarding how changes in global and local network properties can be quantified and related to cognitive behavior. In this work, we define a novel measure of brain connectivity based on the correlation of network centrality during task and rest. We show that this measure predicts individual differences in attention task performance.
Using task and resting-state fMRI data collected on the same subject, we constructed 268x268 connectivity matrices for each condition and calculated network strength for each node (defined as the absolute value of weighted degree). Next, we correlated the strength for each node across every pair of task or resting-state runs to create a higher order measure of brain organization. For each subject, we summarized this measure as the difference of the correlation between task sessions and the correlation between rest sessions. We related our measure of brain organization to task performance using linear regression and leave-one-out cross-validation prediction models. We used three difference task datasets each with three task runs and two resting-state runs. The three tasks were an n-back task (25 subjects), a continuous performance task (gradCPT; 18 subjects), and the Attention Network Task (ANT; 27 subjects).
Nodal behavior is significantly more similar within an individual across three attention tasks relative to resting-state (ANOVA: $p<10^{-5}$). Moreover, the difference of the correlation between task runs and the correlation between resting-state runs was significantly correlated with task performance (n-back: $r=0.47$, $p<0.01$; gradCPT: $r=0.58$, $p<0.01$; ANT: $r=-0.38$, $p<0.05$). Next, for all three tasks, we employed leave-one-out cross-validation and observed significant prediction of task performance using the same difference metric (n-back: $r=0.64$, $p<10^{-3}$; GradCPT: $r=0.75$, $p<10^{-4}$; ANT: $r=0.41$, $p<0.03$). Finally, we performed cross-dataset prediction

and observed significant prediction of task performance between the n-back and gradCPT ($r=0.75$, $p<0.001$ and $r=0.55$, $p<0.008$).
Using our higher order brain measure, we showed that the change in nodal measures (network strength) between task and resting-state significantly predicts task performance. These observations suggest that individuals who display greater flexibility during rest, but higher consistency during task exhibit better task performance.

Disclosures: **M. Salehi:** None. **D. Scheinost:** None. **E.S. Finn:** None. **M.D. Rosenberg:** None. **M.M. Chun:** None. **R. Constable:** None.

Poster

851. Computational Tools for Human Data II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 851.18/OOO6

Topic: I.06. Computation, Modeling, and Simulation

Support: ARL grant W91CRB-13-C-000

Title: Multifaceted mental workload classifier - PHYSIOPRINT

Authors: ***D. POPOVIC**[1], M. STIKIC[1], D. KLYDE[2], G. PARK[2];
[1]Res. and Develop., Advanced Brain Monitoring, San Diego, CA; [2]Systems Technol. Inc., Los Angeles, CA

Abstract: Mental workload is difficult to quantify because it results from an interplay of the objective task load, ambient and internal distractions, capacity of mental resources, and strategy of their utilization. Furthermore, different types of mental resources are mobilized to a different degree in different tasks even if their perceived difficulty is the same. Thus, an ideal mental workload measure needs to quantify the degree of utilization of different mental resources in addition to providing a single global workload measure. Here we present a novel assessment tool (called PHYSIOPRINT) that derives workload measures in real time from multiple physiological signals (EEG, ECG, EOG, EMG). PHYSIOPRINT is modeled after the theoretical IMPRINT workload model developed by the US Army that recognizes seven different workload types: auditory, visual, cognitive, speech, tactile, fine motor and gross motor workload. Preliminary investigation on 25 healthy volunteers proved feasibility of the concept and defined the high level system architecture. The classifier was trained on the EEG and ECG data acquired during tasks chosen to represent the key anchors on the respective seven workload scales. The trained model was then validated on over 100 volunteers in realistically simulated environments (driving and flight simulator). The classification accuracy was 88.7% for speech, 86.6% for fine motor,

89.3% for gross motor, 75.8% for auditory, 76.7% for visual, and 72.5% for cognitive workload. The utilized classification approach is not computationally expensive, so it can be easily integrated into various research and industrial applications.

Disclosures: **D. Popovic:** A. Employment/Salary (full or part-time): Advanced Brain Monitoring. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Advanced Brain Monitoring. **M. Stikic:** A. Employment/Salary (full or part-time): Advanced Brain Monitoring. **D. Klyde:** None. **G. Park:** None.

