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Poster

PSTR051: Neurogenesis and Neural Stem Cell Dynamics in Health and Disease

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR051.01/A1

Topic: A.02. Postnatal Neurogenesis

Support: NIH Grant NS086965
NIH Grant NS085171

Title: Single-nucleus RNA sequencing reveals early transcriptomic changes that may drive dysregulation of neurogenesis in a mouse model of Alzheimer's disease neuropathology

Authors: *Y. FURUTA[1], T.-C. LU[2], J. WANG[1], H. CHEN[4,3], Y. QI[2], H. LI[2], J. CHIN[1]; [1]Dept. of Neurosci., [2]Dept. of Mol. and Human Genet., [3]Dept. of Pediatrics, Baylor Col. of Med., Houston, TX; [4]Jan and Dan Duncan Neurologic Res. Institute, Texas Children's Hosp., Houston, TX

Abstract: Neural stem cells (NSCs) in the dentate gyrus (DG) produce new neurons throughout adulthood, which are important for mood regulation and cognitive function. Reduced numbers of newborn neurons are observed in chronic stages of temporal lobe epilepsy and Alzheimer's disease (AD), suggesting that disrupted neurogenesis dynamics may contribute to cognitive deficits. Using transgenic mice that express mutant human amyloid precursor protein (APP mice) as a model of AD neuropathology, we previously reported that NSC division and neurogenesis were aberrantly increased in young APP mice, which was followed by accelerated depletion of a finite pool of NSCs, and reduced neurogenesis. These results suggest that therapeutic interventions normalizing the excessive increase in NSC division at early disease stages may preserve the NSC pool, ensure lifelong neurogenesis, and prevent later cognitive deficits. However, the precise molecular mechanisms causing dysregulation of NSCs and neurogenesis remain elusive. To elucidate the early transcriptomic changes that might drive such dysregulation, we performed single nucleus RNA-sequencing of the DG of young APP mice and nontransgenic (NTG) littermates. Supervised and unsupervised annotation identified all major cell types in the DG and enabled the identification of genes that were differentially expressed in NTG and APP mice in each cell type. We found numerous differentially expressed genes (DEGs) in some cell types including mature granule cells, immature granule cells/neuroblasts, and GABAergic interneurons. However, other cell types including mossy cells, oligodendrocytes, and endothelial cells showed fewer DEGs, indicating that not all cell types are similarly sensitive to gene expression changes in very early disease stages. We investigated the most highly up/downregulated genes in different cell types and identified DEGs in multiple cell types that might contribute to aberrant NSC activation in early disease states. These findings suggest that there are cell type-specific transcriptomic changes early in the disease process that could drive early dysregulation of NSCs and neurogenesis, prior to the appearance of major pathological hallmarks such as amyloid-beta plaque accumulation. This data set may serve as a

valuable resource to identify the earliest events that occur in the DG that could set the stage for or give rise to downstream alterations in DG (dys)function.

Disclosures: Y. Furuta: None. **T. Lu:** None. **J. Wang:** None. **H. Chen:** None. **Y. Qi:** None. **H. Li:** None. **J. Chin:** None.

Poster

PSTR051: Neurogenesis and Neural Stem Cell Dynamics in Health and Disease

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR051.02/A2

Topic: A.02. Postnatal Neurogenesis

Title: The bidirectional role of $GABA_A$and $GABA_B$receptors during the differentiation process of neural precursor cells of the subventricular zone

Authors: *N. E. GUTIÉRREZ[1], V. A. MARTINEZ-ROJAS[2], E. J. GALVAN[3]; [1]Farmacobiología, CINVESTAV, Coyoacan, Mexico; [2]Cinvestav Sede Sur, Mexico City, Mexico; [3]Farmacobiologia, CINVESTAV SUR, Mexico City, Mexico

Abstract: The intricate process of neuronal differentiation integrates multiple signals to induce transcriptional, morphological, and electrophysiological changes that reshape the properties of neural precursor cells during their maturation and migration process. An increasing number of neurotransmitters and biomolecules have been identified that serve as molecular signals that trigger and guide this process. In this sense, taurine, a sulfur-containing, non-essential amino acid widely expressed in the mammal brain, modulates the neuronal differentiation process. In this study, we describe the effect of taurine acting via the ionotropic $GABA_A$ receptor and the metabotropic $GABA_B$ receptor on the neuronal differentiation and electrophysiological properties of precursor cells derived from the subventricular zone of the mouse brain. Taurine stimulates the number of neurites and favors the dendritic complexity of the neural precursor cells, accompanied by changes in the somatic input resistance and the strength of inward and outward membranal currents. At the pharmacological level, the blockade of $GABA_A$ receptors inhibits these effects, whereas the stimulation of $GABA_B$ receptors has no positive effects on the taurine-mediated differentiation process. Strikingly, the blockade of the $GABA_B$ receptor with CGP533737 stimulates neurite outgrowth, dendritic complexity, and membranal current kinetics of neural precursor cells. The effects of taurine on the differentiation process involve Ca^{2+} mobilization and the activation of intracellular signaling cascades since chelation of intracellular calcium with BAPTA-AM, and inhibition of the CaMKII, ERK1/2, and Src kinase inhibits the neurite outgrowth of neural precursor cells of the subventricular zone.

Disclosures: N.E. Gutiérrez: None. **V.A. Martinez-Rojas:** None. **E.J. Galvan:** None.

Poster

PSTR051: Neurogenesis and Neural Stem Cell Dynamics in Health and Disease

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR051.03/A3

Topic: A.02. Postnatal Neurogenesis

Support: APVV-20-0344
VEGA 2/0150/24

Title: A daily rhythm of neurogenesis in a diurnal species, zebra finch

Authors: *V. HODOVA, L. NIEDEROVA-KUBIKOVA;
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Abstract: Neurogenesis takes place in the ventricular zone (VZ) along the lateral cerebral ventricle in songbirds, similarly to mammals. Newly formed neurons migrate from there to many areas of the forebrain, including the pallial HVC and the striatal AreaX. Neurogenesis is influenced by several processes and factors. The cell cycle is phase-linked to the circadian system generating circadian rhythms of molecular, physiological, and behavioral processes over approximately 24 hours. The aim of this study was to determine whether the creation and/or loss of new neurons in songbirds has a daily rhythm, and in which phase of the day they reach their maximum. Thirty-six male zebra finches (*Taeniopygia guttata*) were used in the experiment. They were divided into 6 groups according to the complexity of the song and kept under a 12L:12D regime. An exogenous neurogenesis marker, 5-ethynyl-2'-deoxyuridine (EdU), was administered every four hours and the birds were sacrificed by decapitation 2 hours after the EdU administration (ZT2, 6, 10, 14, 18, 22) and the brains were quickly frozen. The brains were cut into 10 µm thick coronal sections capturing four levels of the VZ, each containing a different area serving as an anatomical marker (VZ_X, VZ_{TSM}, VZ_{CA}, VZ_{HVC}) for EdU detection. The brains were also cut into 60 µm coronal sections containing the central part of the VZ and the hypothalamus, from which gene expression of clock genes (*Per2*, *Per3*, *Cry1*, *Cry2*, *Bmal1*, *Clock*), proliferation marker (*PCNA*) and apoptotic genes (*caspase 3*, *Bax*, *Bcl-2*) were analyzed by qPCR. Firstly, we confirmed that the rhythm of clock genes was preserved. Cosinor analysis revealed that the formation of newly formed EdU^+ cells at any level of the VZ or along the entire VZ does not show a daily rhythm ($p > 0.17$). However, we specifically examined the rhythm of proliferation also in the "hotspot" part of the VZ, where the intensity of the formation of new neurons is significantly higher. We found that this central ventral part of the VZ, at the level of the VZ_{TSM} ($p < 0.05$) and the VZ_{CA} ($p < 0.05$), shows a daily rhythm in the number of EdU^+ cells. The highest production of newborn cells occurs in the dark phase of the day with acrophase at approximately ZT15. At the mRNA level, we did not detect a rhythm of PCNA and any of the three apoptotic genes during 24 hours. Our results show that the neurogenesis in the "hotspot" part of the VZ exhibits rhythmic activity over a 24-hour period. Interestingly, the most intensive production in diurnal zebra finch occurs during the dark phase, similar to nocturnal rodents. Our data suggest that similar circadian mechanisms may control neurogenesis in diurnal and nocturnal animals.

Disclosures: V. Hodova: None. **L. Niederova-Kubikova:** None.

Poster

PSTR051: Neurogenesis and Neural Stem Cell Dynamics in Health and Disease

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR051.04/A4

Topic: A.02. Postnatal Neurogenesis

Support: R01MH105416

Title: Deciphering Cortical Circuitry Signaling Pathways Regulating Quiescent Neural Stem Cell Proliferation in the Subventricular Zone

Authors: *M. NAFFAA[1], H. H. YIN[2];
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Abstract: Neural stem cells (NSCs) in the subventricular zone (SVZ) undergo transitions between quiescent and activated states, a process tightly regulated by intrinsic and extrinsic factors. We studied cortical circuit modulation of lateral ventricle NSCs (LV NSCs) that facilitate the transition to the activated proliferation state. We observed that cortical circuits activate muscarinic 3 receptors on quiescent neural stem cells within the lateral ventricle, resulting in IP3 receptor activation and intracellular calcium release via store-operated channels. This cytoplasmic calcium influx governs a diverse array of cellular processes, including neurotransmitter release, intracellular signaling, and transcriptional regulation. We showed subsequent activation of CAMK2D and MAPK10 signaling pathways, resulting in the phosphorylation of MAPK10 and its nuclear translocation within LV qNSCs, thereby initiating symmetrical proliferation. Understanding neural circuit regulation of LV NSCs can shed light on mechanisms underlying brain cancers and the possibility of harnessing NSC proliferation for neural repair and regeneration.

Disclosures: M. naffaa: None. **H.H. Yin:** None.

Poster

PSTR051: Neurogenesis and Neural Stem Cell Dynamics in Health and Disease

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR051.05/A5

Topic: A.02. Postnatal Neurogenesis

Support: JUST-Deanship of Research

Title: Neurotrophic Factors and ERK Expression in Rat Brains: Effects of Early Pain and Enriched Environment.

Authors: *K. NUSEIR[1], F. ZAHIR[2], L. AL-EITAN[2];
[1]Clin. Pharm., Jordan Univ. of Sci. and Technol., Irbid, Jordan; [2]Jordan Univ. of Sci. and Technol., Irbid, Jordan

Abstract: An enriched environment (EE) is defined as one that provides greater sensory, motor, and cognitive stimulation in comparison to a standard environment (SE). It has been suggested that exposure to an EE result in biochemical, morphological, and functional changes in the adult brain via increasing neuronal plasticity throughout the entire brain. It has been demonstrated to be correlated with the amounts of neurotrophic factors, particularly brain-derived neurotrophic factor (BDNF), in the hippocampus of the brain. It is commonly acknowledged that infant pain has negative short- and long-term effects. This is especially important for mature babies and preterm newborns who are hospitalized in the Neonatal Intensive Care Unit (NICU), as procedures like examinations and therapies can cause pain. Studies have demonstrated the potential of an enriched environment to mitigate neuropathic and chronic pain. Furthermore, research on rats has shown that early EE can affect Neurotrophic factors (NTs) expression during development and maturity on both males and females. The proposed work, which is based on these findings, is to investigate whether changes in neurotrophic factors may be brought about by an EE following repeated nociceptive stimulation.A tiny needle is inserted and quickly removed from the rat pups' paws within the first two weeks of their lives as part of the experimental design. The rats were assigned to either a standard environment (SE) or an enriched environment (EE).Following a series of behavioral assessments, the adult rats were decapitated at 10 weeks of age, and their brains were extracted to assess the amounts of mRNA and protein of the BDNF and ERK levels. To investigate potential sex differences, the study employed both male and female rats.Preliminary results showed similar for both mRNA and protein levels of BDNF. Whereas BDNF protein and mRNA levels were highest in male rats noxiously stimulated during infancy and raised under a standard environment since weaning. While ERK was highest in the enriched environment group with tactile stimulation compared to noxiously stimulated. Moreover, males in EE-Tactile group had the highest levels of ERK. These markers may shed light on the fundamental mechanisms by which the EE influences pain perception and other associated functions. This study sought to explore the long-term effects of early pain experiences as well as how an enriched environment affects the response to produced repetitive nociceptive stimulation.

Disclosures: K. Nuseir: None. **F. Zahir:** None. **L. AL-Eitan:** None.

Poster

PSTR051: Neurogenesis and Neural Stem Cell Dynamics in Health and Disease

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR051.06/A6

Topic: A.02. Postnatal Neurogenesis

Support: Intramural Program of NIAAA/NIH

Title: GPR110 modulates anxiety-like behaviors and memory function in mice potentially through neuronal and neuroimmune alterations during neurodevelopment

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Abstract: GPR110 is an adhesion G protein coupled receptor (GPCR) that is widely expressed in developing brains but diminished in adult stage except in the hippocampus, a region involved in learning and memory. Previous studies have shown that ligand-induced GPR110 signaling potently stimulates neurogenesis and synaptogenesis during development, and its absence causes object recognition and spatial memory deficits in adulthood and increased neuroinflammatory responses. Nevertheless, the role of GPR110 signaling in behavioral consequences has not been fully explored. This study aimed to understand the effects of GPR110 on mouse behaviors in relation to neurodevelopmental and neuroimmune gene and protein expression. Anxiety and memory function were tested using both male and female mice at 5-6 month of age. To evaluate anxiety-like behaviors, we used the open field, elevated plus maze, and elevated zero maze tests. For memory function, the y-maze, novel object recognition, and radial 8-arm maze tests were employed. The elevated plus maze test using 9-10 male mice indicated increased anxiety-like behaviors in GPR110 KO mice as shown by the decreased time spent in the open arms, although no significant differences were observed by the elevated zero maze test. GPR110 KO male mice had trends for increased anxiety-like behaviors as shown by the decreased time spent in the center in the open field test. The novel object recognition test showed a trend toward fewer investigations of the novel object, less time investigating the novel object, and a lower discrimination index in the GPR110 KO mice, suggesting that there may be an impaired memory in GPR110 KO mice compared to WT mice. The y-maze showed a significant sex by genotype interactions with GPR110 KO male mice having increased number of correct alterations and errors, while the GPR110 KO females had fewer correct alterations and errors. The radial 8-arm maze showed significant genotype effects, with GPR110 KO mice having worse reference memory as evidenced by reduced number of entries into the baited arms. RNAseq data indicated significantly impaired developmental gene expression for neuronal differentiation, axonogenesis, and synaptogenesis, as well as altered neuroinflammatory marker expression in GPR110 KO mouse brains. Further studies exploring the protein expression and neural activity of these mouse brain will give insight on the mechanism underlying the behavioral consequences associated with the GPR110 receptor.

Disclosures: M. Melkumyan: None. **J. Toro:** None. **B.X. Huang:** None. **H. Kim:** None.

Poster

PSTR051: Neurogenesis and Neural Stem Cell Dynamics in Health and Disease

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Topic: A.02. Postnatal Neurogenesis

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VA CDA2 1IK2BX005761 (CRB)
NIH P30 NS061800 (SKP)

Title: Functional dentate gyrus reorganization and altered hippocampal adult neurogenesis after targeted hilar mossy cell loss

Authors: *C. BUTLER[1], A. ISAKHAROV[2], G. L. WESTBROOK[3], **E. SCHNELL**[4]; [1]Oregon Hlth. & Sci. Univ., Portland, OR; [2]Neurosci., OHSU Neurosci. Grad. Program, Portland, OR; [3]Vollum Inst., Portland, RI; [4]OHSU, Portland, OR

Abstract: The neurogenic niche in the subgranular layer of the hippocampus generates adult-born dentate granule cells (abDGCs) in adult mice, and circuit integration of abDGCs requires excitatory innervation. Aberrant abDGC precursor proliferation and integration occurs in various models of brain injury, coincident with prominent hilar mossy cell loss. As hilar mossy cells form the first glutamatergic synaptic inputs onto developing abDGCs, we tested the hypothesis that mossy cell loss drives aberrant adult neurogenesis. We selectively ablated or functionally silenced hilar mossy cells via viral vector-induced apoptosis or virus-mediated tetanus toxin in transgenic Crlr-Cre mice, and used bromodeoxyuridine or retrovirus to label abDGCs generated in the absence of functional mossy cell inputs. Overall, both mossy cell ablation and silencing transiently accelerated the dendritic outgrowth of adult-born DGCs while having minimal impact on the overall process of adult neurogenesis. Neither model demonstrated sprouting of granule cell axons, even up to a year after deletion of these interneurons. Although more mature (21 day old) abDGCs that developed in the absence of mossy cell inputs appeared structurally similar to their control counterparts, there was an unexpected increase in the excitation:inhibition (E:I) ratio of inner molecular layer inputs in abDGCs following mossy cell ablation, which was not observed after permanent silencing of mossy cells. Interestingly, dendritic spine density on proximal dendrites, a surrogate for glutamatergic inputs, was only reduced in granule cells that developed when mossy cells were permanently silenced but remained unchanged in granule cells that developed following mossy cell ablation. Immunohistochemical, viral tracing, and electrophysiogical assays identified a collapse of the molecular layer inputs after mossy cell ablation, that was not observed when mossy cells were silenced, which could account for the differential effects on E:I circuit balance changes. These results not only demonstrate that mossy cell input onto abDGCs is important for early development and integration of these neurons, but also highlight a previously unknown compensatory change within the molecular layer of the dentate gyrus following extensive and selective mossy cell loss, in the absence of recurrent granule cell axon sprouting.

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Poster

PSTR051: Neurogenesis and Neural Stem Cell Dynamics in Health and Disease

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Topic: A.02. Postnatal Neurogenesis

Support: ANR Rewired (ANR-22-CE16-0019)
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Doctoral school 340 BMIC : PhD funding

Title: Bmpr1a signaling modulates germinal activity within the postnatal subventricular zone

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Abstract: We have recently uncovered a role for Bone morphogenetic protein (BMP) signaling pathway in silencing pallial germinal activity in mice, at birth. At this stage, increased Bmpr1a activation in the dorsal subventricular zone (SVZ) correlates with the blockade of neuronal differenciation and the progressive entry into quiescence of pallial neural stem cells. Here, we expanded those original observations by testing if manipulation of Bmpr1a-signaling during postnatal stages influences NSCs germinal activity, and explored transcriptional datasets to identify the source of BMP ligands expression. We first used postnatal electroporation (EPO, in male and female OF1 mice, n>7) to overexpress dominant negative and dominant active forms of Bmpr1a within NSCs of the dorsal and lateral SVZ domains, respectively. Different regimes of BrdU administration were used to assess the effect of these manipulations on activation of NSCs, while analyses at different timepoints allowed investigating the fate of the electroporated cells. Our results show that inhibition of Bmpr1a signaling in the dorsal SVZ results in an increased neurogenesis while its activation in the lateral SVZ results impairs newborn neurons migration and maturation within the olfactory bulb. We next complemented these findings by performing a single-cell RNA-seq analysis to explore the sources of Bmpr1a signaling within the postnatal SVZ. To this end, we took advantage of proprietary as well as publicly available single cell RNA-sequencing datasets covering embryonic and postnatal development of the pallium/dorsal SVZ and isocortex. Integration and comparison of these datasets reveal that both local and long-distance sources of Bmpr1a ligands are likely to act onto pallial NSCs to change their germinal activity at birth. Together, our findings provide novel insights into the regulatory mechanisms shaping postnatal NSC germinal activity at birth, and shed light on the cell types involved in mediating these effects.