Poster

851. Computational Tools for Human Data II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 851.19/OOO7

Topic: I.06. Computation, Modeling, and Simulation

Support: USUHS Grant HU0001-08-0001

Title: Small World Analyses of Resting State fMRI imaging comparing path length using both weighted and unweighted graphs

Authors: ***M. L. MEHALICK**[1], J. HUGHES[2], P. WALKER[2], A. GLUECK[3], A. TSCHIFFELY[3], C.-T. KUO[4], A. CHEN[4];
[1]Psychology, [2]Neurotrauma, Naval Med. Res. Ctr., Silver Spring, MD; [3]Henry M. Jackson Fndn., Bethesda, MD; [4]Univ. of California, Davis, CA

Abstract: Previous research has argued for "small-world" architecture of functional connectivity when using a graph-based representation of functional MRI (fMRI) activity. In small-world representations, activation is characterized by high clustering coefficient and a small path length. It has been argued that these small-world-like networks may be optimal for information exchange between different brain regions. Most work examining small world properties of resting state functional connectivity has used unweighted graphs in order to provide a more consistent and reliable cut of the graph. In contrast to unweighted graphs, which may be limited to utilizing the top k nearest neighbors to each voxel in calculating small-world indices, a weighted graph retains the relative strength of the connections for all nodes within the graph. In the current study, we offer a formal comparison of the small-world properties of unweighted and weighted graphs using Contrast Cuts. Resting state functional connectivity was analyzed using data from twelve individuals (6 PTSD, 6 Non-PTSD/healthy controls) from the Department of Defense Alzheimer's Disease Neuroimaging Initiative (ADNI-DOD) database. Small-world

indices (clustering coefficient C, and path length L) were assessed across groups using both weighted and unweighted graphs. The results indicate that when using unweighted graphs, the patients with PTSD demonstrate a reduction of small-world properties, or the graph theoretic analysis demonstrates a longer path length and lower clustering coefficient relative to non-PTSD patients. However, when using a weighted graph, a much different pattern emerges. Patients with PTSD illustrate much stronger connections in terms of regional connection strength compared to patients without PTSD. In conclusion, earlier research studies exploring the small-world properties has focused on unweighted graphs where path length is assessed as the number of edges connected voxel i to voxel j. However, the use of unweighted graphs loses information contained within the edge itself, specifically, the edge weight. Here, we demonstrate that for resting state activation, "path strength" is actually stronger in patients with PTSD than patients without PTSD.

Disclosures: **M.L. Mehalick:** None. **J. Hughes:** None. **P. Walker:** None. **A. Glueck:** None. **A. Tschiffely:** None. **C. Kuo:** None. **A. Chen:** None.

Poster

851. Computational Tools for Human Data II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 851.20/OOO8

Topic: I.06. Computation, Modeling, and Simulation

Title: Effectiveness of screw ecog:feasibility test

Authors: *S. LEE;
Hanyang Univ., Seoul, Korea, Republic of

Abstract: Electroencephalography (EEG) is generally used for measuring brain waves. AnThe EEG measuresd brain waves as non-invaded methodnon-invasively byto attaching electrodes on to the scalp. So Thus itthat can collect data simply. However, the signals are damped due to low conductivitye of the skull. To be complement supplement of the EEG's fault, the electrocorticographhpy (ECoG) has been developed. The eElectrodes of ECoG areis implanted in the epidural space. It is difficult to measureing data using implanted electrodes of patch type ECoG under the skull. The surgery time is long, and implantableed location is limited. ThereforeSo, the screw ECoG is recommended. The screw ECoG does notn't needrequire to craniotomy, and spend it takes only ato short time to install the electrodes. And Also, the screw ECoG, compared with the existing patch type ECoG, can be implanted in a wider range on the skull. The patch type ECoG can measure signals only in a localized field., hHowever the screw ECoG is able to get acquire data fromin the whole brain. For determininged the feasibility of

screw ECoG, we measured the visual evoked potential (VEP) in the occipital area region of a monkey. The A checker board is set to flickeredash in 2Hz on in each quadrant after holding securing the sight of monkey's focus. In one day, we have executed the session five times . And trials havewith 400 trialstime per session. The checker boards turn up randomly per quadrant. We had gotacquired the VEP data using EEG during 4 months. After obtaining enough EEG data, the screw ECoG was operatedutilized. The location of the electrodes is was the same location ofas the EEG electrodes of EEG. After surgery, VEP data was obtained for four months in the same way as from the EEG experiments of EEG. After surgery the screw ECoG surgery, the any symptoms of the infection were not appearedabsent. As a result, the safety of the developed screw ECoG has been proven. And Also it is difficult to distinguish the quadrant when usinged latency time and amplitude of VEP data using EEG. However, when usinged of VEP obtained VEP withfrom screw ECoG, distinction of each quadrant is certainclear.