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Poster

PSTR051: Neurogenesis and Neural Stem Cell Dynamics in Health and Disease

Location: MCP Hall A

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Program #/Poster #: PSTR051.09/A9

Topic: A.02. Postnatal Neurogenesis

Support: MEXT KAKENHI Grants 24K10498

Title: The role of neurotrophin-3 in the regulation of hippocampal dentate gyrus function

Authors: *N. KASAKURA[1], K. SUZUKI[2], E. SEGI-NISHIDA[3];
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Abstract: Neurotrophin-3 (NT-3) is a type of neurotrophic factor and regulates neural differentiation, survival, and plasticity in both peripheral and central nerves. NT-3 expressed in the adult hippocampal dentate gyrus (DG) and has been reported to be upregulated by stress. On the other hand, our previous studies have shown that the expression of NT-3 is reduced in the hippocampal DG of fluoxetine-treated mice. However, the role of NT-3 in hippocampal DG is unclear. Therefore, we examined the effects of increased or decreased NT-3 on functional modulation in hippocampal DG. To investigate the effects of increased NT-3, we generated NT-3 overexpressing mice in the hippocampal DG by administering adeno-associated virus carrying NT-3 gene (AAV-NT-3). Four weeks after AAV-NT-3 injection, more than 35-fold expression of NT-3 mRNA was observed in AAV-NT-3 group. Also, to investigate the effects of decreased NT-3, we generated NT-3 knocking down (KD) mice in the hippocampal DG by administering AAV carrying artificial microRNA with sequences complementary to NT-3 gene (AAV-NT-3 KD). Eight weeks after AAV-NT-3 KD injection, the NT-3 KD group expressed half as much NT-3 as the control group. To evaluate neural activity, we performed immunostaining for an immediate-early gene (IEG); FosB. The number of FosB positive cells were increased in NT-3 overexpression group while they were decreased in the NT-3 KD group. Moreover, the gene expression levels of other IEGs, such as *Arc* and *Egr1*, were increased in NT-3 overexpression group while they were decreased in the NT-3 KD group. These results suggest that NT-3 in the hippocampal DG regulate activity of mature neurons. We next examined the effect of NT-3 overexpression on the process of adult hippocampal neurogenesis. To examine cell proliferation, EdU was also administered 2 hours before sacrifice. The number of EdU-positive cells were decreased in the overexpression group. To examine the number of immature neurons, we performed immunostaining for doublecortin, immature neuron maker. The number of doublecortin-positive cells were decreased in the overexpression group. These results indicate that NT-3 can regulate neuronal activity and that increased NT-3 in the hippocampus DG suppresses early phase of neurogenic processes. In the future, we would like to further reveal the role of NT-3 by investigating the effects of NT-3 reduction on neurogenesis. Since neurogenesis in the hippocampal dentate gyrus is associated with depression, we would like to clarify whether NT-3 can be involved in depression.

Disclosures: N. Kasakura: None. **K. Suzuki:** None. **E. Segi-Nishida:** None.

Poster

PSTR051: Neurogenesis and Neural Stem Cell Dynamics in Health and Disease

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Program #/Poster #: PSTR051.10/A10

Topic: A.02. Postnatal Neurogenesis

Support: NIAAA GRANT RO1 AG072900
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Title: Effects of prenatal alcohol exposure on the development of AD/ADRD in WT and 3xTg-AD mice

Authors: *P. MONTENEGRO[1], M. ZEDEK[2], P. YEH[1], H. YEH[1];
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Abstract: Alzheimer's disease (AD) and Alzheimer's disease-related dementia (AD/ADRD) are the mostcommon neurodegenerative disorders genetically caused by mutations in the *Presenilin* (*PSEN1*and *PSEN2*) genes. Presenilin 1 is the catalytic subunit of the γ-secretase complex, which cleavestype I transmembrane proteins, such as Notch and the amyloid precursor protein (APP), and playsan evolutionarily conserved role in both early development and aging of the brain. The Notchsignaling pathway is involved in the regulation of neurogenesis and neuronal differentiation. It issuggested that APP facilitates the migration of nerve cells during early development and, in theadult brain, plays a pathologic role in AD/ADRD. Additional evidence points to impaired PS1protein affecting the essential function of the γ-secretase complex, leading to synaptic dysfunction,learning and memory deficits, and neuronal degeneration in cortical brain regions. Environmentalfactors, such as prenatal alcohol exposure (PAE), affect cortical development, which can constitutea crucial factor contributing to the development of AD/ADRD pathoetiology. This project aims totest the hypothesis that PAE may alter the function of γ-secretase complex during earlydevelopment, leading to defects in neurogenesis, neuronal differentiation, and neuronal migrationthat contribute to the manifestation of neurodegeneration, synaptic dysfunction, and memoryimpairments later in life. Our goal is to identify neuronal deficits related to PS1 dysfunctioninduced by PAE employing a binge-type drinking paradigm in both wild-type (WT) mice, and a3xTg-AD mouse model expressing *PSEN1* M146V knock-in allele and the AD/ADRD humanmutations Tau P301L and APP K670_M671delinsNL. Our initial experimental strategy includedbiochemical and histological analysis of neurodegeneration. Our results indicate that PAE duringembryonic days 13 to 15 affects APP processing in WT mice, showing an accumulation of APP C-terminal fragment (CTF) in the cortex at post-natal day 0, and variable protein levels of PS1 CTFand APP CTFs at 2 months, and 4 months of age. The preexistence of AD-linked mutationscontributes to severe γ-secretase complex functional

deficit and neurodegeneration in prenatalalcohol-exposed transgenic mice. Ongoing outcome studies will evaluate learning and memoryskills to define the mechanistic link between PAE and AD/ADRD development.

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Poster

PSTR051: Neurogenesis and Neural Stem Cell Dynamics in Health and Disease

Location: MCP Hall A

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Topic: A.02. Postnatal Neurogenesis

Support: CONACHYT CF-2023-G-206
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INPER 2022-1-13

Title: Socio-sexual stimulation and epigenetic modifications: implications for adult neurogenesis in prairie voles

Authors: *G. D. RIVERA BAUTISTA[1], A. E. CASTRO[2], D. AVILA-GONZÁLEZ[3], F. J. CAMACHO[1], R. G. PAREDES[4], N. F. DIAZ[5], W. PORTILLO[1];
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Abstract: In the prairie vole, a monogamous species among mammals, socio-sexual incentives generate pair bonds throughout the animal's life cycle. Both, our research group and others have demonstrated that socio-sexual stimulation influences adult neurogenesis in prairie voles. Additionally, epigenetic modifications, such as methylation of lysine 4 in histones 3 (H3K4), may alter the proliferative and differentiative potential of neural stem cells residing in the subventricular zone (SVZ), as H3K4 methylation plays a fundamental role in the activation of gene expression. In this study, we aimed to determine whether cohabitation with a male for 24 induces changes in the global H3K4 methylation pattern of adult neural stem cells in the SVZ of female prairie voles. We examined a group of gonadally intact adult females cohabitating with vasectomized adult male prairie voles for 24h to establish a pair bond. A control group of gonadally intact females cohabitating with their sisters was also included. After this period, all females were sacrificed to dissect the brain, and sagittal slices of the SVZ were obtained. Immunofluorescence was subsequently employed to identify the adult neural stem cell population (positive for Nestin and Sox2) and determine their H3K4me3 and H3K4me1

methylation patterns. The analysis was performed using confocal microscopy and a semi-automatized counting protocol. These findings suggest a global increase in the methylation patterns of H3K4 associated with socio-sexual stimuli in the SVZ neurogenic niche, potentially correlating with increased gene expression. Further studies are required to evaluate the enrichment of the methylation marks on specific genes related to cell proliferation in response to these stimuli.

Disclosures: G.D. Rivera Bautista: None. **A.E. Castro:** None. **D. Avila-González:** None. **F.J. Camacho:** None. **R.G. Paredes:** None. **N.F. Diaz:** None. **W. Portillo:** None.

Poster

PSTR051: Neurogenesis and Neural Stem Cell Dynamics in Health and Disease

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR051.12/A11

Topic: A.02. Postnatal Neurogenesis

Support: The Swedish Childhood Cancer Foundation (BCF)
The Swedish Cancer Society (CF)
Karolinska Institutet (Cancer Research KI)

Title: A putative role for TET3/GADD45A/RARalpha in lithium-mediated DNA demethylation after irradiation in human neural progenitors: implications for treatment of cognitive deficits after cranial radiotherapy

Authors: C. NEOFYTOU, A. BACKLUND, M. RIDDER, ***O. HERMANSON**;
Dept. of Neurosci., Karolinska Institutet, Stockholm, Sweden

Abstract: Patients with childhood neural tumors show significantly increased survival by improvements in cranial radiotherapy and other treatments. However, many of these survivors display late side effects by the irradiation, including cognitive deficits, that prohibit normal life quality. Efficient therapies for this rapidly growing population are thus urgent. In collaboration with Klas Blomgren's group at KI, we showed that lithium (Li) could ameliorate negative effects after irradiation (IR) treatment of the rodent brain (Mol Psychiatry, 2021). We identified **GAD2** (GAD65), a crucial enzyme in GABA production, as a key gene for the Li-induced increase in neuronal differentiation of postnatal neural progenitors post-IR. GAD2 was identified in a group of genes that specifically showed decreased DNA methylation and up-regulated expression after IR followed by Li treatment in rodents. In a follow-up study, we confirmed the up-regulation of GAD2 by Li after IR in human iPS-derived neural stem and progenitor cells (hNSPCs). In addition, the important role for DNA methylation alteration was strengthened (Transl. Psychiatry, 2023). Notably, global DNA methylation was dramatically altered in the hNSPCs already after IR but displayed no systematic pattern when analyzed by gene ontology approaches. However, after Li post-IR, DNA methylation was preferentially altered at regulatory sequences of neuronal- and glial-associated genes.

This observation lead to the critical question: how are these neuro-glia-selective alterations in DNA methylation mediated by Li after IR regulated?
We have observed an increase in the expression of the DNA demethylation-associated dioxygenase TET3, but not TET1 or TET2, in Li/IR-treated hNSPCs. In parallel, we noted an increase in the expression of GADD45A. GADD45A binds RNA/DNA complexes and plays a crucial role in recruiting TETs to their target areas. An *in silico* analysis of protein interactions revealed a direct interaction between GADD45A and the neurogenic transcription factor retinoic acid receptor alpha (RARα). Treatment of various types of stem cells with retinoic acid induces GAD2/65-expression and GABAergic differentiation. We performed pilot experiments using RNA knockdown of TET3 in hNSPCs, and indeed, siTET3 in Li+IR-treated cells resulted in a clear decrease in GAD2 expression. Our data point to an Li-induced RARα-GADD45A-TET3-mediated regulation of neuronal differentiation post-IR that have implications for on-going clinical trials (LiBRA). Current work is testing this hypothesis further, and updates will be presented.

Disclosures: C. Neofytou: None. **A. Backlund:** None. **M. Ridder:** None. **O. Hermanson:** None.

Poster

PSTR051: Neurogenesis and Neural Stem Cell Dynamics in Health and Disease

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR051.13/A12

Topic: A.02. Postnatal Neurogenesis

Support: NIH Grant DP2NS1118180-1
NIH Grant R56NS130450-01A1
Shaw Scientist Program Award by Greater Milwaukee Foundation

Title: In vivo characterization of adult neural stem cell behavior in a novel vimentin-reporter mouse

Authors: *S. MHATRE[1,2,3], O. BRYAN[1], S. FARHADOVA[2], L. ENGLISH[5], T. PORTER[4], C. S. MORROW[6], S. KNAACK[4], M. HOSSEINI[4], E. W. DENT[2], A. M. SOUSA[2], D. L. MOORE[2]; [2]Neurosci., [1]Univ. of Wisconsin-Madison, Madison, WI; [3]Cell and Mol. Biol. Grad. Program, [4]Univ. of Wisconsin Madison, Madison, WI; [5]Neurosci., Univ. of Wisconsin Madison Neurosci. Training Program, Madison, WI; [6]Harvard Univ., Boston, MA

Abstract: Adult neural stem cells (NSC) are primarily quiescent, in reversible G0 of the cell cycle, and lose their ability to exit quiescence with aging and disease. We have previously found in vitro that as qNSCs exit, they traffic accumulated misfolded proteins to the centrosome, forming an aggresome. The intermediate filament vimentin collapses around this aggresome, forming a vimentin cage, and bringing with it bound proteins, such as chaperones and proteasomes. As the NSC divides, it asymmetrically segregates these cellular cargoes to one

daughter cell, leading to a decrease in its proliferation rate, while the other daughter remains able to rejuvenate the niche. Although the role of vimentin in quiescence exit has been shown in vitro, its function in vivo remains unknown. To study how vimentin protein is regulated in vivo, we developed a transgenic mouse line with vimentin tagged to a linker and the fluorophore mScarlet at its 3' end using CRISPR/Cas9. First, we asked what cell types are labelled with vimentin. To answer this question and benchmark this line with current NSC reporter lines, we crossed the Vimentin-mScarlet mouse line with either Nestin-GFP or GFAP-GFP mice and performed RNA sequencing on purified hippocampal cells, identifying unique vimentin-mScarlet populations. To further characterize the cell behaviors of mScarlet+ and/or GFP+ cells, we sorted the purified hippocampal cells using FACS and compared their ability to form neurospheres, and their proliferation and differentiation behavior in vitro. We observed that a larger fraction of GFP+ cells formed neurospheres than mScarlet+ cells, suggesting that vimentin is not a NSC specific marker. Further, we also performed timelapse analyses of these purified populations to observe NSC behaviors such as time to first division and lineage progression. To determine the role of vimentin in NSC quiescence exit in vivo, we treated the transgenic mice with temozolomide to ablate the dividing cells and enriched for quiescence exit, analyzing which fluorescent populations were most likely to exit quiescence. Finally, to visualize the dynamics of vimentin in vivo in the hippocampal NSC niche, we surgically removed the cortical tissue above the corpus callosum and implanted a 3mm metal canula with glass coverslip. These mice were imaged daily through the cranial windows using a two-photon microscope to observe vimentin's dynamic behaviors in the adult neurogenic niche. In summary, these studies will provide a stem cell-focused characterization of a novel vimentin-mScarlet mouse line, providing a new resource to the scientific community, and reveal the role of vimentin in NSC dynamics in the adult brain.

Disclosures: S. Mhatre: None. **O. Bryan:** None. **S. Farhadova:** None. **L. English:** None. **T. Porter:** None. **C.S. Morrow:** None. **S. Knaack:** None. **M. Hosseini:** None. **E.W. Dent:** None. **A.M. Sousa:** None. **D.L. Moore:** None.

Poster

PSTR051: Neurogenesis and Neural Stem Cell Dynamics in Health and Disease

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR051.14/A13

Topic: A.02. Postnatal Neurogenesis

Support: NIH Grant NS120664

Title: Single-cell RNAseq profiling to investigate postnatal neuroblast migration

Authors: *C. DE SILVA[1], D. YEROSHENKO[2], A. BURLI[3], S. BELLIZZI[3], J. C. CONOVER[4];
[1]Univ. of Connecticut, STORRS MANSFIELD, CT; [2]Physiol. and Neurobio., Univ. of Connecticut, Storrs, CT; [3]Univ. of Connecticut, Storrs, CT; [4]Dept Physiol & Neurobiol, Univ. of Connecticut, Storrs Manfld, CT

Abstract: We used single-cell RNAseq to characterize the expression profiles of migration factors, specifically the Eph receptor tyrosine kinases and their ephrin ligands, in postnatal neuroblasts from their starting point of origin in the subventricular zone (SVZ), through the rostral migratory stream (RMS) and to their destination within the olfactory bulb (OB). This migration requires precise control of directed cell guidance and topographical mapping. Ephs and ephrins are widely expressed in the SVZ, RMS and OB and our previous studies have shown that EphA4-ephrin interactions regulate important cell-to-cell interaction along the RMS. Missing from this study was the contribution of other Eph receptors and analysis of how migratory control is mediated at the different sites along the migration route (SVZ, RMS and OB). Additionally, whether specific Eph-ephrin signaling is required at distinct developmental timepoints (postnatal days 6, 12 and 60) is unclear and complicated by the large number of Eph-ephrin combinations.
We first examined whether subtypes of neuroblasts express unique transcripts that may promote their distribution within the OB by high-resolution clustering. Other cell types along the migration route that may coordinate Eph-ephrin cell-cell interactions were also examined. Additionally, we assessed Eph/ephrin phosphorylation status and found differential activation based on location along the migration pathway. We also detected age-dependent changes in phosphorylation patterning. Different Eph/ephrin activation profiles within the SVZ, RMS and OB imply that Eph-ephrin signaling is important in guiding neuroblasts within changing microenvironments and based on cellular interactions. To understand these interactions, we used CellChat software to model likely Eph-ephrin pairings with the highest probability of communication between migratory neuroblasts and other cell types along the migration pathway.

Disclosures: C. de Silva: None. **D. Yeroshenko:** None. **A. Burli:** None. **S. Bellizzi:** None. **J.C. Conover:** None.

Poster

PSTR051: Neurogenesis and Neural Stem Cell Dynamics in Health and Disease

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR051.15/A14

Topic: A.02. Postnatal Neurogenesis

Support: NINDS R01 NS124775 to EDK

Title: Hippocampal neural stem and progenitor cell proximity to vasculature emerges during postnatal development in mice

Authors: *I. CARTER[1], N. DEVASTHALI[1], A. I. SAULSBERY[2], E. D. KIRBY[3];
[1]The Ohio State Univ., Columbus, OH; [2]Psychology, The Ohio State Univ., Columbus, OH; [3]Psychology, Ohio State, Columbus, OH

Abstract: Adult neurogenesis is the process of creating new neurons in adulthood. It is observed in many mammalian species and occurs in two main areas of the brain, the subventricular zone

and the dentate gyrus (DG) of the hippocampus. The DG, in particular, has especially dense vasculature. DG neural stem cells (NSCs) along with their immediate progeny, intermediate progenitor cells (IPCs), exist in close proximity to these local blood vessels during adulthood. This unique relationship is believed to support the process of neurogenesis in several ways, such as providing NSCs access to circulating support molecules like growth factors and providing scaffolding for progenitors to migrate tangentially in the DG. Though the proximity of NSCs and IPCs to blood vessels in adulthood is well known, little is known about how it develops. To characterize the development of the proximity of NSCs and IPCs to blood vessels, we quantified the distance from radial glial-like NSC bodies as well as IPC bodies to the nearest blood vessel in mice from 2 to 9 weeks of age, an age range covering the formation of the DG cell layers up to adulthood. We used immunofluorescent phenotypic markers to identify NSCs, IPCs, and endothelial cells in wildtype mice perfused at 2, 3, 5, and 9 weeks of age. We found that there was a progressive reduction in the distance between NSC bodies and the nearest blood vessel from 2 to 9 weeks of age, and the same developmental pattern was true for IPCs. Our results suggest that the proximity between NSCs and IPCs with vasculature is not a preserved feature from early development, but is instead one that arises de novo during postnatal maturation. Additionally, these results imply that the DG neurogenic vascular niche is not finished developing until adulthood. Further, we are characterizing the DG vascular niche in mice at 2, 3, and 9 weeks of age by using EZ clear, a tissue clearing protocol, and IMARIS imaging software to create 3D renderings of the vasculature at each developmental time point. Additional investigations into the development of the DG neurogenic niche and the surrounding vasculature will shed light on the mechanisms that preserve neurogenesis into adulthood.

Disclosures: I. Carter: None. **N. Devasthali:** None. **A.I. Saulsbery:** None. **E.D. Kirby:** None.

Poster

PSTR051: Neurogenesis and Neural Stem Cell Dynamics in Health and Disease

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR051.16/A15

Topic: A.02. Postnatal Neurogenesis

Support: NIH/NINDS R01 N5124775

Title: Neural stem cell-derived vascular endothelial growth factor is neuroprotective against excitotoxic injury in adult mouse dentate gyrus

Authors: *L. N. MILLER[1], E. D. KIRBY[2];
[1]Ohio State Univ., Columbus, OH; [2]Psychology, Ohio State, Columbus, OH

Abstract: Emerging evidence indicates that the endogenous neural stem cells (NSCs) of the mammalian hippocampus generate a multifaceted secretome with potential to regulate hippocampal function. Our lab has shown that endogenous adult hippocampal NSCs express and secrete the pleiotropic growth factor vascular endothelial growth factor (VEGF), and that NSC-

expressed VEGF is critical for maintaining adult neurogenesis. Previous studies suggest that VEGF may prevent neuronal damage in pathological conditions, therefore we hypothesized that NSC-derived VEGF has a neuroprotective effect in the adult mouse dentate gyrus (DG) following seizure-related excitotoxic damage. To investigate this hypothesis, we used the glutamatergic agonist kainic acid (KA) to model seizure-induced injury in both wildtype mice and mice in which NSC-derived VEGF was selectively knocked down. Following KA treatment, VEGF knockdown mice showed exacerbated gliosis and neuronal injury at both acute (1d post-KA) and long-lasting (7d post-KA) time points, as compared to wildtype littermates similarly treated with KA. To explore the relationship between NSC-derived VEGF and neuroinflammation further, we also injected retrovirus in the DG of male and female WT mice to drive overexpression of VEGF in NSCs prior to treatment with KA. Analysis is ongoing to investigate whether VEGF overexpression will show decreased gliosis and neuronal injury following KA as compared to mice that were injected with control virus. Ultimately, these data suggest that NSC-derived VEGF plays an important role in protecting the DG, which is a valuable aspect to consider when developing therapeutic interventions for epilepsy that harness endogenous neurogenic processes.

Disclosures: L.N. Miller: None. **E.D. Kirby:** None.

Poster

PSTR051: Neurogenesis and Neural Stem Cell Dynamics in Health and Disease

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR051.17/A16

Topic: A.02. Postnatal Neurogenesis

Support: NSF GRFP to ND
R21 NS123797 to EDK

Title: Neural stem cell-expressed excitatory amino acid transporter 1 supports normal hippocampal functioning

Authors: *N. DEVASTHALI[1], E. CORBETT[1], E. D. KIRBY[2];
[1]The Ohio State Univ., Columbus, OH; [2]Psychology, Ohio State, Columbus, OH

Abstract: The subgranular zone of the hippocampus is one of two neurogenic niches in the adult mammalian brain where neural stem cells (NSCs) reside and can proliferate to give rise to functional neurons. These newly-born neurons integrate into existing hippocampal circuitry where they support learning, memory, and affect regulation. NSCs abundantly express excitatory amino acid transporter 1 (EAAT1), which transports the neurotransmitter glutamate from the extracellular space to inside the cell. We have found NSC-EAAT1 is expressed in the NSC bodies and likely in the molecular layer terminals that wrap around and ensheathe glutamatergic synapses on dentate granule cells. NSC-EAAT1 may therefore have contact with peri-synaptic and extra-synaptic glutamate from a variety of sources. Clearance of glutamate is an essential

process in maintaining effective synaptic function and in the DG may be critical to maintaining low levels of activity hypothesized to underpin effective pattern separation. Most previous work on the role of EAATs in glutamate clearance to date has focused on the role of EAAT2 expressed by astrocytes. The contribution of NSC-expressed EAAT1 to normal hippocampal functioning is unclear. We therefore investigated the hypothesis that NSC-EAAT1 modulates hippocampal functioning. To investigate this, we used CRISPR technology to generate a new $EAAT1^{fl/fl}$ mouse, in which a critical exon of EAAT1 was bracketed by LoxP sites. Crossing $EAAT1^{fl/fl}$ mice with $NestinCreER^{T2+/-}$ mice yielded a tamoxifen (TAM) sensitive NSC-specific knockout of the EAAT1 gene. TAM treated $EAAT1^{fl/fl}$;$NestinCreER^{T2+/-}$ mice (EAAT1cKO) showed significant loss of EAAT1 protein in NSCs compared to Cre-negative littermates (Wt). EAAT1cKO resulted in increased granule cell activity after a cognitive task compared to similarly treated Wt mice, as measured by immunolabelling for the immediate early gene cFos. Additionally, EAAT1cKO mice showed a trend for impaired hippocampus-dependent memory in a Y-maze task compared to Wt mice. Together, these findings suggest that NSC-EAAT1 is required to maintain sparse firing of dentate granule cells, and may support hippocampus-dependent memory.

Disclosures: N. Devasthali: None. **E. Corbett:** None. **E.D. Kirby:** None.

Poster

PSTR052: Mechanisms and Therapeutics in Animal Models for Autism

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR052.01/A17

Topic: A.07. Developmental Disorders

Support: P50HD103526

Title: Gait and electroencephalogram pairing as a novel biomarker in genetic neurodevelopmental disorders

Authors: *E. MONSEN[1], J. L. SILVERMAN[2];
[1]Dept. of Psychiatry and Behavioral Sci., UC Davis, Sch. of Med., Sacramento, CA; [2]UC Davis MIND Inst., Sacramento, CA

Abstract: Numerous neurodevelopmental disorders (NDDs) including Angelman's Syndrome (AS), Phelan McDermid syndrome, and Dup 15q syndrome display pronounced gait impairments and distinct electroencephalogram (EEG) features in preclinical models and affected individuals. However, EEG and gait cycle metrics have not been paired simultaneously in preclinical models to evaluate their potential as a quantitative biomarker for diagnostics and novel therapeutic assessment. Given the existing literature on AS gait anomalies and their distinct EEG signature, we began our project using an established AS mouse model. This study aims to generate a cortical synchronization profile during gait in *Ube3a-del*$^{m-/p+}$ (AS) mice to compare to WT, age, sex matched controls (N = 8-10). We hypothesize that we will discover corroborative biomarkers

to be potentially employed in clinical trials and as a diagnostic measure. EEG data was gathered by HD-X02 DSI implants and analyzed through Neuroscore (DSI). Gait was recorded using DigiGait's paired treadmill system and ventral plane videography. These videos were analyzed through DigiGait's MATLAB analysis software. Gait, which is immune to test-retest bias, was recorded one week prior to surgery and one week after post-operative recovery to control for bias the implant may introduce. No significant differences were found in hindlimb measurements when comparing gait metrics before and after surgery. Findings were also not significant from historical WT control data. Therefore, DigiGait offers a robust quantitative gait measurement in implanted animal models. Preliminary data also illustrates specific EEG signatures are predictive of spatial characteristics of gait in C57BL6/J mice. We have acquired and are currently testing this assay in *Ube3a-del* $^{m-/p+}$ mice and WT controls. Analysis will be finalized and presented which illustrates EEG phenotypes during gait assessment. The broad scope in which this assay may be utilized offers a novel translational dual-domain metric, which is crucial individuals with neurodevelopmental disorders such as AS.

Disclosures: E. Monsen: None. **J.L. Silverman:** None.

Poster

PSTR052: Mechanisms and Therapeutics in Animal Models for Autism

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR052.02/A18

Topic: A.07. Developmental Disorders

Support: NIH: NS112706-01
FRAXA Research Foundation

Title: C-subunit leak channel in the mitochondrial inner membrane regulates synaptic plasticity and behavior.

Authors: *P. LICZNERSKI, V. K. GRIBKOFF, E. PEYTON, L. SHEN, E. A. JONAS;
Yale Univ., New Haven, CT

Abstract: Hippocampal long-term potentiation (LTP) is the enhancement of synaptic transmission that serves as a model to study memory formation. Insertion of AMPA receptors in response to neuronal stimulation is critical for modulation of synaptic strength and cellular mechanisms of learning. We reported recently that a leak channel in the inner mitochondrial membrane formed by the ATP synthase c-subunit octamer drives key characteristics of aberrant neuronal plasticity in Fragile X (autism) syndrome, in particular the increased mitochondrial inner membrane conductance causes high constitutive mRNA translation rates and prevents synaptic stimulation induced protein synthesis. In our current study we test how the leak channel affects the ability of mitochondria to contribute to LTP in WT hippocampus. We find that manipulation of mitochondrial inner membrane ion conductance (by c-subunit over-expression) prevents stimulus induced changes in ATP synthesis efficiency which in turn inhibit the

phosphorylation events required for plasma membrane insertion of AMPA receptors. We also find that increasing the leak by pharmacological inhibition of the anti-apoptotic ATP synthase regulator Bcl-xL or by Bcl-xL conditional KO causes loss of synaptic plasticity and prevents normal memory formation.

Disclosures: P. Licznerski: None. **V.K. Gribkoff:** None. **E. Peyton:** None. **L. Shen:** None. **E.A. Jonas:** None.

Poster

PSTR052: Mechanisms and Therapeutics in Animal Models for Autism

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR052.03/A19

Topic: A.07. Developmental Disorders

Support: ADNP Foundation
Somia Family
5T32MH073124

Title: Restoration of ADNP rescues behavioral phenotypes in a mouse model of ADNP Syndrome

Authors: *S. L. OLGUIN[1], A. MARROQUIN[2], J. A. HALMAI[3], J. D. BUXBAUM[4], K. FINK[5], J. L. SILVERMAN[6];
[1]Dept. of Psychiatry and Behavioral Sci., UC Davis, sacramento, CA; [2]UC Davis, Sacramento, CA; [3]Neurol., UC Davis Med. Ctr., Sacramento, CA; [4]Mount Sinai Sch. of Med., New York, NY; [5]Dept. of Neurol. and Stem Cell Program, UC Davis Med. Ctr., Sacramento, CA; [6]UC Davis MIND Inst., Sacramento, CA

Abstract: Pathogenic disruptions to the *Activity Dependent Neuroprotector Homeobox* (*ADNP*) gene are among the most common heterozygous genetic mutations associated with autism spectrum disorders (ASD). In 2014, ADNP syndrome was discovered with the hallmark features of intellectual disability, global developmental delays, global motor planning delays and ASD. Our laboratory, in collaboration with Drs. Fink and Buxbaum, have rigorously characterized translational outcome measures and developed first in class, genetic rescue of *ADNP* loss. We hypothesize that translationally relevant phenotypes detected following *ADNP* loss can be restored with intervention. Behavioral testing (N=12-14/sex/genotype) targeting motor and cognitive domains found no overt genotype or sex differences in gross motor abilities with differences in gait including shorter stride length. Additionally, loss of *ADNP* resulted in decreased novelty exploration suggesting decreases in learning and memory. Additional animals (N=6-8/treatment) underwent intracerebroventicular injections with custom adeno-associated virus (AAV) or CRISPRa to restore *ADNP* at 4 weeks of age and tested for motor and cognitive ability at adulthood (7-8 weeks old). After behavioral testing animals were euthanized via perfusion and rapid decapitation, and brains collected for IHC or western blot to determine level

of ADNP restoration. Preliminary results suggest restoration of *ADNP* via AAV resulted in the most improvement in novel exploration with no effect on gross motor ability. These studies show for the first-time restoration of *ADNP* expression can lead to improved behavioral outcomes in a mouse model of ADNP syndrome.

Disclosures: S.L. Olguin: None. **A. Marroquin:** None. **J.A. Halmai:** None. **J.D. Buxbaum:** None. **K. Fink:** None. **J.L. Silverman:** None.

Poster

PSTR052: Mechanisms and Therapeutics in Animal Models for Autism

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR052.04/A20

Topic: A.07. Developmental Disorders

Support: SB-129 Jordan's Guardian Angels

Title: Translational Behavioral Assessment of Three Pathogenic Variants of the β-subunit of the Protein Phosphatase 2A (PP2A) that Results in Jordan Syndrome

Authors: *A. S. MARROQUIN[1], K. TRAN[1], J. FINDLEY[1], S. L. OLGUIN[1], K. FINK[1], S. STRACK[2], J. NOLTA[1], J. L. SILVERMAN[1];
[1]UC Davis, Sacramento, CA; [2]Univ. Iowa, Iowa City, IA.

Abstract: PPP2 syndrome type R5D, or Jordan's Syndrome (JS), is a neurodevelopmental disorder (NDD) caused by a number of different pathogenic missense variants in PPP2R5D, a β-subunit of the Protein Phosphatase 2A (PP2A). Although highly heterogenous, JS is characterized by global developmental delays, seizures, macrocephaly, hypotonia (lacking muscle tone), inattention, social and sensory challenges often associated with autism and disruptions in sleep[JS1] . Most variation in symptom severity is specific to pathogenic variant. Our laboratory, in collaboration with Drs. Stracke, Fink and Nolta of Jordan's Guardian Angels (JGA), acquired three preclinical mouse models, each with a pathogenic variants of the β-subunit of PP2A (E200K, E198K, and E420K). We hypothesize that translationally relevant phenotypes will be detected and quantifiable in each of model of JS. We further hypothesize that phenotypic severity will be correlated with specific variants. For example, the E420 variant is more profoundly affected than the E198, while the E200 variant is the mildest variant of the three. Subject mice (N=12-14/sex/genotype/variant) were assayed through a series of behavioral assessments targeting indices of development, motor and sensory abilities, seizure thresholds and the cognitive domain. Preliminary results suggest no differences in developmental milestones in the E200K variant, as hypothesized, with hyperactivity and reduced working memory in the Y-maze. Additional animals (N=6-8/sex/genotype) will be characterized for baseline electroencephalography (EEG), spike trains and power spectral density, sleep, and apneas via whole body plethysmography. Preliminary results suggest low overall spectral power, alterations in sleep-wake patterns, increased delta power in the E200K variant. These studies provide a

framework for future evaluation of functional efficacy following repurposed FDA approved pharmaceutical compounds. We anticipate these studies will also help inform updates to clinical care guidelines for affected individuals with Jordan's Syndrome and guide future therapeutic endeavors.

Disclosures: A.S. Marroquin: None. **S.L. Olguin:** None. **J.L. Silverman:** None.

Poster

PSTR052: Mechanisms and Therapeutics in Animal Models for Autism

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR052.05/A21

Topic: A.07. Developmental Disorders

Support: Bill and Melinda Gates Millennium Scholarship
William Randolph Hearst Fellowship
NIH R01 NS088566
New York Stem Cell Foundation
Gabrielle's Angels Foundation for Cancer Research #135
Pew Biomedical Scholar

Title: Multi-omic analysis of mouse embryonic ChP-CSF contributions to brain development following maternal immune activation (MIA)

Authors: *T. LACEY[1,2], B. PETROVA[4], N. KANAREK[5,7,3], M. LEHTINEN[6,3];
[1]Pathology Dept., Harvard University/ Boston Children's Hosp., Brookline, MA; [2]Biol. and Biomed. Sci. PhD Program, [3]Harvard Med. Sch., Boston, MA; [4]Core Facilities, Med. Univ. of Vienna, Vienna, Austria; [5]Pathology Dept., Boston Children's Hosp., Brookline, MA; [6]Pathology, Boston Children's Hosp., Boston, MA; [7]Harvard-MIT Div. of Hlth. Sci. and Technol., MIT, Cambridge, MA

Abstract: Maternal immune activation (MIA) by viral, bacterial, or parasitic infection that results in hospitalization enhances the risk in offspring for neurodevelopmental disorders including autism spectrum disorders (ASD). During cerebral cortical development, neural progenitors first proliferate along cerebrospinal fluid (CSF)-filled ventricles and then differentiate into neurons and glia that form the cerebral cortex. The choroid plexus (ChP), located in each brain ventricle, is both a barrier and a secretory tissue. The ChP not only protects the brain from peripheral insults but also regulates CSF production and composition, providing instructive cues and nutrients for developing brain cells. Previously, in a mouse model of MIA our lab found that maternal intraperitoneal injection of viral mimetic, polyinosinic:polycytidylic acid (polyI:C), leads to a pro-inflammatory state marked by elevated cytokines in the embryonic CSF and accumulation of macrophages at the embryonic ChP. This led us to speculate that ChP-mediated secretion into the CSF is also perturbed in MIA, and we tested this using multi-omic techniques over the trajectory of MIA-induced inflammation. We analyzed the embryonic CSF

metabolome and both the maternal and embryonic ChP transcriptomes. We profiled MIA-induced changes in the embryonic CSF with untargeted metabolomics by liquid chromatography-mass spectrometry. This revealed elevation of glucocorticoids and kynurenine pathway related metabolites in embryonic CSF, which we validated by subsequent targeted metabolomics analyses. The kynurenine pathway elevation following inflammation is in accordance with previous findings in adult CSF. Glucocorticoids, among the most prescribed drugs for the treatment of inflammatory and immune disorders for their anti-inflammatory and immunosuppressive effects, respectively, commonly repress the expression of cytokines by macrophages. To compare responses in maternal and embryonic ChP to inflammation, we performed bulk RNA-sequencing of ChP following MIA. We found distinct age- and ventricle-dependent responses. The embryonic ChP in fourth ventricle had more long-lasting transcriptional changes associated with inflammation compared to the maternal ChP. Currently, we are investigating the effects of regionalized ChP responses to inflammation on brain development. Our multi-omic characterization of the mouse maternal and embryonic ChP-CSF compartments should reveal mechanistic insights underlying missteps of neural development following MIA.

Disclosures: T. Lacey: None. **B. Petrova:** None. **N. Kanarek:** None. **M. Lehtinen:** None.

Poster

PSTR052: Mechanisms and Therapeutics in Animal Models for Autism

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR052.06/A22

Topic: A.07. Developmental Disorders

Support: 1R01NS097808-A1
P50HD103526

Title: A novel mouse model of 15q11.2-q13.3 duplication syndrome with construct validity and translationally relevant phenotypes

Authors: A. Y. YOTOVA[1], D. H. YASUI[2], J. LASALLE[3], *J. L. SILVERMAN[1];
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Abstract: Chromosome 15q11-q13 duplication syndrome (Dup15q) is the most penetrant and the second most common genetic copy number variations (CNVs) associated with autism spectrum disorder (ASD). It results from maternally derived duplications or triplications of 15q11.2-113. Characteristic features of Dup15q syndrome are moderate to severe intellectual disability (ID), hypotonia, speech impairments, anxiety, impaired motor coordination, recurring uncontrollable seizures that do not respond to traditional anti-epileptic therapies (AEDs), and ASD. Perhaps most critically, individuals with Dup15q have a markedly high rate of Sudden Unexpected Death due to Epilepsy (SUDEP). The major theory suggests that the overexpression

of UBE3A, the gene encoding ubiquitin ligase E3A, is responsible for the majority of Dup15q phenotypes. However, a gap in our understanding of this phenomenon is the lack of available animal models of Dup15q that exclusively overexpress Ube3a and exhibit key clinical phenotypes for both construct face validity. Our team, in collaboration with the LaSalle laboratory, generated a novel mouse model of Ube3a overexpression using the PiggyBac-on-Bac methodology. We strategically inserted Ube3a into an intergenic region of mouse chromosome 6 to avoid interference with downstream gene expression. We utilized a C57Bl6/N background strain to circumvent the well-known seizure resistance of C57Bl6/J mice. We employed standardized methods of qPCR, Western blotting, and ELISA to confirm that the novel transgenic mice have higher levels of Ube3a transcript and protein compared to their WT littermates. We also conducted standardized behavioral phenotyping and observed several translationally relevant phenotypes, including heightened seizure susceptibility, cognitive impairments, and elevated spiking events during electroencephalographic analysis. Our ongoing work is focused on determining whether this model will exhibit sleep disturbances, behavioral seizures, and SUDEP phenotypes. Our research with this novel model offers a promising platform for evaluating the underlying etiology of Dup15q and testing potential therapeutic interventions.

Disclosures: A.Y. Yotova: None. **D.H. Yasui:** None. **J. LaSalle:** None. **J.L. Silverman:** None.