Disclosures: S. Lee: None.

Poster

851. Computational Tools for Human Data II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 851.21/OOO9

Topic: I.06. Computation, Modeling, and Simulation

Title: Exploiting spatiotemporal structure in connecting electrocorticographic neural activity with human perception and behavior

Authors: *A. OMIGBODUN[1], W. K. DOYLE[2], O. DEVINSKY[3], D. FRIEDMAN[3], T. THESEN[3], V. GILJA[1];
[1]Electrical and Computer Engin., Univ. of California San Diego, La Jolla, CA; [2]New York Univ. Dept. of Neurosurg., [3]New York Univ. Sch. of Med., New York, NY

Abstract: We employed Hidden-Markov Factor Analysis (HMFA) to look at the spatiotemporal structure of electrocorticographic (ECoG) recordings from 2 patients undergoing monitoring prior to epilepsy surgery. The patients responded with button presses to audiovisual speech stimuli in an experimental task. An HMFA was performed with a finite set of factor analyzers to model the relationship between the high-dimensional ECoG neural space and a low-dimensional latent neural space while the factor analyzers at different time points were linked together in a hidden Markov process. Without the knowledge of the experimental trial types, HMFA learned a factor analyzer structure that enabled us to discriminate among trials based on audio content and button responses. The patients were instructed to click a button whenever they heard or saw the speaker on a screen say one of two words: "café" and "avenue". In terms of the audiovisual

stimuli, there were 7 trial types in the experiment: (1) stimuli for which the word heard matched the word seen (2) audio-only stimuli (3) stimuli for which the word heard did not match the word seen (4) video-only stimuli (5) video with the speaker making gurning mouth movements (6) phase-scrambled audio with the speaker making gurning mouth movements and (7) phase-scrambled audio alone. For patient 1 (2), we analyzed a total of 236 (245) trials with 105 (109) electrodes. Each 5-second trial was divided into nonoverlapping 50-millisecond windows in which the rms high gamma (76-100Hz) power was computed. We then used HMFA to summarize each trial as a sequence of numbers, denoting factor analyzers or states at different time points or windows. For each trial, we computed the percentage of time spent in each state. We used 4 states in our analyses as we found that with fewer states we were unable to discriminate between trials with and without button presses for patient 1. With patient 1 (2), for trials with audio, the percentages of time in states 1 and 2 (2, 3, and 4) were different (Wilcoxon rank-sum test, $P < 0.05$) from the percentages of time in the respective states for trials with phase-scrambled audio; trials with phase-scrambled audio in turn had percentages of time in states 3 and 4 (2, 3, and 4) that were different (Wilcoxon rank-sum test, $P < 0.05$) from those for trials with no audio. We also found that for trials with a button press, the percentage(s) of time in state 3 (1 and 4) were different (Wilcoxon rank-sum test, $P < 0.05$) from those for the other trials. In summary, we were able to discriminate among experimental trials based on audio content and button responses, using the proportions within each trial of time points assigned to different factor analyzers.

Disclosures: **A. Omigbodun:** None. **W.K. Doyle:** None. **O. Devinsky:** None. **D. Friedman:** None. **T. Thesen:** None. **V. Gilja:** None.

Poster

851. Computational Tools for Human Data II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 851.22/OOO10

Topic: I.06. Computation, Modeling, and Simulation

Title: Towards a theory of conscious systems

Authors: *S. R. DEISS[1,2];
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Abstract: Predictive coding models of perception and action suggest that consciousness can be defined in terms that go beyond the necessary operational definitions used in the surgical theater. In predictive coding models the perceiver is presumed to have an evolving causal model of the body-self and the environment that allows to generate actions and predict sensory consequences.