Poster

PSTR052: Mechanisms and Therapeutics in Animal Models for Autism

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR052.07/A23

Topic: A.07. Developmental Disorders

Support: ISS20-a0eebb8da213

Title: Role of the histone variant macroH2A1.1 in a mouse model of autism spectrum disorder

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Abstract: MacroH2A1 (mH2A1) is an ubiquitous variant of histone H2A present in two alternatively exon-spliced isoforms, mH2A1.1 and mH2A1.2, both expressed in mouse brain (1). Recently, we found that mH2A1.1 knock-out (KO) mice exhibit enhancement of sociability, active stress-coping behavior and hippocampal synaptic plasticity (2). Since mH2A1 functions as a chromatin component and transcriptional regulator, and defects in the mechanisms of

chromatin silencing are involved in neurodevelopmental disorders, we assessed whether mH2A1.1 may play a role in the development of autism spectrum disorder (ASD). For this purpose, we used the valproic acid (VPA) model of ASD in mice. Rodent prenatal exposure to VPA leads to behavioral abnormalities recapitulating features of human disease and thus is considered a suitable model of ASD (3). Pregnant heterozygous (HT) mH2A1.1 female mice, mated with HT mH2A1.1 males, were treated with VPA (500 mg/kg, i.p.) or vehicle (VEH) on gestational day 12.5. Offspring were assessed for somatic growth, reflex maturation, ultrasonic vocalizations (USVs), and spontaneous motor behavior on post-natal day 8. Results were analysed by three-way ANOVA followed by Tukey's post-hoc test. We found that VPA treatment did not affect body weight or righting reflex in any genotype. However, VPA exposed mice exhibited higher frequency of head rising than VEH mice, regardless of genotype ($p<0.01$). In addition, VPA exposed KO females emitted higher number of USVs as compared to KO/VPA males ($p<0.01$) and KO/VEH females ($p<0.05$). In electrophysiology experiments in hippocampal slices (CA1 area) from 2 week-old mice, low frequency stimulation (LFS) of Schaffer collaterals induced Long Term Depression (LTD) in WT/VEH mice (81±6% of basal values, $p<0.05$, paired t-test), but not in WT/VPA or in KO/VEH and KO/VPA mice. Finally, prenatal exposure to VPA significantly reduced hippocampal serotonin levels with respect to VEH in WT mice ($p<0.05$, two-way ANOVA followed by Tukey's post-hoc test) in two week-old mice, while no changes were observed in KO mice. Basal serotonin levels were significantly lower in KO/WT with respect to WT/VEH ($p<0.01$). Given the role of the serotonergic system and synaptic plasticity in neurodevelopment, these results suggest an involvement of mH2A1.1 in ASD. Further analyses are underway to clarify the role of mH2A1.1 in adult mice prenatally exposed to VPA. (1) Bereshchenko et al., Clin Epigenetics 2019;11:121. (2) Chiodi et al., FASEB J. 2021 Aug;35(8):e21793. doi: 10.1096/fj.202100569R. PMID: 34320234. (3) Tartaglione et al., Neuropharmacology. 2019 Nov 15;159:107477. doi: 10.1016/j.neuropharm.2018.12.024.

Disclosures: V. Chiodi: None. **A. Tartaglione:** None. **I. Coppola:** None. **N. La Maida:** None. **A. Di Giorgi:** None. **M. Pellegrini:** None. **M. zini:** None. **M. Vinciguerra:** None. **V. Micale:** None. **P. Popoli:** None. **M. Domenici:** None.

Poster

PSTR052: Mechanisms and Therapeutics in Animal Models for Autism

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR052.08/A24

Topic: A.07. Developmental Disorders

Support: Taconic Biosciences, Academic Grant

Title: Investigation of parvalbumin expression and behavioral effects after subchronic administration of an NMDA receptor partial agonist in the human 22q11.2 [Df(h22q11)/+] deletion syndrome mouse model

Authors: J. STEPHENSON[1], S. PAOLINO[1], K. YODER[1], B. GOODMAN[1], E. TOXEY[1], J. HECTOR[1], J. TRIMBER[1], D. A. MITRANO[2], J. W. BOGENPOHL[2], *J. BURKET[1];
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Abstract: Schizophrenia and Autism Spectrum Disorder represent two highly polygenic and phenotypically heterogeneous neurodevelopmental disorders whose genetic signatures are composed of common, rare, and de novo risk alleles and copy number variations. Specifically, mutations within chromosomal region 22q11.2 correlate with a high prevalence of neuropsychiatric and neurodevelopmental disorders. 22q11.2 deletion syndrome (DS) results in a 1.5Mb or typical 3Mb deletion within this locus and may be involved in complex phenotypes observed within affected individuals. The genetic human 22q11.2 [Df(h22q11)/+] mouse displays behavioral phenotypes present in the 22q11DS. Prior studies show deficits in behavior and decreased parvalbumin (PV) expression within PFC in young adult male mice suggesting alterations in prefrontal cortex connectivity and possible dysregulation within GABAergic interneuron circuitry. Additionally, Df(h22q11)/+ mice display NMDA receptor (NMDAR) hypofunction shown by their behavioral sensitivity to NMDAR antagonists. The NMDAR is important for regulation of social-cognitive processes that could have relevance as a novel therapeutic target in 22q11.2 DS. This study examined the effects of an NMDAR agonist intervention in adolescent male and female Df(h22q11)/+ mice on behavior and PV expression in medial orbital (mo) PFC. Specifically, 4-6 week old C57BL/6-Del (16Dgcr2-Hira)1Tac mice (n=60) or WT control were administered a 1-week subchronic dose of the NMDAR partial agonist, D-cycloserine (DCS, 30 mg/kg, i.p.), or saline. Behaviorally, several significant and/or trending differences were observed on measures of stereotypic, anxiety, and cognitive behavior in 22q11.2 mice compared to WT. Specifically, the 22q11.2 mice showed a reduced percentage of spontaneous alternations in the y-maze, a higher rate of marble burying, and a decreased amount of time spent in open arms of the elevated plus maze compared to the saline-treated WT mice. Following behavioral testing, a subset of brains was perfused for immunostaining using a PV and WFA lectin antibodies (1:1000); the latter selectively labels neuronal extracellular matrix, perineuronal nets (PNN), which surround PV^+ interneurons. Preliminary molecular data show that 22q11.2DS mice have decreased PV expression in the moPFC compared to WT which was restored by administration of DCS. Differences in the number of colocalized cells (PV^+/PNN^+) were observed after DCS treatment in the WT mice. Overall, these data encourage future investigation of pharmacological interventions that target NMDAR to alleviate behavioral and molecular phenotypes exhibited in 22q11.2DS.

Disclosures: J. Stephenson: None. **S. Paolino:** None. **K. Yoder:** None. **B. Goodman:** None. **E. Toxey:** None. **J. Hector:** None. **J. Trimber:** None. **D.A. Mitrano:** None. **J.W. Bogenpohl:** None. **J. Burket:** None.

Poster

PSTR052: Mechanisms and Therapeutics in Animal Models for Autism

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR052.09/A25

Topic: A.07. Developmental Disorders

Support: NIH T32 DA050560-04
NIH T32 DA007234-37
NIH RO1 MH123661

Title: Male-specific vulnerability to psychostimulant-induced repetitive behaviors in 16p11.2 hemideletion revealed by pose estimation

Authors: *E. M. GIGLIO[1], E. TRAMM[2], G. R. ROJAS[2], D. MUELLER[3], N. M. GRISSOM[4]; [1]Dept of Neurosci., Univ. of Minnesota, Minneapolis, MN; [2]Univ. of Minnesota, Minneapolis, MN; [3]Psychology, Univ. of Minnesota, Minneapolis, MN; [4]Dept. of Psychology, Univ. of Minnesota, Minneapolis, MN

Abstract: Neurodevelopmental disorders like autism spectrum disorder (ASD) have strong male biases in diagnosis, but the underlying mechanisms controlling interactions between sex differences and genetic variation remains unclear. A key diagnostic feature of ASD is the development and expression of stereotypic motor behaviors, which employ the same neural systems involved in social and non-social reward learning. We use a mouse model of human 16p11.2 hemideletion (del/+) - a copy number variation linked to neurodevelopmental diagnoses including ASD - to delve into these interactions. 16p11.2 del/+ mice have previously been demonstrated to have changes in their striatal molecular function and learning deficits as well as sex-divergent deficits in motivational behaviors. Dopaminergic signaling is involved in repetitive locomotor behavior, motivation, and decision-making, and amphetamine locomotor sensitization is a well-established paradigm of probing dopamine function. Here we investigate both the time scale and specific expression on sex- and genotype-specific response to amphetamine sensitization using markerless pose estimation software (SLEAP). We find differences between both sexes and genotypes in behavioral responses to amphetamine perturbation, including changes in behavior bout frequency, duration, distance traveled, and total proportion of time spent moving within 90 minutes of injection. In particular, we find that male del/+ exhibit stronger behavioral responses to smaller quantities of amphetamine, both in terms of distance traveled and in terms of perseverative behavioral sequences produced at low doses of amphetamine stimulation. Current analyses include counts of specific stereotypies within individuals, identifying bouts of behavior and poses within animals, modeling behavioral transitions and identifying specific motor behaviors that increase both in response to greater stimulant doses and in terms of sensitization within a single dose. These results suggest that sex and genotype can act syncretically to create neurodivergent patterns of stereotypy evoked by amphetamine stimulation, implicating catecholamine mechanisms.

Disclosures: E.M. Giglio: None. **E. Tramm:** None. **G.R. Rojas:** None. **D. Mueller:** None. **N.M. Grissom:** None.

Poster

PSTR052: Mechanisms and Therapeutics in Animal Models for Autism

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR052.10/A26

Topic: A.07. Developmental Disorders

Title: Constant light alters exploratory behavior in a mouse model of autism spectrum disorder - male BTBR mice

Authors: *C. A. MURPHY[1], G. GUINDON[2], G. ROJAS[2], M. MILANO[2], S. TADROS[2], J. A. SEGGIO[2];
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Abstract: Light-at-night is becoming an increasingly common form of circadian disruption, leading to poorer sleep and impaired behavioral outcomes. For individuals with autism spectrum disorder (ASD), maintaining a stable circadian rhythm is crucial as it may impact various aspects of their functioning. When circadian rhythms are disturbed, it can lead to impairments in cognitive function and emotional regulation, including increased anxiety, irritability, and difficulties in communication, and social interaction in individuals with ASD. This study aims to uncover whether exposure to light-at-night exacerbates the behavioral issues seen in an autistic-like mouse model. Male BTBR T+ Itpr3tf/J (BTBR #002282) and C57BL/6J (B6 #000664) mice were exposed either to a standard 12:12 light:dark cycle (LD) or constant light (LL), so that there were four groups: 1) B6/LD, 2) BTBR/LD, 3) B6/LL, and 4) BTBR/LL. All mice were then evaluated for explorative, depressive-like, cognitive, and social behaviors via open field, sucrose preference, novel object, and social interaction tests, respectively. In the open field, B6/LL mice exhibited increased distance traveled compared to B6/LD mice; however, BTBR mice in LL exhibited reduced distance and velocity, and marginally increased center-zone time compared to BTBR/LD. In both LD and LL, BTBR mice exhibited reduced sucrose preference than B6 mice. Additionally, LL lead to reductions in the exploration of the novel objects only in BTBR mice manifested by reduced interactions, but had no effect on object recognition to a new object. Lastly, B6 had increased non-aggressive encounters with a novel mouse compared to BTBR mice, but light cycle had no effects on sociability. In summary, LL negatively affected explorative behaviors in novel environments, while not affecting cognition, anhedonia, or social behavior in autistic-like BTBR mice. As explorative behavior plays a role in the adaptation to new situations, sensory processing, and attentional mechanisms, circadian disruptions (such as exposure to artificial light at night) can contribute to sensory overload, potentially impacting the behavioral health of individuals with AUD.

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Poster

PSTR052: Mechanisms and Therapeutics in Animal Models for Autism

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR052.11/A27

Topic: A.07. Developmental Disorders

Support: NYS Office for People with Developmental Disabilities

Title: The effect of URB597 on repetitive/restricted behaviors in the BTBR mouse model of Autism Spectrum Disorder

Authors: *A. DESTEFANO[1], M. OLKHOVETSKY[2], K. K. CHADMAN[3];
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Abstract: Autism Spectrum Disorder (ASD) is a neurodevelopmental disorder characterized by repetitive behaviors/restricted interests (RRBs) and deficits in social interactions. These impairments in ASD may be linked to an under-stimulation of the endocannabinoid system (ECS), a neuromodulatory system. Anandamide is one of the major endogenous endocannabinoids that acts on cannabinoid receptors (CBRs). URB597 is a fatty acid amide hydrolase inhibitor that blocks the breakdown of anandamide. The effects of URB597 on RRBs were examined in a mouse model of ASD. The BTBR T+Itpr3 tf/J (BTBR) inbred strain, an idiopathic mouse model of ASD, has been shown to display RRBs and deficits in social communication innately. The RRBs tested were marble burying, spontaneous grooming, and water T-maze reversal assays. The tests were conducted with both male and female BTBR mice and C57BL/6J mice. URB597 had sex-specific effects on RRBS. Repetitive marble burying and spontaneous grooming were reduced in BTBR female mice administered URB597. However, BTBR male mice were not affected by URB597 in these tasks. URB597 did not affect reversal learning in the BTBR mice in the water T-maze, suggesting that URB597 does not work on higher-order RRBs at the doses tested. These results suggest that the effects of URB597 may be specific to the sex of the mouse and the type of RRBs (i.e., lower-order or higher-order repetitive behaviors) tested.

Disclosures: A. DeStefano: None. **M. Olkhovetsky:** None. **K.K. Chadman:** None.

Poster

PSTR052: Mechanisms and Therapeutics in Animal Models for Autism

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR052.12/A28

Topic: A.07. Developmental Disorders

Support: NYS Office for People with Developmental Disabilities

Title: The effect of JZL-184 on social behavior in the BTBR mouse model of Autism Spectrum Disorder

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Abstract: There is currently no cure for Autism Spectrum Disorder (ASD), and treatment usually involves a combination of therapies that aim to improve social communication and reduce repetitive and restrictive behaviors (RRBs). The BTBR T^{+} *Itpr*$^{3\ tf/J}$ (BTBR) inbred strain is an idiopathic mouse model of ASD that displays RRBs and deficits in social communication. The endocannabinoid system (ECS) has been shown to play a role in the development and function of the brain, including the areas associated with ASD. Understimulation of the endocannabinoid (EC) signaling may underlie some of the symptoms of ASD. JZL-184 is an inhibitor of monoacylglycerol lipase (MAGL), the enzyme that hydrolyzes the endocannabinoid, 2-arachidonoyl glycerol (2-AG). Stimulating the ECS with JZL-184 may lead to improvements in the behaviors related to ASD. The effects of JZL-184 (0, 1.6, and 16 mg/kg) were tested on the social behavior and other behaviors related to ASD in the BTBR mice. The following behavioral tests were used: social approach, elevated plus maze, and accelerating rotarod. JZL-184 increased social behavior in the BTBR mice, but did not affect anxiety-like behavior or motor behavior.

Disclosures: K.K. Chadman: None. **N. Salce:** None.

Poster

PSTR052: Mechanisms and Therapeutics in Animal Models for Autism

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Topic: A.07. Developmental Disorders

Support: LSAMP Grant 1826696
NYS Office for People with Developmental Disabilities

Title: The effect of JZL-184 on repetitive behavior in the BTBR mouse model of Autism Spectrum Disorder

Authors: *M. E. OLKHOVETSKY[1], A. DESTEFANO[2], K. K. CHADMAN[3];
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Abstract: Autism Spectrum Disorder (ASD) is a neurodevelopmental disorder that is characterized by impairments to social communication and the presence of repetitive, restricted behaviors (RRB). The BTBR T+Itpr3 tf/J (BTBR) inbred strain, an idiopathic mouse model of ASD, has been shown to display RRBs and deficits in social communication innately. Understimulation of the endocannabinoid (EC) signaling may underlie some of the symptoms of ASD. JZL-184 is an inhibitor of monoacylglycerol lipase (MAGL), the enzyme that hydrolyzes

the endocannabinoid, 2-arachidonoyl glycerol (2-AG). JZL-184 is expected to increase the levels of 2-AG, potentially enhancing endocannabinoid stimulation. To determine the effects of increased endocannabinoid stimulation on repetitive behaviors, JZL-184 (0, 1.6, and 16 mg/kg) was administered to a mouse model of ASD prior to these behavioral tests: marble burying, spontaneous grooming, and water T-maze reversal learning. The reversal learning task specifically focuses on perseveration, the trait of ASD thought to underlie the rigid routines and behaviors in people with ASD. The BTBR strain was used as a mouse model of ASD with the C57BL/6J strain serving as the control. JZL-184 did not affect marble burying or spontaneous grooming and only had a mild effect on learning.

Disclosures: M.E. Olkhovetsky: None. **A. DeStefano:** None. **K.K. Chadman:** None.

Poster

PSTR052: Mechanisms and Therapeutics in Animal Models for Autism

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR052.14/A30

Topic: A.07. Developmental Disorders

Title: Optimization of cannabidiol-based medicine and developmental assessment in mice

Authors: *J. S. KAPLAN[1], **T. MCGILLIS**[1], J. MUCKERHEIDE[2], W. LELAND[2], J. VELIZ[2], S. PATTERSON[2], G. QUINN[2], J. DAEP[2], A. FISHER[2], N. SCHNEIDER[2], S. TAUXE[2], M. KOCH[2];
[1]WESTERN WASHINGTON Univ., BELLINGHAM, WA; [2]Western Washington Unviversity, Bellingham, WA

Abstract: Cannabidiol (CBD) is a non-intoxicating phytocannabinoid with rapidly escalating popularity for the treatment of numerous off-label conditions in children and adults including anxiety and autism spectrum disorder (ASD). However, these benefits are often difficult to achieve in many users. This challenge likely results from the wide range of CBD's pharmacodynamic targets that are differentially impacted with escalating doses; expanding the dose-efficacy range will improve CBD's medicinal utility. We've demonstrated that the addition of cannabis-inspired volatile organic compounds ("terpenes") leads to more pronounced prosocial effects and higher reliability in the BTBR mouse model of ASD. Therefore, we hypothesize that the addition of prominent cannabis terpenes can enhance CBD's therapeutic efficacy by expanding its dose-efficacy relationship, and elevations to GABAergic and anandamide signaling, which together, restore the brain's excitatory:inhibitory (E:I) balance, underlie these effects. To test this hypothesis, we made stimulated local field potential recordings from hippocampal slices which revealed that BTBR mice are deficient in GABAergic signaling compared to control C57BL/6J mice, and simulated seizure activity in a pro-epileptic solution indicated that BTBR mice have a more pronounced E:I imbalance. Further, MALDI-TOF mass spectrometry confirmed that BTBR mice are also deficient in anandamide signaling, which was restored by acute passive inhalation of vaporized CBD oil. These effects are associated with

reduced anxiety behavior on the elevated plus maze and improved social interaction in the 3-Chamber Test. We did not find that estrogen fluctuations across the estrus cycle, which often account for sex differences in phytocannabinoid effects, impacted anxiety or social behavior in C57BL/6J or BTBR mice. CBD exposure at different developmental stages may impact the decision if or when to recommend CBD-based treatments in children with ASD or other conditions. To address this concern, we tested the impact of CBD vapor exposure at three developmental stages: PND 7-21, PND 14-28, and PND 28-42. Vaporized CBD increased risk-taking behavior and impaired learning and memory on the Barnes Maze, particularly in the PND 14-28 exposure group. Together, we find that CBD's therapeutic effects may be optimized by examining molecular and physiological targets that correlate to behavioral outcomes, but our findings should be considered as cautionary for off-label CBD administration to children.