The key adaptation of living systems is avoidance of prediction errors that can be potentially fatal. This approach builds upon Helmholtz' intuitions about unconscious inferences used to fill out perceptual experiences, and is similar to the "analysis by synthesis" tradition in cognitive psychology. The predictive coding approach has been gaining traction for some time as it explains a wide range of experimental results. It is congenial with a definition of consciousness that was presented at SfN in 2008 by this author. This definition implicated memory use in the interpretation of sensations ("top down) and the update of memory resulting from the new interpretation ("bottom up"). Thinking causally comes to us naturally and is the basis of virtually all scientific study. The question that begs to be asked is whether our human fixation on causal models and explanations is itself a heuristic that works for daily survival but does not accurately reflect the world we are navigating. Until Copernicus, we thought the earth was the center of the universe, then later the sun. The early faulty views were the result of making assumptions based upon our human viewpoint when analyzing nature. We need predictive models to survive, and causal models came naturally from our experience of muscle forces and effort to overcome our own inertia. However, maybe causality is a cognitive crutch just as believing that the objects in front of us are solid and not mostly empty space. What we can measure are correlations and patterns. Governing laws and their support for causality are a human interpretation. This presentation will question the causality assumption from intuitive and fundamental physical perspectives in order to introduce and justify a different way of thinking about perception in scale free conscious systems released from anthropomorphic preconceptions. [See references: 1. "Time, Consciousness and the Foundations of Science," 2010, Jnl. of Consciousness Exploration and Research, Vol 1, #5. , and 2. "Universal Correlates of Consciousness," Chapter 7 (pp 137-158) in *Mind That Abides: Panpsychism in the new millennium* (Advances in Consciousness Research series), David Skrbina (ed.), John Benjamins, 2009, ISBN-10: 9027252114.]

Disclosures: S.R. Deiss: None.

Poster

851. Computational Tools for Human Data II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 851.23/OOO11

Topic: I.06. Computation, Modeling, and Simulation

Support: John D. and Catherine T. MacArthur Foundation, the Alfred P. Sloan Foundation

Army Research Laboratory and the Army Research Office through contract numbers W911NF-10-2-0022 and W911NF-14-1-0679

National Institute of Mental Health (2-R01-DC-009209-11)

National Institute of Child Health and Human Development (1R01HD086888-01)

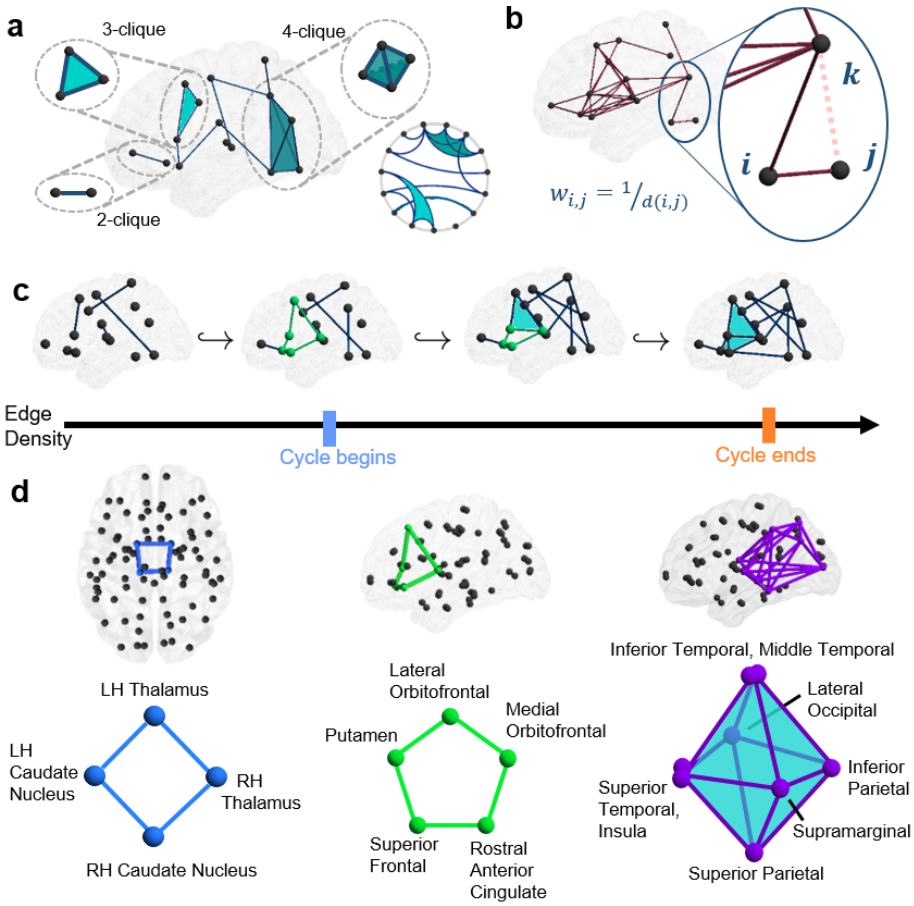
Office of Naval Research

National Science Foundation (BCS-1441502, BCS-1430087, and PHY-1554488)

Title: Functional role of topological cycles in the human structural connectome.