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Poster

PSTR052: Mechanisms and Therapeutics in Animal Models for Autism

Location: MCP Hall A

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Program #/Poster #: PSTR052.15/A31

Topic: A.07. Developmental Disorders

Title: Sulforaphane Treatment Effects on Autistic-like Behaviors in Male and Female BTBR Mice

Authors: *S. PAPALIA[1], E. CRAIG[1], S. RIEBESELL[2], M. POMPY[3], C. CULLIGAN[4], N. TOUMANIOS[5], R. FREEDMAN[6], N. KERNAN[3], L. A. GABEL[1], M. RIEBESELL[3]; [1]Neurosci., Lafayette Col., Easton, PA; [2]Neurosci., Lafayette Col., Manalapan, NJ; [3]Lafayette Col., Easton, PA; [4]Lafayette Col., Madison, NJ; [5]Neurosci., Lafayette Col., Yorktown Heights, NY; [6]Lafayette Col., Boston, MA

Abstract: Autism spectrum disorder (ASD) is a neurodevelopmental disorder characterized by impaired social interaction and restricted or repetitive behaviors. Its etiology is complex, involving an interplay between genetic and environmental factors. Oxidative stress, caused by reduced antioxidant capacity, the accumulation of reactive oxygen species, and mitochondrial dysfunction, is a significant factor in the development of ASD. BTBR T + Itpr3tf/J (BTBR) mice exhibit autistic-like behaviors, such as poor social interaction and repetitive behaviors. Sulforaphane (SFN), a chemical derived from cruciferous vegetables, has been shown to have neuroprotective effects based on its antioxidant and anti-inflammatory properties. In this study we examined the efficacy of SFN (50 mg/kg, oral self-administration) to ameliorate autistic-like behaviors in male and female BTBR mice. We controlled for estrous cycle stages in females due to potential hormonal influences on behavior. Our results indicate that male and female BTBR mice exhibit repetitive behavior, measured by marble burying, which was reduced with SFN

treatment. However, only male BTBR exhibited increased grooming compared to C67Bl6/J (BL6) mice, but SFN had no effect. Male and female BTBR mice exhibited hyperactive behavior compared to the BL6 controls across multiple tests; however SFN had no effect. Interestingly, neither male nor female BTBR mice exhibited an anxiety phenotype on the elevated plus maze, however male BTBR mice exhibited anxiety-like behavior on the open field test, vehicle females did not differ from controls. SFN treatment exacerbated the anxiety phenotype in male BTBR mice on the open field test. Lastly, neither male or female BTBR mice differed from BL6 mice on the social approach task when treated with the vehicle-control. However, SFN treatment increased social interaction in the three-chamber test for both the female and male BTBR mice, but not BL6 mice.Overall, SFN effectively reduced repetitive behaviors and increased sociability, but had no impact on hyperactivity, indicating the need for further research to understand its impact on ASD symptoms.

Disclosures: S. Papalia: None. **E. Craig:** None. **S. Riebesell:** None. **M. Pompy:** None. **C. Culligan:** None. **N. Toumanios:** None. **R. Freedman:** None. **N. Kernan:** None. **L.A. Gabel:** None. **M. Riebesell:** None.

Poster

PSTR052: Mechanisms and Therapeutics in Animal Models for Autism

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Program #/Poster #: PSTR052.16/A32

Topic: A.07. Developmental Disorders

Support: CONAHCYT 30242
CONAHCYT CF-2023-G-77

Title: Insights into gut-brain axis: Colonic mucosa-associated microbiota alterations in a rat model of autism

Authors: *E. LEYVA-FIGUEROA[1], N. CARAM-SALAS[1,4], C. E. GALINDO-SANCHEZ[2], C. VENTURA-LÓPEZ[3], M. A. MARTINEZ-MERCADO[5];
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Abstract: Autism spectrum disorder (ASD) is a neurodevelopmental condition characterized by social abnormalities and repetitive behaviors, often accompanied by both behavioral (e.g., anxiety and hyperactivity) and non-behavioral comorbidities, including gastrointestinal issues such as inflammation, leaky gut, and mucosal alterations. Previous research has emphasized the significant role of the intestinal microbiota in these comorbidities, mediated through the gut-brain axis. However, conventional studies primarily utilize fecal or luminal samples, which do not adequately reflect the complexity of intestinal microbiota, particularly communities with

direct interaction with the host, such as the mucosa-associated microbiota (MAM). This exploratory study investigates the colonic MAM alterations in the well-validated valproic acid (VPA) rat model of autism. This model was induced by administering VPA at 500 mg/kg to pregnant Wistar rats at 12.5 gestational days; subsequently, the pups were analyzed. Behavioral assessments of autism-related traits were conducted on both male and female juveniles (30-40 days postnatal), including open field, three-chamber social, marble burying, and Y-maze tests. The model presented significant behavioral alterations, including decreased social interaction, increased repetitive behavior, and elevated levels of anxiety and hyperactivity. Both mucosal and luminal microbiota were profiled using high-throughput sequencing of the V3-V4 region of the 16S rRNA gene. Notably, differences in diversity and composition between luminal and mucosal microbiota were observed, underscoring the importance of investigating specific communities within the intestinal microbiota. Specifically, the composition of colonic MAM in the VPA rat model showed increases in *Prevotellaceae UCG-001*, *Lachnospiraceae ASF356*, *Rothia sp.*, *Turicibacter sp*., and *Anaeroplasma sp*., along with a decrease in *Oscillospiraceae UCG-003* compared to controls. These findings provide compelling evidence of alterations related to dysbiosis in the previously unexplored colonic MAM within the VPA rat model for autism, highlighting the need for further exploration to elucidate the implications of these changes in gastrointestinal alterations and the gut-brain axis in ASD.

Disclosures: E. Leyva-Figueroa: None. **N. Caram-Salas:** None. **C.E. Galindo-Sanchez:** None. **C. Ventura-López:** None. **M.A. Martinez-Mercado:** None.

Poster

PSTR052: Mechanisms and Therapeutics in Animal Models for Autism

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR052.17/A33

Topic: A.07. Developmental Disorders

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The Robert & Janice McNair Foundation, McNair Medical Institute
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Gulf Coast Center for Precision Environmental Health NIH P30ES030285
John S. Dunn Collaborative Research Award FY2023

Title: Maternal microbiome-targeted probiotic intervention prevents developmental programming of autism-like social dysfunction in offspring in a mouse model for maternal obesity

Authors: *C. M. DI GESU[1], L. M. MATZ[1], R. FULTZ[2], I. BOLDING[1], S. A. BUFFINGTON[1,3];
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Abstract: Dysbiosis of the maternal gut microbiome during pregnancy increases risk for neurodevelopmental disorders in offspring. We previously showed that high-fat diet (HFD)-induced dysbiosis of the maternal gut microbiome during pregnancy drives autism-like social deficits in male and female offspring across two generations (F_1 and F_2). Post-weaning supplementation with the probiotic species *Limosilactobacillus reuteri* prevents F_1 and F_2 social dysfunction and remodels host microbial ecology, particularly among females. This previously unreported heightened sensitivity of the female gut microbiome to probiotic modulation led us to hypothesize that periconceptional targeting of the maternal gut microbiome could represent a novel approach to mitigating adverse effects of maternal obesity on offspring behavior. Hence, we developed a novel 7-strain probiotic cocktail (PC) dominated by immunomodulatory taxa and administered it antenatally to control and HFD-fed dams. Maternal PC treatment was sufficient to prevent social dysfunction in male and female offspring of HFD+PC dams. Importantly, neurotypical social behavior was maintained in offspring of control +PC dams. Metataxonomic sequencing of the maternal fecal microbiome showed a significant increase of beneficial taxa in HFD+PC *vs*. HFD dams. Interestingly, maternal PC drove enduring changes in the MHFD offspring microbiome, with a significant decrease in *Bacteroides*, the taxa most increased by maternal HFD compared to MRD controls. Together, these data suggest that PC-induced modulation of the maternal gut microbiome during early development prevents neuropathology underlying social dysfunction and produces long-lasting changes in offspring gut ecology. To identify the underlying mechanism, we performed unbiased metabolomics on serum and fecal samples of dams and offspring, as well as the offspring brain. We observed multiple differentially abundant metabolites, in particular bile acids, between HFD and HFD+PC dams, which correlated with changes in levels of neurotransmitters and other metabolites in the offspring brain. Collectively, these results suggest that targeting of the maternal gut microbiome may represent a new strategy to decrease risk for neurodevelopmental disorders associated with environmental disruption of maternal gut ecology, a key determinant of fetal neurodevelopment. Current investigation into the efficacy of maternal PC in genetic and idiopathic mouse models for ASD could identify key interactions between host and microbial genes.

Disclosures: C.M. Di Gesu: E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); C.M.D. is an inventor on a submitted patent describing use of a probiotic cocktail to reduce risk for neurodevelopmental disorders. **L.M. Matz:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); L.M.M. is an inventor on a submitted patent describing use of a probiotic cocktail to reduce risk for neurodevelopmental disorders. **R. Fultz:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); R.F. is an inventor on a submitted patent describing use of a probiotic cocktail to reduce risk for neurodevelopmental disorders. **I. Bolding:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); I.B. is an inventor on a submitted patent describing use of a probiotic cocktail to reduce risk for neurodevelopmental disorders. **S.A. Buffington:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); S.A. B. is an inventor on a submitted patent describing use of a probiotic cocktail to reduce risk for neurodevelopmental disorders..

Poster

PSTR052: Mechanisms and Therapeutics in Animal Models for Autism

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR052.18/A34

Topic: A.07. Developmental Disorders

Support: K99ES027869
R00ES027869
deArce-Koch Memorial Endowment Fund

Title: Developmental pyrethroid exposure in prairie voles causes an autism-related phenotype that is prevented by folate supplementation

Authors: N. SAFERIN[1], K. ZADE[2], R. E. MCCULLUMSMITH[2], F. S. HALL[3], *J. P. BURKETT[1];
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Abstract: Pesticide exposure has been linked to an increased risk of neurodevelopmental disorders (NDDs) such as autism spectrum disorder (ASD) and attention deficit hyperactivity disorder (ADHD), with evidence suggesting that early life exposure may be particularly harmful. Pregnant women exposed to pyrethroid pesticides are at a higher risk of their child being diagnosed with autism or other neurodevelopmental disorders. Our laboratory is investigating the effects of developmental pyrethroid exposure (DPE) to the pyrethroid pesticide deltamethrin on brain and behavior in prairie voles. In this study, we exposed female prairie voles to low doses of deltamethrin (3 mg/kg every third day), with or without supplementation with 5-MTHF, a folate vitamer, during pregnancy and lactation. We then tested the resulting adult offspring for behavioral changes relevant to NDDs and analyzed brain tissue to understand the molecular underpinnings of these effects. DPE caused changes in four behavioral domains relevant to NDDs, including communication, cognition, repetitive behavior, and locomotion (including circadian rhythms), several of which were rescued by maternal folate supplementation. In the brain, DPE impacted the expression of SHMT1, an enzyme in the folate pathway; while folate supplementation caused compensatory changes in two other folate-related proteins, FOLR1 and MTHFR. DPE also caused increases in serum and brain folate which were rescued by maternal folate supplementation. These results show the DPE causes an autism- and NDD-relevant behavioral phenotype which is rescued by folate supplementation, and that direct effects on folate metabolism may be a mechanism of these effects.

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Poster

PSTR052: Mechanisms and Therapeutics in Animal Models for Autism

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Program #/Poster #: PSTR052.19/A35

Topic: A.07. Developmental Disorders

Support: Conahcyt 1101287

Title: Effect of enriched environment on cerebellum and social behavior of valproic zebrafish

Authors: B. FLORES[1], F. D. CAYCHO SALAZAR[2], J. MANZO[3], M. HERNANDEZ[4], G. A. CORIA-AVILA[5], D. HERRERA-COVARRUBIAS[6], F. ROJAS-DURÁN[4], G. E. ARANDA-ABREU[7], C. A. PEREZ-ESTUDILLO[8], ***R. TOLEDO-CARDENAS**[6];
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Abstract: The etiology of autism spectrum disorder (ASD) has been linked to both genetic and epigenetic factors. Among the epigenetic factors, exposure to valproic acid (VPA), an antiepileptic and mood-modulating drug, has been shown to induce characteristic traits of ASD when exposed to during embryogenesis. Conversely, in animal models, enriched environment (EE) has demonstrated positive behavioral and neural effects, suggesting its potential as a complementary treatment to pharmacological approaches in central nervous system disorders. In this study, we utilized zebrafish to model ASD characteristics induced by VPA and hypothesized that sensory stimulation through EE could ameliorate the behavioral and neuroanatomical features associated with ASD. To test this hypothesis, we assessed social behavior, cerebellar volume, and Purkinje cell populations via histology and immunohistochemistry after exposing the fish to EE. The results revealed that zebrafish exposed to VPA exhibited social deficits, reduced cerebellar cortex volume, and a decrease in c-Fos-positive cells in the Purkinje layer. In contrast, VPA-exposed fish treated with EE showed increased socialization, augmented cerebellar cortex volume, and an elevation in c-Fos-positive Purkinje cells. These findings suggest that alterations induced by VPA may be ameliorated through EE treatment, highlighting the potential therapeutic impact of sensory stimulation in conditions related to ASD.

Disclosures: B. Flores: None. **F.D. Caycho salazar:** None. **J. Manzo:** None. **M. Hernandez:** None. **G.A. Coria-Avila:** None. **D. Herrera-Covarrubias:** None. **F. Rojas-Durán:** None. **G.E. Aranda-Abreu:** None. **C.A. Perez-Estudillo:** None. **R. Toledo-Cardenas:** None.

Poster

PSTR052: Mechanisms and Therapeutics in Animal Models for Autism

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Program #/Poster #: PSTR052.20/A36

Topic: A.07. Developmental Disorders

Support: Woodcock Institute Research Grant
Texas Woman's University internal funding mechanisms: Research Enhancement Program Awards, Chancellor's Research Fellowships, small grant and startup funds

Title: Early Social and Environmental Enrichment May Improve Behavioral Deficits in MeCP2 Mouse Model of ASD

Authors: *P. FRAYRE[1], S. VASQUEZ[2], E. NA[3];
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Abstract: Autism spectrum disorder (ASD) is a neurodevelopmental disorder that afflicts 1 in 36 children in the United States, according to the Centers for Disease Control and Prevention. It is characterized by repetitive and restricted behaviors, impaired communication, learning and memory deficits, and abnormal social behaviors. Despite considerable progress in understanding ASD, the efficacy of early intervention, such as social or environmental enrichment, is not completely understood. Previous studies have implicated a neuroepigenetic factor known as methyl-CpG binding protein 2 (MeCP2) in ASD etiology. In order to investigate the role that MeCP2 plays in ASD pathology, we utilized an MeCP2 knockout (KO) mouse model of ASD. In this study, both KO and wildtype (WT) mice were weaned into environmental enrichment (EE) or single housed (SH) conditions. The EE cages provided a stimulating environment with varied toys, textures, and running wheels for grouped housing. After 12 weeks of EE or SH exposure, anxiety-like behavior of WT and KO mice were evaluated with open field test (OFT), elevated plus maze (EPM), dark light test (DLT), and social interaction (SI). Results from EPM and DLT indicated a reduction in anxiety-like behaviors in EE KO mice compared to SH KO mice. Additionally, KO EE mice exhibited increased social interaction with a conspecific in SI. These findings suggest that early intervention in the form of social and environmental enrichment may improve behavioral deficits in MeCP2 KO mouse models of ASD.

Disclosures: P. Frayre: None. **S. Vasquez:** None. **E. Na:** None.

Poster

PSTR052: Mechanisms and Therapeutics in Animal Models for Autism

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR052.21/A37

Topic: A.07. Developmental Disorders

Title: Molecular and cellular phenotyping of an Emx1-Cre; Wac mouse model in cortical pyramidal neurons

Authors: *D. PACHECO CRUZ[1], A. M. STAFFORD[2], A. M. GILL[3], D. VOGT[4];
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Abstract: DeSanto-Shinawi Syndrome (DESSH) is a rare neurodevelopmental disorder caused by mutations in the WW-domain containing adaptor with coiled coil (*Wac*) gene. DESSH presents clinically with cognitive and behavioral symptoms that include seizures, autism, ADHD, and developmental delay. DESSH is a very rare disorder, and vertebrate models to understand the mechanisms underlying its pathology are lacking. Our lab has developed a clinically relevant mouse model for DESSH that is a constitutive heterozygous loss of function. This model exhibits susceptibility to seizures, relevant behavioral changes and sex-specific alterations in brain volume. Despite these changes we were not able to generate a constitutive knockout. Thus, to better understand the role of *Wac* in cortical development we have generated an *Emx1-Cre* conditional model to delete *Wac* in glutamatergic cortical neurons. *Emx1-Cre* conditional KOs can be produced and exhibit dramatic morphological phenotypes including agenesis of the corpus callosum, delamination of the hippocampus and microcephaly. Here, we will explore the molecular and cellular phenotypes during development that could underlie the mechanisms causing these morphologies. Our results will provide a better understanding of the roles of select neuronal populations in a mouse model of DESSH.

Disclosures: D. Pacheco Cruz: None. **A.M. Stafford:** None. **A.M. Gill:** None. **D. Vogt:** None.

Poster

PSTR053: Structural Plasticity: Neurons and Networks

Location: MCP Hall A

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Program #/Poster #: PSTR053.01/

Topic: B.05. Synaptic Plasticity

Support: Ministry of Education, Culture, Sports, Science and Technology (MEXT) Grant-in-Aid for Scientific Research, grant #: 21H02585
Ministry of Education, Culture, Sports, Science and Technology (MEXT) Grant-in-Aid for Transformative Research Areas (A), grant #: 2 3 H 0 4 9 4 4

Title: Memory of memory - Traces of memory explored from the dynamics of astrocytes during artificial hibernation

Authors: *T. YOSEYAMA[1], Y.-J. LIN[1], V. SAITO[1], H. ASHITOMI[1], D. MERCIER[1], T. HIGUCHI[2], B. KUHN[2], J. NAGAI[3], T. SAKURAI[4], K. Z. TANAKA[1];
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Kunigami-gun, Japan; [3]RIKEN Ctr. for Brain Sci., Saitama, Japan; [4]Fac. of Med., Univ. of Tsukuba, Tsukuba, Japan

Abstract: Synaptic plasticity, the ability of neurons to modify their connections, is considered one mechanism supporting the formation of memory traces in the brain. The phenomenon of hibernation weakens the fundamental view of synaptic plasticity being the unique basis of memory. Indeed, during hibernation, the length of dendritic spines shrinks, many synapses are lost, and the brain's activities decrease simultaneously with metabolism and body temperature. Despite the drastic changes in the brains, hibernating animals retain their memory after hibernation. This paradox hints at a memory storage mechanism outside of synapses. In this study, we hypothesize that astrocytes mediate memory retention through extreme plasticity during hibernation and that astrocyte leaflets and synapses work together to form memory traces. We assume astrocyte leaflets fill the spaces left by the shrinking or disappearance of synapses and reconstitute them after arousal. To investigate the role of astrocytes in memory retention throughout artificial hibernation, we examine their involvement and structural changes in mice. We used a hibernation-like state called Q-neuron-induced hypothermia and hypometabolism (QIH) to study hibernation in a laboratory setting (Takahashi et al., 2020). During QIH, we characterized astrocyte calcium activity dynamics and morphological changes using calcium imaging and electron microscopy (EM). Our preliminary results revealed elevated c-Fos expression in astrocytes and altered interactions of astrocytes with larger spines during QIH. Furthermore, attenuation of the Gq GPCR pathway using iβARK (Nagai et al., 2021) in astrocytes impaired memory retention during QIH. This study will elucidate an unexplored role of astrocytes in memory retention and reveal the broader entity of memory trace.

Disclosures: T. Yoseyama: None. **Y. Lin:** None. **V. Saito:** None. **H. Ashitomi:** None. **D. Mercier:** None. **T. Higuchi:** None. **B. Kuhn:** None. **J. Nagai:** None. **T. Sakurai:** None. **K.Z. Tanaka:** None.

Poster

PSTR053: Structural Plasticity: Neurons and Networks

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR053.02/A38

Topic: B.05. Synaptic Plasticity

Title: Anisomycin selectively inhibit the shifts of optimal orientations in the visual cortex of mouse.

Authors: *E. JAIN[1], R. LUSSIEZ[2], S. MOLOTCHNIKOFF[3];
[1]Univ. de Montreal, Montreal, QC, Canada; [2]Univ. of Montreal, Montreal, QC, Canada; [3]Univ. of montreal, Outremont, QC, Canada

Abstract: The phenomenon of neuronal orientation selectivity, which refers to the capacity to efficiently react to a preferred orientation, has been widely observed in visual cortex. This

selectivity serves as the underlying framework for cortical organization and the development of functional networks. While traditionally considered fixed in the mature brain, recent studies have explored plasticity in adult V1 by modifying orientation selectivity through visual adaptation which is achieved by presenting non-preferred orientation for several minutes. Orientation selectivity arises from the spatial clustering of synapses that have distinct preferences onto a dendritic branch. Our investigation was carried out through electrophysiological recordings which were done on CD-1 female mouse (9-11 weeks). The analysis was done on 85 cells recorded from 6 mice. Our research aims to ascertain whether antibiotics impact orientation selectivity by spine formation. Anisomycin, inhibits protein synthesis by interfering with peptidyl transferase activity in eukaryotic ribosomes. Our data has demonstrated a change in preferred selectivity of orientation following visual adaptation which induces a shift of preferred orientation. The detection of polyribosomes within the spines suggests that protein synthesis takes place directly within the postsynaptic compartment. Dendritic protein synthesis plays a role in stabilizing recently inserted glutamate receptors, thereby contributing to excitatory synaptic transmission in the spines. Application of Anisomycin can therefore impede the morphogenesis of dendritic spines and the associated receptors, consequently blocking neuronal communication. Our results demonstrate that the application of antibiotics prevented a shift in the preferred orientation after adaptation suggesting a hindrance to the formation of new spines. Moreover, the antibiotic also interfered with the association between orientation selectivity and the change in preferred orientation. This suggests that Anisomycin application disrupts the transmission of signals among neurons. Our results show that optimal orientation selectivity depends on spine cluster activity.