Authors: *A. E. SIZEMORE, C. GIUSTI, R. BETZEL, D. S. BASSETT;
Univ. of Pennsylvania, Philadelphia, PA

Abstract: Encoding brain regions and their connections as a network of nodes and edges captures many of the possible paths along which information can be transmitted as humans prepare and perform complex behaviors. Because cognitive processes involve large and distributed networks of brain areas, a principled examination of multi-node routes within larger connection patterns could offer fundamental insights into the complexities of brain function. Current network analysis methods are imperceptive to many such features, often focusing on local structure and exclusively considering pairwise interactions between nodes. To address these limitations, we draw on concepts from the field of algebraic topology to define sets of all-to-all connected nodes as structural units, called *cliques* (Fig. 1a), and then to use the clique architecture of the network to detect structural cavities called *cycles*. Both cliques and cycles are not uncovered by traditional graph metrics. We apply these tools to the structural connectomes of 8 healthy adults scanned in triplicate, and we reveal the presence of high-dimensional cliques, indicating sizeable collections of brain regions that may readily share information to perform a coordinated function. Importantly, these cliques are much larger than those expected in null networks constructed via wiring minimization (Fig. 1b). To complement the study of locally dense structures, we also use *persistent homology* to detect and track multiple cycles that form topological cavities of different dimensions through repeated thresholdings of the original weighted net-work (Fig. 1c). These cycles exist consistently across subjects, are not observed in the null networks, and join regions in the subcortex, frontal cortex, and higher order visual areas (Fig. 1d). These results offer a first demonstration that techniques from algebraic topology offer a novel perspective on structural connectomics, highlighting loop-like paths as crucial features in brain structure.



Disclosures: **A.E. Sizemore:** None. **C. Giusti:** None. **R. Betzel:** None. **D.S. Bassett:** None.

Poster

851. Computational Tools for Human Data II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 851.24/OOO12

Topic: I.06. Computation, Modeling, and Simulation

Support: Grant-in-Aid for JSPS Fellows

MEXT/JSPS Grants-in-Aid for Scientific Research 24119002

Title: Developmental changes in cortical folding patterns affect scalp EEG profiles: A large-scale cortex simulation study

Authors: *K. FUJII[1,2], H. KANAZAWA[1,2], Y. KUNIYOSHI[1];
[1]Grad. school of information science and technology, Univ. of Tokyo, Bunkyo, Japan; [2]JSPS Res. Fellow, Tokyo, Japan

Abstract: Neonatal scalp electroencephalography (EEG) has been used for assessment of brain injury and neonatal seizures. It is also well known that neonatal EEG can show the developmental changes which might reflect brain maturation. However, it is unclear how neuronal maturation affects the developmental changes in neonatal EEG due to the presence of technical challenges to investigate, and the existence of a large number of candidate factors. Here we examined the effect of the cortical folding patterns on EEG profiles. To achieve this goal, we developed a large-scale computational simulation with cortical morphological data, and compared two simulated EEG profiles derived from two different cortical morphological models of an adult and neonate.
First, 3D surface data of an adult and neonate cortex were extracted from MRI data. Next, we ran a cortex simulation composed of more than 80,000 conductance-based leaky integrate-and-fire neuron models. Simulation time step was 1msec, and at every step the excitatory post synaptic potentials (EPSPs) and inhibitory post synaptic potentials (IPSPs) for all neuron models were recorded. Then the electrical fields on the cortex surfaces were estimated. In this process, we placed electrical dipoles along the cortical surfaces. Charges of electrical dipoles were calculated based on EPSPs and IPSPs. EPSPs and IPSPs were common between the adult and neonate experiments in this study, and therefore the difference between the electrical fields reflected the difference of cortical folding patterns. Finally, voltages at 128 electrodes on a scalp were estimated from the electrical fields.
We found that the directions of the electrical field vectors on the neonatal cortex model tend to synchronize with each other, while those on the adult cortex model are diverse. In addition, the neonatal cortex model showed higher power spectrum between low frequency band (4~13Hz) than that of the adult model, which is a characteristic of neonatal EEG. These results suggest that immature cortical folding patterns can be an influential factor of neonatal EEG characteristics.