Disclosures: E. Jain: None. **R. Lussiez:** None. **S. Molotchnikoff:** None.

Poster

PSTR053: Structural Plasticity: Neurons and Networks

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Topic: B.05. Synaptic Plasticity

Support: NSFC/RGC/JRS (N_HKU735/21)
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HMRF (09200966)

Title: The role of protein arginine methyltransferase 8 in dendritic spine plasticity and excitatory/inhibitory balance during learning

Authors: *B. W. SO[1,3], X.-Q. HU[1], K.-Y. WONG[2,3], C. S. LAI[1];
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Abstract: Protein arginine methylation is a major post-translational modification in synaptic proteins. Among the arginine methyltransferase (PRMT) family, PRMT8 is the only member with brain-specific expression. *In vitro* studies have shown the localization of PRMT8 in dendritic spines of pyramidal neurons, and parvalbumin-positive interneurons. However, the role of PRMT8 in dendritic spine plasticity and excitatory/inhibitory balance is poorly understood *in vivo*. Potential therapeutic interventions in PRMT8-related neuropsychological diseases, such as autism, remain largely undiscovered. Here we found that $Prmt8^{KOF}$ mice exhibited a male-specific auditory-cued fear learning deficit. While the developmental dendritic spine plasticity across various cortical regions were normal in $Prmt8^{KOF}$ male, they displayed a significant deficit in fear learning-induced dendritic spine formation of layer 5 pyramidal neurons (PNs) in the auditory cortex. Besides, $Prmt8^{KOF}$ male showed a significantly higher percentage of *c-fos* positive parvalbumin interneurons (PVINs) 1 hour after fear learning. Further electrophysiological investigation revealed that $Prmt8^{KOF}$ had a significant reduction in membrane excitability of PVINs. Selective chemogenetic activation of PVINs in the auditory cortex restored the excitatory-inhibitory (E/I) balance, fear learning behaviour, and spine plasticity deficits of $Prmt8^{KOF}$ male. Collectively, our results suggest that PRMT8 plays critical roles in auditory fear learning, PVIN excitability, and PV plasticity.

Disclosures: B.W. So: None. **X. Hu:** None. **K. Wong:** None. **C.S. Lai:** None.

Poster

PSTR053: Structural Plasticity: Neurons and Networks

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Program #/Poster #: PSTR053.04/A40

Topic: B.05. Synaptic Plasticity

Support: 2R01MH116500-06A1

Title: Visual cortical circuits for generating visual experience-dependent oscillations

Authors: *X. CHENG[1], A. A. CHUBYKIN[2];
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Abstract: Sensory representation, learning, and memory in the visual cortex correlate with neural oscillations across the laminar cortical layers. These oscillations are generated by circuits comprising excitatory pyramidal cells (PCs) and inhibitory interneurons (INs). Typically, INs are grouped with neighboring PCs to create specific local recurrent microcircuits, which regulate or modulate neural information flow. We found that visual familiarity induced low-frequency oscillations in the primary visual cortex (V1). Elevations of L5 PC input on L4 fast-spiking interneurons in V1, detected in ex vivo circuit mapping after visual experience, may underlie the 4-8 Hz low-frequency oscillations induced by visual familiarity. The local recurrent circuit in V1 involving excitatory PCs and parvalbumin (PV) inhibitory INs plays a crucial role in visual experience-dependent oscillations. To investigate the visual familiarity-induced synaptic

plasticity in the local recurrent microcircuit between PV INs and PCs, we applied channelrhodopsin-2-assisted circuit mapping (CRACM) in acute brain slices to map the reciprocal connectivity between PV INs and PCs in mice naive or experienced with the perceptual familiarity paradigm. We found a decrease in average IPSCs after visual experience from PV+IN to PCs in L2/3 and an increase in L4, while no changes were detected in L5. The average EPSC inputs from L5 PCs to L5 and L4 PV INs increased, whereas there was no difference in L2/3 PV INs after the visual experience. Overall, perceptual experience elicited synaptic plasticity in the microcircuit that was layer-specific in V1 with distinct patterns in deep layers and superficial layers. Our studies provide direct measurements of the synaptic connectivity between PV INs and PCs in V1 before and after visual experience, revealing the mechanisms of the emergence of visual experience-dependent neural oscillations.

Disclosures: X. Cheng: None. **A.A. Chubykin:** None.

Poster

PSTR053: Structural Plasticity: Neurons and Networks

Location: MCP Hall A

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Program #/Poster #: PSTR053.05/A41

Topic: B.05. Synaptic Plasticity

Title: Distinct neural effects of psilocin, ketamine, and LSD compared to other psychedelics

Authors: *C. DUCHEMIN, L. PETER, **E. ANDRIAMBELOSON**, S. WAGNER; NEUROFIT, ILLKIRCH, France

Abstract: In recent years, there has been growing interest in the therapeutic potential of psychedelics for treating various mental health conditions, such as addiction, anxiety, depression, and PTSD. Despite promising clinical trial results, understanding the biological effects of psychedelics, particularly at low doses, remains challenging.
This study aimed to explore the morphological changes in rat primary cortical neurons induced by various psychedelics. We focused on assessing the number of primary neurites, total neurite length, branch points, and neurite critical value "r" – crucial indicators of neurite ramification and arborization.
We examined the effects of psilocin, low-dose ketamine (1 µM), LSD, DOI, MDMA, DMT, and 5-MeO-DMT, alongside comparative analysis with the neurotrophin, BDNF, and cognitive enhancer drug, donepezil.
Our findings revealed that psilocin, ketamine, and LSD do not significantly affect the number or length of primary neurites at either early (DIV3) or later (DIV5) stages. However, an increase in branch points and neurite critical value "r" was observed at the later stage (DIV5), indicating a need for prolonged exposure to unveil these effects.
In contrast, DOI, MDMA, DMT, and 5-MeO-DMT induced an increase in primary neurite number, total neurite length, and branch points at both DIV3 and DIV5. However, there was no significant impact on neurite critical value "r" at both timepoints. Donepezil exhibited a similar

profile of effects to this group of psychedelics.
Furthermore, BDNF stimulated all assessed parameters of neurite outgrowth, with a more pronounced increase observed at DIV5.
Our findings suggest that while psilocin, ketamine, and LSD may not extend neurite length significantly, they modulate neurite arborization, hinting at unconventional neural circuit rewiring. These insights deepen our understanding of psychedelics' neural effects, paving the way for novel therapeutic strategies.

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Poster

PSTR053: Structural Plasticity: Neurons and Networks

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Program #/Poster #: PSTR053.06/A42

Topic: B.05. Synaptic Plasticity

Support: SNSF Starting grant TMSGI3_211261

Title: Synapticplasticity in mice treated with single-dose psilocybin

Authors: *Z. LI, F. SELLITTI, R. BIELER, L. D. SIMMLER;
Univ. of Basel, Basel, Switzerland

Abstract: Psilocybin-induced antidepressant effects last for up to weeks after a single dose. Psilocybin is a classical psychedelic that acts via 5-HT2A receptor agonism, yet the neurobiological mechanisms that underlie its antidepressant effect are still unknown. To look for long-lasting forms of synaptic plasticity induced after a single dose of psilocybin, we injected mice intraperitoneally with psilocybin 1 mg/kg or saline and performed ex vivo whole-cell patch clamp recordings 24 h after treatment, with or without optogenetically identifying neuronal projections. We also screened for cortical areas acutely activated by psilocybin using c-Fos immunostaining of tissue which was fixed 90 min after injections of psilocybin or saline. Miniature excitatory postsynaptic currents recorded from prelimbic cells showed increased frequency in psilocybin-treated mice, compared to saline-treated mice, suggesting an increase of presynaptic input and corresponding to increased c-Fos expression, which we observed in the immunofluorescence group. With psilocybin treatment, we also found an increased ratio of AMPA vs. NMDA receptor currents in optogenetically defined synapses from the thalamus to the prelimbic cortex; further evidence for drug-induced plasticity in the prelimbic cortex. Ongoing research will reveal if our findings underlie the antidepressant actions of psilocybin.

Disclosures: Z. Li: None. **F. Sellitti:** None. **R. Bieler:** None. **L.D. Simmler:** None.

Poster

PSTR053: Structural Plasticity: Neurons and Networks

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Topic: B.05. Synaptic Plasticity

Support: NIH R01NS124592
NIH R01NS121084

Title: Non-synaptic propagating epileptiform activity can induce LTD-like plasticity in the hippocampal slices

Authors: *C.-C. CHIANG, L. ZUKOWSKI, D. M. DURAND;
Case Western Reserve Univ., Cleveland, OH

Abstract: Beyond the immediate manifestations of seizures, individuals with epilepsy commonly contend with a range of cognitive challenges, with memory impairment standing out as particularly prevalent. Research in both human intra-cortical studies and in-vivo rodent experiments consistently highlights a significant association between the prevalence of interictal epileptiform discharges (IEDs) and memory deficits. These IEDs predominantly occur in critical brain regions such as the cortex and hippocampus, propagating as waves throughout the brain. Moreover, our laboratory has demonstrated that IEDs can propagate without synaptic transmission in both in-vivo and in-vitro rodent hippocampi. Consequently, it is possible that an interplay between non-synaptic waves and synaptic function contributes to the cellular and physiological mechanisms of memory impairment in epilepsy patients. To investigate this hypothesis, we utilized an in-vitro mouse model to explore whether IEDs induce downregulation and depression of synapses within the hippocampus. By inducing non-synaptic propagating epileptiform activity using 4-Aminopyridine (4-AP), we assessed changes in excitatory evoked postsynaptic potentials (EPSPs) measured from the CA1 apical dendrite following single pulse stimulation at the Schaffer collaterals. The slope changes in EPSP were indicative of long-term depression or potentiation. Our findings reveal a significant correlation between 4-AP-induced IEDs and synaptic depression over time, with an average decrease of 82.31 ± 5.42% in EPSP slope post-IED generation. Furthermore, retrospective analysis suggests that lower spiking IED frequency is associated with more pronounced synaptic downregulation. This in-vitro investigation aims to directly evaluate the impact of non-synaptic IEDs on synaptic plasticity and propose a potential mechanism for memory impairment. This study can contribute to the currently underexplored area of research targeting IEDs as a potential therapy for memory dysfunction, a distressing condition frequently encountered in epilepsy.

Disclosures: C. Chiang: None. **L. Zukowski:** None. **D.M. Durand:** None.

Poster

PSTR053: Structural Plasticity: Neurons and Networks

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR053.08/A44

Topic: B.05. Synaptic Plasticity

Title: Hebbian Homeostatic Plasticity and Noise Lead to Drift in Learning of Synaptic Weights

Authors: *M. MILLER, C. MIEHL, B. DOIRON;
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Abstract: Synaptic changes underlying learning and memory are believed to be implemented by Hebbian plasticity based on pre- and postsynaptic activity. Many studies of neural circuit plasticity have shown that Hebbian plasticity on it's own is unstable, requiring negative feedback control mechanisms mediated by inhibitory interneurons and plasticity of their projecting synapses. These homeostatic mechanisms play a crucial role in stabilizing and shaping neuronal dynamics, and are ubiquitous throughout the brain. Further, these studies rarely incorporate noise into the system, which is also ubiquitous in the brain.
Here we investigate the dynamics, of a two population recurrent rate network with excitatory to excitatory (E) plasticity and inhibitory (I) to excitatory plasticity. By using timescale separation between weights and rates dynamics, we derive conditions of stability for the weight dynamics given our homeostatic Hebbian plasticity rules. This produces an upper bound on the plasticity threshold in both models. We show that the region of stability in the recurrent case can be constrained to a basin of attraction around a line attractor in the weight dynamics, which is fully parameterized by the initial conditions, recurrent E to I and I to I weights, and the stimulus parameter. Further, in the brain, these circuits are formed in the presence of noise. To probe how robust such attractors are when noise is present, we feed white Gaussian noise as an input to the firing rates. Surprisingly, we observe a positive drift of the weights until the circuit becomes unstable on a timescale of seconds. We analytically derive the drift term due to the input noise, which is proportional to the variance of the noise. Therefore, we identify the drift term following from noisy firing rates which Hebbian plasticity or homeostatic mechanisms need in order to keep weight dynamics stable in noisy systems.

Disclosures: M. Miller: None. **C. Miehl:** None. **B. Doiron:** None.

Poster

PSTR053: Structural Plasticity: Neurons and Networks

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR053.09/A45

Topic: B.05. Synaptic Plasticity

Support: R01 NS126816
R21 DA055166

Title: Comparing the effects of right and left vagus nerve stimulation on motor performance

Authors: *H. F. WELCH, M. RAJENDRAN, C. A. THORN;
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Abstract: Left vagus nerve stimulation (l-VNS) paired with motor rehabilitation is FDA-approved for aiding in stroke recovery. Improvements in motor function with VNS are thought to depend on increased neuroplasticity in the motor cortex facilitated by multiple neuromodulatory systems. Dopamine is recognized as a plasticity-promoting neuromodulator and its signaling plays a critical role in motor learning. Still, cortical dopamine is unnecessary for l-VNS induced plasticity. Right vagus nerve stimulation (r-VNS), however, activates midbrain dopaminergic nuclei, a mechanism not shared by l-VNS. Previous research indicates that this distinct mechanism of r-VNS can lead to behavioral differences, including the ability to sustain self-administration behavior and induce appetitive responses. We propose that, because of this differential engagement of dopaminergic circuitry, r-VNS may promote greater plasticity in the motor system or greater task engagement compared to l-VNS, or both. However, the efficacy of r-VNS to induce plasticity in the motor cortex has not been evaluated, nor is it known whether r-VNS impacts engagement in an overlearned motor task. To address these questions, female Long-Evans rats were trained on a VNS-paired skilled lever-pressing task. The task required the rats to fully depress and release a lever to receive a food pellet as a reward. After achieving stable performance, rats received a VNS cuff implanted around the left or right cervical vagus nerve. After surgical and behavioral recovery, rats underwent 5 final days of training-paired VNS treatment, in which VNS pulses were triggered immediately upon detection of a correct lever press. Sham treatment groups underwent the same procedures but did not receive stimulation in the final five days of training. Within 24 hours after the last training session, the motor cortex was mapped using intracortical microstimulation. Preliminary results from these experiments suggest that both l-VNS and r-VNS treatment enhanced the representation of task-relevant proximal forelimb musculature within the motor cortex. Unexpectedly, both l-VNS and r-VNS treatment decreased task engagement. These results suggest that, unlike in the prior self-administration studies, the mechanisms through which r-VNS and l-VNS promote cortical plasticity and affect motor task performance are likely similar. This research aims to elucidate the functional effects of the reward-related lateralization of the vagus nerve and how the therapeutic potential of VNS can be optimized.

Disclosures: H.F. Welch: None. **M. Rajendran:** None. **C.A. Thorn:** None.

Poster

PSTR053: Structural Plasticity: Neurons and Networks

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR053.10/A46

Topic: B.05. Synaptic Plasticity

Support: RGPIN/05255-2020

Title: Contribution of Astrocytes in the Remodeling of the Axon Initial Segment

Authors: *R. SANZ-GÁLVEZ[1,2], Y. INGLEBERT[1,2], D. VERDIER[1,2], A. KOLTA[1,2,3]; [1]Dept. of Neurosciences, Univ. de Montréal, Montréal, QC, Canada; [2]Ctr. Interdisciplinaire de Recherche sur le Cerveau et l'Apprentisage (CIRCA), Montréal, QC, Canada; [3]Dept. of Stomatology, Fac. of Dentistry, Univ. de Montréal, Montréal, QC, Canada

Abstract: It is increasingly acknowledged that astrocytes can control neuronal excitability and regulate synaptic plasticity in various areas of the brain. However, their contribution to axonal structural plasticity is only beginning to be explored. Findings in the last decade led to the acceptance of the axon initial segment (AIS) as a highly dynamic structure, which adapts to external perturbations. Structural changes in the AIS may occur on different time scales (from milliseconds to days) and have been associated with changes in intrinsic excitability as a compensatory mechanism to maintain the stability of neuronal activity. This structural remodeling of the AIS has been analyzed by comparing the AIS in large populations of neurons differently treated, both *in vivo* and *in vitro*. To address this spatiotemporal limitation, we monitored AIS remodeling at the single-cell level in layer 5 of the visual cortex, utilizing a new knock-in mouse line that express the green fluorescent protein (GFP) labeled with AnkyrinG (AnkG). AnkG is considered as the main scaffolding protein and the central organizer of the AIS. First, we established different stimulation protocols eliciting long lasting excitability changes in the recorded cells and obtained preliminary data showing how activation or blocking of astrocytes influence these forms of plasticity. Here, using the newly generated mouse line (from P. Jenkins lab) we compare, in real-time, the remodeling of the AIS in these different forms of plasticity (synaptic and non-synaptic) in *in vitro* slice preparations. Our preliminary findings (n=6) suggest that long-term potentiation of intrinsic excitability induces rapid elongation of AIS length (~4.15 μm length increase) within 30 minutes. Ulteriorly, we will reassess these changes to the AIS length after manipulation of the astrocytes and confirm these findings *in vivo* in an attempt at further elucidating the mechanisms responsible for this effect. This project provides a novel approach to neuron-glia communication in other forms of activity-dependent structural plasticity.

Disclosures: R. Sanz-Gálvez: None. **Y. Inglebert:** None. **D. Verdier:** None. **A. Kolta:** None.

Poster

PSTR053: Structural Plasticity: Neurons and Networks

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR053.11/A47

Topic: B.05. Synaptic Plasticity

Support: Midwestern University Intramural Funding

Title: Evaluation of Marine Natural Products for Neuritogenesis in Murine Primary Cortical Cultures

Authors: *M. L. PIERCE[1], S. SEO[2], Z. CIESIELSKI[2], J. ABURAS[1], J. DRAVES[2], M. ADAMSON[3], J. DICKSON[2], A. SHARMA[2], L. RODRIGUEZ[2], M. HAMANN[4], A. M. MAYER[1];
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Abstract: Marine organisms produce a wide variety of primary and secondary metabolites with unique scaffolds that are biologically active. Approximately 100 manzamine-type polycyclic alkaloids have been isolated from marine sponge species, with some compounds reported to have anti-inflammatory and neuritogenic properties. Additional compounds evaluated include sesquiterpines with a tetronic acid moiety from marine sponges. Initial neurite outgrowth screens identified seven of the 21 compounds evaluated as potentially neuritogenic, based on total neurite outgrowth and complexity. Neurite outgrowth assays at a single dose identified the following compounds for further analyses: manzamine A, 8-methoxymanzamine A, 12-propoxymanzamine A, 12-isobutoxymanzamine A, ATL 2-97, ircinin-1, and palinurin. To assess the neuritogenic potential, this study conducted neurite outgrowth assays to build dose-response curves for these compounds in murine primary cortical cultures. The neurite outgrowth analyses showed that iricinin-1 and palinurin induced neurite outgrowth in a statistically significant manner for logarithmic doses between 1 nanomolar and 10 micromolar and a statistically significant increase in neuronal complexity via number of processes and number of branches. Moreover, there were no indications of toxicity up to 10 micromolar. Analyses showed that 8-methoxymanzamine A induced neurite outgrowth in a statistically significant manner at the 1 micromolar dose and a statistically significant increase in neuronal complexity via number of processes and number of branches. However, at the 10 micromolar dose, 8-methoxymanzamine A appears to be somewhat toxic, showing a reduction neurite outgrowth at complexity as well as some nuclear blebbing indicative of apoptosis. In contrast, manzamine A did not show increased neurite outgrowth or complexity at any dose and appears potentially toxic at the 10 micromolar dose. Likewise, ATL 2-97, 12-propoxymanzamine A, and 12-isobutoxymanzamine A did not show increased neurite outgrowth or complexity at any dose and no indications of potential toxicity except 12-isobutoxymanzamine A at the 10 micromolar dose. Together, these data show that sesquiterpenes iricinin-1 and palinurin, and manzamine compound 8-methoxymanzamine A induced neurite outgrowth and complexity, with minimal toxicity noted up to 10 micromolar doses. Further studies will be performed to assess live and dead cells to determine compound toxicity as well as identifying factors contributing to neurite outgrowth. Together, these studies will help identify novel neuroactive compounds for the marine natural products preclinical pipeline.

Disclosures: M.L. Pierce: None. **S. Seo:** None. **Z. Ciesielski:** None. **J. Aburas:** None. **J. Draves:** None. **M. Adamson:** None. **J. Dickson:** None. **A. Sharma:** None. **L. Rodriguez:** None. **M. Hamann:** None. **A.M. Mayer:** None.

Poster

PSTR053: Structural Plasticity: Neurons and Networks

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR053.12/A48

Topic: B.05. Synaptic Plasticity

Title: Dominance of Basal Dendritic Innervation in Cortical Neurons

Authors: *N. MEDINA[1], A. M. SOROKINA[2], N. B. KASTHURI[2];
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Abstract: Cortical neurons have apical and basal dendrites that are thought to receive, in some systems, different types of information - basal dendrites receive inputs that define functional properties like receptive fields, whereas apical dendrites receive contextual information. However, the principles governing their connectivity remain unclear. Using the open-source MiCRONS dataset, the most comprehensive reconstruction of cortex to date, we asked a simple question: how often does an excitatory synapse in cortex occur on a basal dendrite vs. apical? Here, we find a striking dominance of basal dendritic innervation, 70-80% of synapses are on basal dendrites, across most cortical layers, with innervation of Layer 1 unsurprisingly dominated by apical innervation. Another notable exception occurred between layers 4 and 5, where basal innervation falls to ~50%. Such biases were not easily explained by differences in the total length of basal and apical dendrites and correlated with soma density across cortical layers. This pattern extends to individual cortical axon segments, where bias towards basal innervation matches random sampling of synapses. Finally, we are performing similar analyses in developing brains, where apical dendrites are formed earlier than basal, and we predict that apical-basal balance shifts from apical dominance to basal dominance as a product of development. Our results suggest that target availability, and not strict specificity alone, shapes cortical wiring, extending our understanding of how neurons establish and refine their connections.

Disclosures: N. Medina: None. **A.M. Sorokina:** None. **N.B. Kasthuri:** None.

Poster

PSTR053: Structural Plasticity: Neurons and Networks

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR053.13/A49

Topic: B.05. Synaptic Plasticity

Support: NIMH (R01MH077303)
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Title: Molecular mechanism of Contactin 2 homophilic interaction

Authors: *S. FAN[1,2], J. LIU[3], N. CHOFFLET[4,5], A. O. BAILEY[6], W. RUSSELL[6], Z. ZHANG[4], H. TAKAHASHI[4,7,8], G. REN[3], G. RUDENKO[1,2];
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Abstract: Contactin 2 (CNTN2, also known as TAG-1) is a cell adhesion molecule that belongs to the contactin family consisting of six members (Contactin-1 to Contactin-6) and the immunoglobulin superfamily. The ectodomains of CNTN1-CNTN6 consist of six Ig domains (Ig1-Ig6) followed by four fibronectin (FN) domains which are attached to the neuronal membrane through a glycosylphosphatidylinositol (GPI)-anchor. CNTN2 is involved in axon guidance, neuronal migration, fasciculation and neuron-glia interaction via homophilic and heterophilic interactions. However, the molecular mechanisms by which CNTN2 forms homophilic and heterophilic interactions are not well understood. Here, we reveal the molecular mechanism by which CNTN2 assembles into homodimers. CNTN2 forms transient homophilic interactions (K_D ~200 nM) that are highly protein concentration dependent. Cryo-EM structures of full-length CNTN2 and CNTN2 Ig1-Ig6 reveal a T-shaped homodimer formed by intertwined, parallel monomers. Unexpectedly, the horseshoe-shaped Ig1-Ig4 headpieces extend their Ig2-Ig3 tips outwards on either side of the homodimer, while Ig4, Ig5, Ig6 and the FN domains form a central stalk. Cross-linking mass spectrometry confirms the 3D assembly of the CNTN2 homodimer. Site-directed mutagenesis further confirms the critical role of Ig3, Ig4, Ig5 and Ig6 in mediating homophilic interaction of CNTN2 in cell-based assays. Strikingly, the interface mediating homodimer formation differs between the CNTNs, both in terms of amino acid sequence conservation as well as N-linked glycosylation. Likewise, the domains mediating homophilic versus heterophilic interaction in CNTNs are different. Together, our results suggest that the CNTN family encodes a versatile molecular platform that supports a very diverse portfolio of protein interactions which can be leveraged to strategically guide neural circuit development.

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Poster

PSTR053: Structural Plasticity: Neurons and Networks

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR053.14/A50

Topic: B.05. Synaptic Plasticity

Support: NSF GRFP (LD)
NIH R15 (KK)

Title: Comprehensive adult female mouse atlas of cortical perineuronal net expression changes with maternal experience

Authors: *L. DUNN, K. KRISHNAN;
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Abstract: Perineuronal nets (PNNs) are specialized extracellular matrix structures which primarily ensheath parvalbumin-expressing GABAergic interneurons. They are considered restrictive to neuronal circuit plasticity in the adult cortex yet are amenable to physiologically relevant experience-dependent plasticity mechanisms. Many neurodevelopmental and degenerative disorders show changes in PNN expression with disorder pathology and symptom progression. Additionally, adult PNN distribution changes with age, and ethologically relevant behaviors. However, our understanding of the regulation of PNN expression is limited by the lack of highly quantitative maps of high- and low-expressing PNNs across the cortical subregions. Here, we present a comprehensive atlas of PNN distribution for 17 cortical regions across the six-day maternal behavioral paradigm. In addition to 12-week-old adult female wildtype (WT), we also analyzed PNN distribution in age-matched *Mecp2*-heterozygous female mice (Het), which show inefficient pup retrieval. Pup retrieval is an ethologically relevant behavior in female mice emphasizing the use of audition, olfaction, and tactile sensory cues for efficient retrieval of scattered pups to the nest. Using serial sectioning and immunofluorescent staining of PNNs via Wisteria Floribunda agglutinin, we quantified PNN expression before, during, and after behavioral performance. Compared to the naïve controls, WT displayed decreased PNN levels in multiple somatosensory subregions after two days of experience. After six days of trials, PNNs were increased in these same subregions, in addition to increases in the temporal association and primary motor cortices. In Het, we observed bidirectional and region-specific changes in PNNs, which were not consistent with the WT patterns. As Het serve as the female mouse model for Rett syndrome, a severe neuropsychiatric disorder with sensory, motor, social and cognitive behavioral deficits, the observed changes in PNN expression in this behavioral paradigm and time course suggests abnormal plasticity in many cortical regions, albeit in a nuanced manner. In concordance with our previous work, both WT and Het brains also show lateralized expression in specific cortical regions, suggesting hemisphere-specific functional specialization in just those subregions. Together, this atlas will be a resource for understanding and manipulating PNN expression across cortical regions.

Disclosures: L. Dunn: None. **K. Krishnan:** None.

Poster

PSTR053: Structural Plasticity: Neurons and Networks

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR053.15/A51

Topic: B.05. Synaptic Plasticity

Support: NIMH 1P50MH094271

Title: Vasoactive Intestinal Peptide (VIP) Regulation of Extended Critical Period Plasticity

Authors: J. LEFF[1], S. B. HANNAN[2], H. H. C. LEE[3], R. K. REH[4], N. J. KOPELL[5], M. M. MCCARTHY[5], *T. K. HENSCH[1,6,7,8];
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Abstract: Gamma (γ) oscillations are bouts of synchronized neuronal activity at 30-80 Hz that coordinate spike firing and, notably, neuroplasticity, especially during critical periods of brain development. Exactly how γ rhythms control plasticity remains largely unknown. Parvalbumin (PV)-expressing neurons are well-established generators of these rhythms, which are integrated into sub-networks of other interneuron types like somatostatin (SOM) and vasoactive intestinal peptide (VIP)-expressing cells whose roles are much less clear. Computational modeling suggests that VIP cell activity is robustly engaged by 40 Hz activity. Notably, γ frequencies are conducive to peptide release, which motivated us to investigate the impact of VIP secretion in the regulation of adult neuroplasticity. Here, we identify a novel role of VIP peptide in the degradation of perineuronal nets (PNNs), which typically enwrap PV neurons at critical period closure to limit adult plasticity. Acute intracranial injection of a VIP receptor antagonist into primary visual cortex (V1) enhanced PNN dendritic coverage within hours in wildtype (C57Bl/6J) mice. PNN integrity was also restored by the same antagonists in mice bearing persistent γ-oscillations and extended critical period plasticity into adulthood due to targeted deletion of a major $GABA_A$ receptor subunit (α1) specifically in PV cells (PVα1 KO). Conversely, direct optogenetic stimulation of VIP interneurons (at 40 Hz but not 2 Hz) rapidly diminished PNN coverage of PV cells in VIPCre;Ai32 mice. Finally, 3 hours of direct γ rhythm generation by light in PVCre;Ai32 mice was sufficient to reopen critical period plasticity in adulthood. As a potential mechanism regulating PNN integrity, we examined IBA1+ microglia, resident immune cells that may degrade PNNs. Blocking VIP receptors rapidly reduced microglial levels in C57Bl/6J and PVα1 KO mice, consistent with these cells playing an important role in VIP mediated PNN regulation. Suppressing microglial function also eliminated the extended critical period plasticity arising from elevated PV cell excitability in PVα1 KO

mice. Overall, these results demonstrate hitherto unknown roles for the VIP peptide in PNN regulation and adult plasticity in response to γ oscillations. These findings carry profound neurobiological and clinical implications for the utility of VIP peptide as a therapeutic target, regulating neuroplasticity in disorders when it is disrupted or depleted during the course of adulthood. They further offer a potential mechanism by which 40 Hz sensory-stimulation may contribute to beneficial microglia and other effects even in the absence of native γ rhythm entrainment.

Disclosures: J. Leff: None. **S.B. Hannan:** None. **H.H.C. Lee:** None. **R.K. Reh:** None. **N.J. Kopell:** None. **M.M. McCarthy:** None. **T.K. Hensch:** None.

Poster

PSTR053: Structural Plasticity: Neurons and Networks

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR053.16/A52

Topic: B.05. Synaptic Plasticity

Support: R35 NIH grant NS111573

Title: Linking Impaired Sharp-Wave Ripples and Reduced Neuroplasticity in IMAA Mice

Authors: S. SINGH[1], M. FAIRBAIRN[1], I. PEDRONI AMORIM[3], C. L. REMMERS[4], T. GAMAL EL-DIN[4], C. S. CHEAH[4], J. OAKLEY[4], W. A. CATTERALL[4], *R. RODRIGUES PERIM[2,4];
[1]Col. of Osteo. Med., [2]Physiol. and Pharmacol., Marian Univ., Indianapolis, IN; [3]Solvay, Campinas, Brazil; [4]Pharmacol., Univ. of Washington, Seattle, WA

Abstract: The hippocampus plays a fundamental role in the consolidation of memories. In this process, sharp-wave ripples—high-frequency hippocampal oscillations frequently observed during consummatory behaviors—are pivotal in elucidating the role of hippocampal activity in memory and neuroplasticity. This study investigates the patterns and frequency of sharp-wave ripples in IM-AA mice, a model with known neuroplasticity deficits, linking electrophysiological changes to cognitive impairments. CaV2.1 channels are pivotal for spatial memory and long-term potentiation. IM-AA mice, which have a mutation in the IQ-like motif, fail to elicit long-term potentiation due to altered interactions between CaV2.1 channels and CaS proteins. We examined bilateral hippocampal local field potentials in IM-AA mice aged 90 to 120 days, verifying electrode placement with Cresyl Violet staining and 3D imaging. Using Python, we processed these local field potentials during periods when the mice were inactive but awake or sleeping, extracting sharp-wave events and their associated ripples. We analyzed their occurrence and morphology, comparing them between wild-type and IM-AA heterozygous mice. Although the total number of sharp-wave ripple events did not differ significantly, a marked reduction in ripple frequency was noted in IM-AA mice. This finding suggests a potential explanation for their diminished ability to elicit long-term potentiation as previously reported.

Our data reveal a distinct decrease in sharp-wave ripple frequency in IM-AA mice, indicating a possible mechanistic link to their reduced neuroplasticity. These findings highlight the importance of precise electrophysiological assessments for understanding functional cognitive deficits and inform potential therapeutic strategies to address memory impairments in similar neurological conditions.

Disclosures: S. Singh: None. **M. Fairbairn:** None. **I. Pedroni Amorim:** None. **C.L. Remmers:** None. **T. Gamal El-Din:** None. **C.S. Cheah:** None. **J. Oakley:** None. **W.A. Catterall:** None. **R. Rodrigues Perim:** None.

Poster

PSTR053: Structural Plasticity: Neurons and Networks

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR053.17/A53

Topic: B.08. Epilepsy

Support: NIH NS088358

Title: The Effect of Neuron-to-Neuron Forces on Neuronal Activity

Authors: *L. DALIR[1], Y. BERDICHEVSKY[2];
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Abstract: Neurons in the brain experience mechanical forces due to interactions with neighboring cells and the extracellular matrix. Mechanical force balance is disrupted by traumatic brain injury, stroke, and brain tumors, as well as other brain insults. These insults are associated with an increased risk of developing seizures. We have previously shown that attractive mechanical forces are present in 3D aggregate cultures of rat cortical neurons and neurons derived from human induced pluripotent stem cells. These forces are dominated by neuron-to-neuron attraction, resulting in tissue contraction and heightened neuronal activity. An imbalance in cell attraction forces in brain tissue after injury may result in tissue contraction and hyperexcitability, contributing to epileptogenesis. In this work, we used organotypic hippocampal cultures (OHCs) to determine the role of cell-generated mechanical forces in epileptogenesis. First, we embedded OHCs in Matrigel-containing beads and confirmed the presence of mechanical force imbalance at slice edges by measuring tissue contraction and bead displacement. Then, we increased the force imbalance experienced by a selected sub-region of the slice by culturing slices on a substrate printed with patterns of the cell-substrate adhesion molecule poly-D-lysine (PDL). The contraction was accelerated in slice sub-regions cultured over PDL-free regions. Non-seizure and seizure neuronal activity was measured by imaging changes in jRGECO1 (genetically encoded calcium indicator) fluorescence. Distinct effects on neuronal activity were observed in different hippocampal sub-regions. We observed a decrease in seizure activity when contraction occurred along the apical-basal axis in CA3, while both seizure and non-seizure activity increased as the tissue contracted transverse to the apical-basal

axis in CA3. Activity was less affected when enhanced contraction occurred in the subiculum in the transverse direction to the apical-basal axis. Overall, our results suggest that cell-generated mechanical forces in OHCs can affect seizure and non-seizure activity. The effect on neuronal activity is region- and mechanical force vector-specific. The results provide the first evidence that cell-generated mechanical forces may play a role in epileptogenesis.

Disclosures: L. Dalir: None. **Y. Berdichevsky:** None.

Poster

PSTR054: Epilepsy Models: Network Effects, Cellular Mechanisms, and Post-Seizure Modifications

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR054.01/A54

Topic: I.05. Biomarker, Drug Discovery, and Experimental Therapeutics

Title: Impact of Caloric Restriction on Wnt/B-Catenin Pathway in the Hippocampus and Cortex of Kindled Rat Model

Authors: *A. LOPEZ[1], S. VIDAL[2], L. MARIN-CASTAÑEDA[2], N. SERRANO[2], G. GONZALEZ-GARIBAY[2], S. OROZCO-SUAREZ, ej[3], C. MARTÍNEZ ZAMORA[2], H. M. ROMO-PARRA[4], M. RUBIO OSORNIO[2], C. R. OSORNIO[2];
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Abstract: Epilepsy is a prevalent neurological disorder, and despite numerous treatment options, approximately 30% of patients have refractory epilepsy. This situation prompts the exploration of alternative treatments such as caloric restriction (CR), whose mechanisms of antiepileptic action remain to be fully elucidated. One of the key pathways overactivated in epilepsy is the Wnt/β-catenin pathway. To explore the potential regulatory effects of caloric restriction on this pathway, we conducted a study using male Wistar rats divided into four groups: Control, Sham (20% CR), kindling ad libitum (KAL), and kindling with CR (KCR). The hippocampus and frontal cortex were analyzed for protein levels (Wnt, β-catenin, GSK3β, and cyclin D) using immunofluorescence and Western Blot techniques. Electroencephalographically and behaviorally, the KCR group exhibited a shorter duration of seizures and an increased behavioral threshold ($p<0.05$) compared to the KAL group. Protein analysis revealed a significant increase in Wnt pathway proteins (Wnt, β-catenin, and cyclin D) and a significant decrease in GSK3-β ($p<0.01$) in the KAL group compared to the others. Notably, the CR group showed a decrease in these proteins ($p<0.03$) and an increase in GSK3-β inhibitory complex-forming proteins ($p<0.01$). These findings suggest that CR may exert its antiepileptic effects through the regulation of the Wnt pathway by inhibiting its activity in the hippocampus and cortex of kindled rats.

Disclosures: A. Lopez: None. **S. Vidal:** None. **L. Marin-Castañeda:** None. **N. Serrano:** None. **G. Gonzalez-Garibay:** None. **S. Orozco-Suarez:** None. **C. Martínez Zamora:** None. **H.M. Romo-Parra:** None. **M. Rubio Osornio:** None. **C.R. Osornio:** None.

Poster

PSTR054: Epilepsy Models: Network Effects, Cellular Mechanisms, and Post-Seizure Modifications

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR054.02/A55

Topic: B.08. Epilepsy

Support: MEG resource facility, funded by the Department of Biotechnology, Ministry of Science & Technology, Govt. of India [BT/MED/122/SP24580/2018]
IOE, University of Delhi

Title: Unraveling the Crosstalk:CK2 and Wnt signalling Implications in Mesial Temporal Lobe Epilepsy

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Abstract: Abstract: **Background:** Mesial Temporal Lobe Epilepsy (MTLE) is the most common form of Drug Resistant Epilepsy and is conceptualized as the result of an imbalance between excitation and inhibition. NMDARs mediate excitatory synaptic transmission and appear to be substrates of Casein Kinase2(CK2). Wnt/β–Catenin signalling have been reported to regulate synaptic transmission via NMDARs. CK2 and Wnt/β–Catenin signaling is involved in seizure-induced neurogenesis, neuroinflammation, and hyperexcitability. CK2 appears to be a multisite regulator of Wnt signaling, and with the preliminary data from our lab, it will be worth investigating its role in MTLE. This study focuses precisely on understanding the role of regulation of Wnt signalling by Casein Kinase 2(CK2) in MTLE.
Methods: Male Sprague Dawley rat, weighing 200-250 grams were used for the study. Pilocarpine induced TLE chronic model was developed and H&E staining was performed to confirm the pathophysiological changes. mRNA expressions of CK2, NR2B, NR2A and Wnt/ β-Catenin downstream target genes (NEUROD1, FN1, LEF-1, BDNF) were evaluated by quantitative real -time PCR. Protein expressions of CK2α/α', CK2β, NR2B, NR2A, pNR2B, Dvl 2, β-Catenin and LEF-1 were studied by western blotting and Immunohistochemistry. Colocalization was studied using Immunofluorescence. Golgi cox staining was used to study the associated morphological changes in the TLE and Control model.