Disclosures: K. Fujii: None. **H. Kanazawa:** None. **Y. Kuniyoshi:** None.

Poster

851. Computational Tools for Human Data II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 851.25/OOO13

Topic: I.06. Computation, Modeling, and Simulation

Support: Stanford Interdisciplinary Graduate Fellowship (Neuroscience Institute)

Title: Automatic fine-scale correspondence mapping in human white matter

Authors: ***T. GLOZMAN**, L. GUIBAS;
Stanford Univ., Stanford, CA

Abstract: Introduction: Diffusion Weighted Imaging coupled with tractography allows researchers to identify major human white matter tracts in-vivo. Tissue properties of these long range connections correlate with behavior, development, cognitive abilities and emotional states, as demonstrated by many studies comparing the properties of these tracts across populations. Current state-of-the-art available methods either average tissue properties over an entire tract, or perform a longitudinal profile comparison analysis. A major limitation of these methods is lack of localization - local differences in tissue properties are averaged over an entire tract or over a cross-section of the tract. Inspired by FreeSurfer cortical parcellation, our goal was to create a flexible atlas-free framework for automatic fine-scale correspondence mapping between tracts of different subjects in a dataset. We achieve this by parameterizing the 3D shape of a tract. No limit is set on the size of the dataset, rendering it useful for analysis of very large cohorts. The correspondence map can be used for analysis of tissue properties or shape variability in flexibly defined regions of interest (ROIs) - two examples are shown in Fig.1. Results: We create a canonical geometric model to represent a generic tract. The model undergoes 3D deformation to best capture the shape of each individual tract in a given dataset. This parameterization facilitates the mapping among tract regions in different subjects. Our method is fast, robust across different types of tracts, and was verified both by using simulated data and by visual comparison to manually labeled data-sets. Discussion: We introduce a method for automatic generation of consistent mapping between tracts of different subjects. The applications of our method are versatile - a correspondence map can be calculated either between small ROIs within the tracts of different subjects as shown in Fig. 1(a) or between sub-fiber groups in the tract - Fig. 1(b). The method can also be used to compare the properties of different regions within the tract of a single subject.

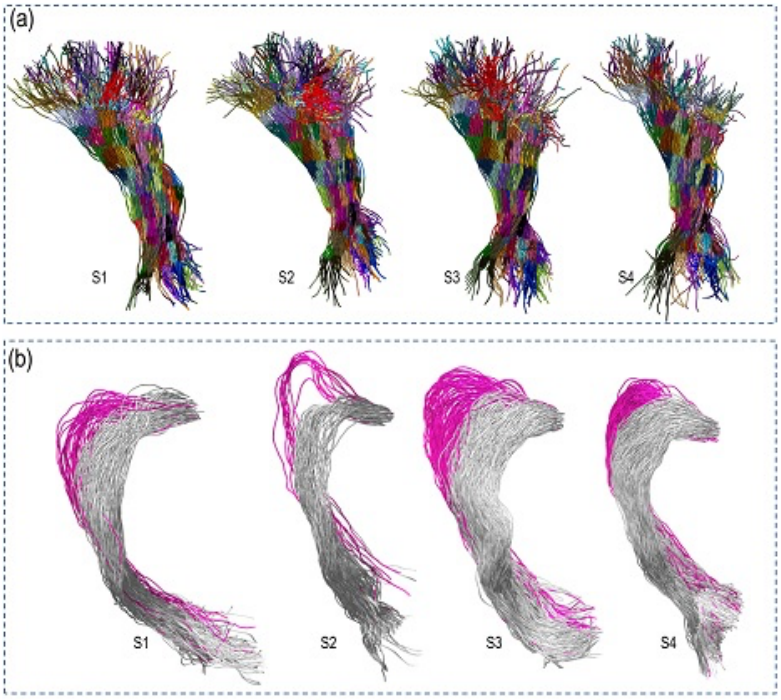


Figure 1: Correspondence mapping versatility example: (a) region-to-region mapping of Left Thalamic Radiation tract in four different subjects. Corresponding regions have the same color across all subjects. (b) fiber-group mapping of Meyer's loop in the Optic Radiation tract in four subjects.

Disclosures: T. Glozman: None. **L. Guibas:** None.

Poster

851. Computational Tools for Human Data II

Location: Halls B-H

Time: Wednesday, November 16, 2016, 1:00 PM - 5:00 PM

Program#/Poster#: 851.26/OOO14

Topic: I.06. Computation, Modeling, and Simulation

Support: Swartz Foundation

Title: Group-level statistics on EEG effective source connectivity

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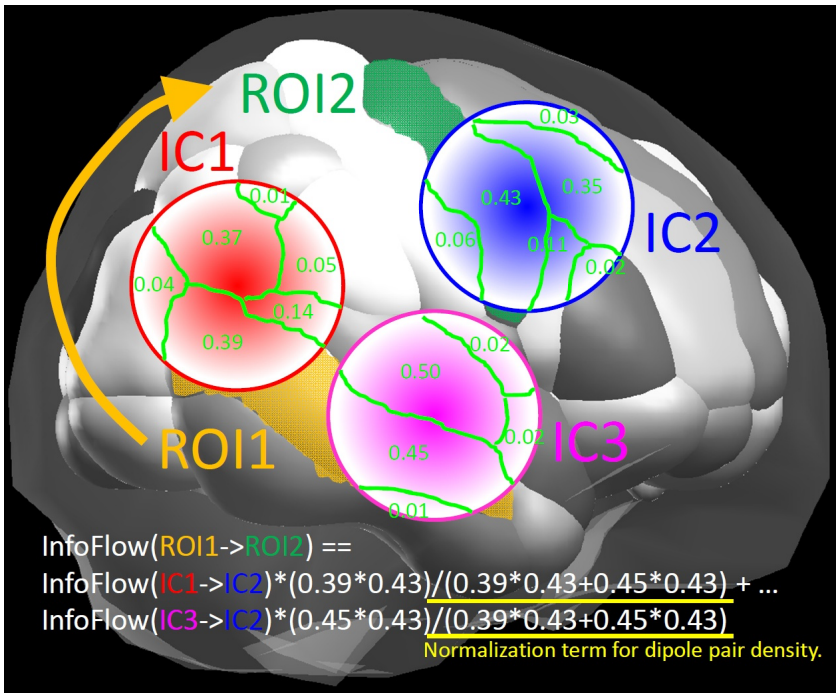
Abstract: Multivariate connectivity measures of EEG data for investigating source-resolved causal information flow have been gathering attention. There are known issues in applying this method to scalp-recorded channel EEG data including volume conductance and scalp mixing which makes the recorded scalp channel data highly correlated. To address these issues, applying independent component analysis (ICA) is an effective preprocessing step. It finds a linear transform of the data into effective source signals that are maximally temporally independent. In this approach, issues raising from volume conductance and scalp mixing are both addressed without regard to an electrophysiological forward model. However, ICA reveals individual differences that create problems in group-level statistics. For example, in conventional EEG analysis, group-level statistics is straightforward; each scalp channel (e.g. Cz) is considered to be equivalent for all the subjects. But following ICA preprocessing, there are no independent component (IC) equivalences across the subjects. Hence we developed the following statistical framework: 1. Preprocess individual data by ICA, estimate IC equivalent current dipoles, and apply multivariate connectivity measures across all pairs of brain ICs; 2. Compute dipole density within the MNI brain space by applying a 3-D Gaussian kernel; 3. Segment dipole density into anatomical ROIs; 4. Compute region-to-region pairwise dipole density weighted by connectivity; 5, Repeat above process for all subjects; 6. Perform between-condition statistics using variance across subjects. We have developed a free, open-source source toolbox that plugs into EEGLAB. Using this solution, group-level statistics of source-resolved EEG effective connectivity can be evaluated in the time-frequency domain with correction for multiple comparisons. The toolbox generates an animation to visualize information flow. We expect it will also be useful for MEG, ECoG, and other electrophysiological data analysis.



Disclosures: **M. Miyakoshi:** None. **N. Bigdely-Shamlo:** None. **C. Lee:** None. **T. Mullen:** None. **S. Makeig:** None.