Result: Neuronal loss was observed in CA1 and CA3 region of Chronic TLE model. Increased protein expression of CK2α', CK2β, NR2A, NR2B, and Wnt/β-Catenin signalling molecules were observed in Hippocampus and ATL region of Chronic TLE model. Immunohistochemistry further confirmed increased protein expression. Significant increase of CK2 and Wnt targeted genes were observed at mRNA level in Chronic TLE model. CK2 and β-Catenin colocalization, was studied in the hippocampus, validating the crosstalk between the two. Alterations in the length of apical and basal dendrites were observed in the chronic model of TLE
Conclusion: Understanding the contribution of CK2 mediated Wnt/β-Catenin signalling in hyperexcitability and pathophysiology of MTLE will not only provide mechanistic insights on the underlying mechanism of epileptogenesis but also may aid in the development of novel anti-epileptogenic treatment for MTLE.

Disclosures: P. Priya: None. **A. Srivastava:** None. **N. Yadav:** None. **S. Anand:** None. **R. Mittal:** None. **J. Banerjee:** None. **A.B. Dixit:** None.

Poster

PSTR054: Epilepsy Models: Network Effects, Cellular Mechanisms, and Post-Seizure Modifications

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR054.03/A56

Topic: B.08. Epilepsy

Support: German research foudation (DFG) Grant no.: LU 2606/1-1

Title: Biomarkers for the ictogenesis of absence seizures - The role of cortical 5-9 Hz oscillations

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Abstract: Spike and wave discharges (SWD) are the electrophysiological hallmark of absence epilepsy seen in multiple forms of genetic generalized epilepsy. In validated genetic rat models a local seizure focus has been identified in the deep somatosensory cortex (S1). From this focal region SWD activity is generalized and sustained through cortico-thalamic and cortico-cortical pathways. Interestingly, inhibition of the centromedian thalamic nucleus (CM) resulted in a selective suppression of the spike component while rhythmic cortical 5-9 Hz oscillations remained present. Such oscillations are often seen to precede SWD activity and might prime the network towards rhythmic seizure activity. However, cortical 5-9 Hz oscillations are also seen in seizure free periods during passive wakefulness. This study aims to characterize pre- and interictal 5-9 Hz oscillations, to investigate if these oscillations induce changes in excitability and coupling with afferent brain structures prior to SWD onset, which might function as a biomarker for SWD generation, and to assess if interictal 5-9 Hz oscillations are high risk moments for SWD generation. Local field potential recordings were obtained in S1, CM and the

secondary motor cortex of freely behaving absence epileptic rats. Time frequency analysis was used to assess spectral power and non-linear association analysis was used to determine coupling strength and directionality between brain areas during pre-ictal and interictal 5-9 Hz oscillations. Timed phase specific single pulse electrical evoked potentials were used to compare cortical excitability. Double-pulse stimulation was used to assess the risk for epileptic afterdischarges. Changes in spectral power and coupling strength were revealed between pre-ictal and interictal 5-9 Hz oscillations. Surprisingly, both coupling strength and spectral power were higher for the interictal- as compared to the pre-ictal 5-9 Hz oscillations. However, coupling strength of the preictal oscillations was higher compared to periods of passive wakefulness. Moreover, double pulse stimulation during interictal 5-9 Hz oscillations was more likely to induce epileptic afterdischarges compared to stimulation during passive wakefulness. No overall differences in cortical excitability were revealed.The results demonstrate that spectral- and coupling profile of cortical 5-9 Hz oscillations can be employed as biomarkers for SWD generation, paving the way for seizure prediction. However, interictal 5-9 Hz oscillations represent high risk moments for seizure generation indicating that there is an optimum intermediate level of synchronization favoring SWD generation.

Disclosures: A. Lüttjohann: None. **E. Nikalexi:** None.

Poster

PSTR054: Epilepsy Models: Network Effects, Cellular Mechanisms, and Post-Seizure Modifications

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR054.04/A57

Topic: B.08. Epilepsy

Support: BrightFocus Foundation

Title: Comparison between normal and pathological neural activity in a mouse model of epilepsy

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Abstract: Epilepsy is a widespread brain disease impacting all age groups and affects nearly 50 million people according to the World Health Organization. Consequently, significant experimental and theoretical research attempts to find the mechanisms underlying the abnormal (and transient) brain electrical activity caused by epilepsy to facilitate the development of therapeutic solutions. In particular, temporal lobe epilepsy (TLE), the most common form of focal epilepsy in adults, is characterized by seizures and behavioral comorbidities (e.g., impaired memory). With no appropriate treatments for seizures and memory loss in TLE, understanding epileptogenesis is essential for therapeutic development. In TLE, seizure-genic circuits are located in the brain regions that support memory formation such as the hippocampus. It is in fact

known that hippocampal CA1 activities are abnormal in epilepsy, yet limited studies have compared CA1 dynamics between normal and pathological neural activity in the same animal. Here, we used a silicon probe to record brain electrical activity in a kainate injection-induced mouse model of acute TLE to analyze hippocampal oscillations before and after seizures in the same animal. We found that 30 mg/kg kainate injection was sufficient to induce behavioral seizures in all animals. Importantly, we demonstrated that in kainate-injected mice, delta (0.5 - 4 Hz) and theta (4 - 8 Hz) powers were significantly reduced while the power of slow (30 - 50 Hz) and fast (50 - 100 Hz) gamma bands was significantly elevated. These findings reveal the importance of analyzing the appropriate network connectivity to investigate epileptiform activity in TLE, which further helps understanding epileptogenesis.

Disclosures: H. Kim: None. **R. Lee:** None. **S. Lee:** None. **S. Kim:** None.

Poster

PSTR054: Epilepsy Models: Network Effects, Cellular Mechanisms, and Post-Seizure Modifications

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Program #/Poster #: PSTR054.05/A58

Topic: B.08. Epilepsy

Support: NIH Grant R01NS107453
NIH Grant R01NS092705
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Title: Sex-related differences in microRNA regulation of the brain: implications for hormonal regulation of seizure susceptibility

Authors: M. RICE[1], H. HEUERMAN[1], D. TIWARI[2], V. RAJATHI[1], A. WELLS[1], J. LEENELLETT[1], L. HUFFMAN[1], J. RYMER[1], A. MCGANN[3], A. BUNK[4], E. PARKINS[5], K. E. SMITH[1], D. RITTER[3], C. DOERNING[6], X. ZHANG[5], S. C. DANZER[7], A. JEGGA[1], ***C. GROSS**[1];
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Abstract: Many brain disorders affect men and women differently. The underlying mechanisms are complex and not fully understood but include influences of sex hormones like estrogens and progesterone on neuronal function. Cyclic fluctuations of estrogens and progesterone in women, for example, alter seizure susceptibility and underly catamenial epilepsy, an often-intractable form of epilepsy in women that is characterized by changes in seizure burden across the

menstrual cycle. Epigenetic mechanisms, such as microRNA-induced silencing, can have profound effects on neuronal function, and are frequently dysregulated in brain disorders; however, their role in sex-related differences in brain function and epilepsy are unclear. Our previous results showed that the activity of specific epilepsy-related microRNAs is correlated with peripheral 17β-estradiol and progesterone levels in female mice, which may alter how they regulate seizure susceptibility. Here, we show that microRNA-induced silencing activity differs between adult male and female mice under baseline conditions, as evident by significantly altered brain region-specific protein composition of the microRNA-induced silencing complex. Using small RNA-Sequencing and mRNA-Sequencing, we show that the subset of active microRNAs and mRNAs associated with the microRNA-induced silencing complex in excitatory hippocampal neurons is differentially regulated in male and female mice. Several microRNAs that show sex-related differences are also altered in male mice after seizure, suggesting that they are involved in regulation of seizure susceptibility. In summary, our results suggest a role of epigenetic regulation of gene expression in altered brain excitability in females and hint towards novel treatment strategies for catamenial epilepsy.

Disclosures: M. Rice: None. **H. Heuerman:** None. **D. Tiwari:** None. **V. Rajathi:** None. **A. Wells:** None. **J. Leenellett:** None. **L. Huffman:** None. **J. Rymer:** None. **A. McGann:** None. **A. Bunk:** None. **E. Parkins:** None. **K.E. Smith:** None. **D. Ritter:** None. **C. Doerning:** None. **X. Zhang:** None. **S.C. Danzer:** None. **A. Jegga:** None. **C. Gross:** Other; US patent 9,932,585 B2.

Poster

PSTR054: Epilepsy Models: Network Effects, Cellular Mechanisms, and Post-Seizure Modifications

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR054.06/A59

Topic: B.08. Epilepsy

Support: R01-NS-062806
Ro1-NS-065020

Title: Impact of Raptor and Rictor Deletion on Hippocampal Dentate Granule Cell Pathology Following Status Epilepticus

Authors: *S. YASER[1], C. M. GODALE[2], A. DRAKE[3], D. TAPP[4], K. KRAUS[5,9], N. MAYER[6], M. DUSING[10], C. L. LASARGE[9,7], S. C. DANZER[11,8];
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Undergraduate Res. Program, [7]Neurosci. Grad. Program, [8]Dept. of Anesthesiol. and Med. Sci. Training Program, Univ. of Cincinnati, Cincinnati, OH; [9]Dept. of Anesthesia, [11]Dept Anesthesia, [10]Cincinnati Children's Hosp. Med. Ctr., Cincinnati, OH

Abstract: Increased mechanistic target of rapamycin (mTOR) signaling is implicated in the development of acquired epilepsy. mTOR functions via mTORC1 and mTORC2 complexes. mTORC1 assembly requires Raptor (rapamycin-sensitive companion of mTOR) while mTORC2 signaling requires Rictor (rapamycin-insensitive companion of mTOR). To determine the roles of mTORC1 and mTORC2 in hippocampal dentate granule cell (DGC) restructuring in epilepsy, either Raptor or Rictor was deleted from a subset of DGCs after pilocarpine status epilepticus (SE). Male and female Raptor$^{fl/fl}$, tdTomato reporter (tdT+/-), Rictor$^{fl/fl}$, tdT+/-, and tdT+/- (WT) mice were treated with either pilocarpine (SE) or saline (no SE). One to two weeks later, all mice received hippocampal injections of a cocktail of AAV9.CamKII.eGFP and AAV9.CamKII.Cre vectors to produce GFP+ WT and tdT+ knockout (KO) DGCs in the same animals. After two months, brains were collected for neuroanatomical analyses of DGC soma area, spine density, mossy fiber (MF) axon structure, and synaptic connectivity. DGC soma area (two-way RM ANOVA with cell genotype and treatment [SE vs no SE] as factors; main effect of genotype, Raptor, $p< 0.001$; Rictor, $p=0.044$) and spine density (main effect of genotype, Raptor, $p = 0.010$; Rictor, $p = 0.007$) were significantly reduced in Raptor and Rictor KO cells relative to WT cells. Reduced granule cell mossy fiber bouton (MFB) volume was observed in Raptor KO cells relative to WT cells (main effect of genotype, $p=0.006$). Znt3 immunostaining revealed increased MF sprouting in pilocarpine-treated mice relative to controls (two-way ANOVA; main effect of treatment, $p< 0.001$). MF sprouting was reduced among Raptor KO cells (one-way ANOVA, $p=0.018$) but not Rictor KO cells ($p = 1$) relative to WT. Findings reveal cell-intrinsic effects of Raptor and Rictor deletion on reducing DGC soma area and spine density. In addition, Raptor deletion, but not Rictor deletion, reduced MFB presynaptic terminal area and MF sprouting. Reduced spine density predicts reduced perforant pathway excitatory input while reduced MFB volume predicts weakened DGC output to CA3. Taken together, findings indicate that both mTORC1 and mTORC2 can act in ways likely to impact granule cell excitability, with the two pathways effecting some overlapping and some distinct morphological readouts. Future studies will examine regulation of inhibitory synapse density by Raptor and Rictor.

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Poster

PSTR054: Epilepsy Models: Network Effects, Cellular Mechanisms, and Post-Seizure Modifications

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR054.07/A60

Topic: B.08. Epilepsy

Support: NIH R01NS112538
NIH P01NS127769-01A1
NIH 5R35NS116852

Title: Voltage imaging derived functional network connectivity, at the single neuron level, evolves during ictogenesis

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Abstract: Seizures arise not only from abnormal activity at the single neuron level, but also from abnormal propagation of activity through brain networks. Our understanding of how brain networks change during seizure onset has been hampered by an inability to record activity at a seizure focus with sufficient resolution and sensitivity. With recent advancements in voltage imaging, it is now feasible to record simultaneously from hundreds of neurons, with high temporal resolution and sensitivity to subthreshold voltage deflections. Here, we use such recordings to quantify changes in functional connectivity of neuronal networks during ictogenesis. We imaged neuronal activity in an ex vivo model of post-traumatic epileptogenesis: the organotypic hippocampal slice culture. Slices were prepared from P7 mice that were transduced with a soma-targeted version of the genetically encoded voltage indicator Varnam2. We then used a novel imaging system constructed inside of a tissue culture incubator, to image slices during spontaneous recurrent seizures (which emerge after ~7 days in vitro). Slices were imaged for 4 minutes to capture states of post-ictal depression, interictal spiking, seizure onset, and frank seizure, with cellular resolution and a field of view spanning the entire epileptic network. Using frame rates of 200Hz, and SUPPORT-based denoising, we simultaneously imaged voltage in >800 neurons. Spike trains for each cell were then used to compute a spike-triggered average post-synaptic network response, with subthreshold sensitivity to both excitatory and inhibitory synaptic activity. Spike-triggered averages were used to create excitatory and inhibitory graphs of network connectivity during different states of epileptiform activity. We found that inhibitory edge density, which represents functional inhibitory synaptic connections, rapidly decreased in the minutes leading up to seizure onset. At the same time, excitatory edge density, which represents functional glutamatergic synaptic connections, increased. The network statistics of clustering coefficient, mean path length, betweenness centrality, and small-world index all evolved toward values consistent with the emergence of a small-world network as seizure onset approached. In this preliminary work, we have identified in sequential seizures, spatially organized, consistent regions of failed inhibition, which we hypothesize drive the observed changes in excitatory network structure. In ongoing analysis and experiments, we are using this framework to gain a better understanding of how inhibition shapes network connectivity and how that can lead to seizure onset in the epileptic brain.

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Poster

PSTR054: Epilepsy Models: Network Effects, Cellular Mechanisms, and Post-Seizure Modifications

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR054.08/A61

Topic: B.08. Epilepsy

Title: Propagation of Interictal Spikes in a Bilateral Epilepsy Network in Mice

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Abstract: Objective: Focal neocortical epilepsy is increasingly recognized as a network disorder wherein epileptiform activity can propagate non-contiguously through the brain via highly interconnected nodes. We created a multi-node epileptic network by injecting bicuculline into S1, which projects monosynaptically to ipsilateral (i)M2 and contralateral (c)S1, and then also recruits cM2. We explored network propagation after blockade of individual nodes. **Methods**: We employed simultaneous Thy-1 and PV-cell mesoscopic calcium imaging to record the initiation and propagation of bicuculline-induced IISs following injections into S1 and M2. We then investigated the impact of knocking out iM2 with Tetrodotoxin (TTx) on IIS propagation. **Results**: IISs originating in iS1 reverberate throughout the network, with the most robust response observed in iM2. In contrast, M2-originating IISs primarily propagate to cM2 and rarely extend to iS1. When iM2 was inhibited with TTx, IISs originating in iS1 no longer propagate to other nodes. **Significance**: Our data demonstrate that blockade of a critical downstream node can impact the propagation of epileptiform discharges through an extended multimodal network.

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Poster

PSTR054: Epilepsy Models: Network Effects, Cellular Mechanisms, and Post-Seizure Modifications

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR054.09/A62

Topic: B.08. Epilepsy

Support: Grant: 964712

Title: Dynamic changes in intracerebral miRNA levels in relation to seizure activity in a rat model of temporal lobe epilepsy

Authors: *E. PEREZ MORRISSEY[1], M. SOUKUPOVA[2], S. ZAHEER[3], A. GUARINO[2], I. WOODS[4], D. C. HENSHALL[5], M. SIMONATO[6], J. H. PREHN[7];
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Abstract: Temporal lobe epilepsy (TLE) is the prevalent form of focal epilepsy in adults. In a previous effort conducted across several European laboratories, the expression levels of microRNAs was analysed across various epilepsy animal models. Three miRNAs, miR127-3p, miR146a-5p, and miR181b-5p - showed consistent alterations in expression levels across 3 models, indicating their potential role as prognostic biomarkers. We here determined the microRNA levels in cerebrospinal fluid (CSF) and plasma in a rat model of TLE, and correlated changes in miRNAs with the occurrence of seizures. **Methods**: TLE was experimentally induced in rats (n=14) by the injection of pilocarpine. Control rats (n=8) received vehicle. CSF and plasma were collected at 5 timepoints during the chronic phase, and EEG activity was continuously recorded to detect seizures and increased inter-ictal activity. The RNA was extracted from the samples and analysed using TaqMan-qPCR. Custom TaqMan primers were designed to measure the expression of the microRNA. Both a *C. elegans* miR39-3p spike-in and an internal control, let-7c-5p, were used to normalise data. Statistical analysis was performed using two-way ANOVA. **Results**: In the TLE model, there was a notable progressive increase in miR146a-5p levels in the CSF samples over time compared to controls. CSF levels of the other two microRNAs were not statistically different from the control group. Plasma levels of miR146a-5p and miR181b-5p exhibited a slight but statistically significant elevation in expression in the TLE model compared to controls. In individual rats, the levels of the microRNAs in the cerebrospinal fluid (CSF) were higher one hour after the seizure occurred. Further studies will determine the correlation of inter-ictal activity with miRNA expression levels. **Conclusion:** Our study suggests miR146a-5p to be promising biomarkers and potential therapeutic target in epilepsy.

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Poster

PSTR054: Epilepsy Models: Network Effects, Cellular Mechanisms, and Post-Seizure Modifications

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Topic: B.08. Epilepsy

Support: 2020-2.1.1-ED-2022-00208
2020-2.1.1-ED-2021-00190

Title: Investigating network level cell activity coupled with interictal epileptiform discharges using 3D acousto-optical microscopy

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Abstract: Epileptic status, characterized by spontaneousseizures, affects approximately 1% of the human population. Although numerousantiepileptic drugs have been approved in recent decades, in about a third ofthe cases, drug treatment does not lead to remission. In such situations,surgical intervention is offered as the only solution that can improve livingconditions, which, however - due to its invasiveness - is impossible in many cases with the toolsused in current clinical practice, and - due to incorrect identification ofepileptic foci - is often also ineffective. All of this raises the need for a method thatenables a more precise and less invasive intervention.According to the idea that has developed inrecent years, interictal epileptiform discharges (IEDs) appearing in theepileptic tissue during the periods between seizures reactivate the elements ofthe epileptic network (sub-networks). Due to this, it may be possible that bymapping the behavior of neurons related to IEDs, the core of the epilepticnetwork can be identified and the cells playing a key role in forming theactivation pattern can be determined. For this purpose, we performed a long-term survey of interneuronal activityin 18 Bl/6 mice that underwent successful epilepsy induction by neocorticalkainate injection. Neurons were measured both in the IED-generator core regionand around it, in the penumbra. Cell activity was detected with a 3Dacousto-optical 2-photon microscope (Femtonics Ltd) in parallel with continuouselectrophysiological recordings, while the head-fixed animals were allowed tomove freely on a rotating disc in a dark environment.After analyzing the data of more than 1,600 (91±38/animal) interneurons, wedetermined that the cells show a characteristic recruitment pattern dependingon the area and layer, based on which they can be classified into separateclusters (3-7 clusters/animal).Wealso found that eliminating a low number of cells with focused laser beam,targeting them based on the cluster structure they form, can perturb theepileptic network, modify, and - in some cases - permanently decrease the IEDsrate.

Disclosures: T. Lorincz: None. **B. Kocsis:** None. **B. Rozsa:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Femtonics Ltd.

Poster

PSTR054: Epilepsy Models: Network Effects, Cellular Mechanisms, and Post-Seizure Modifications

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Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR054.11/A64

Topic: B.08. Epilepsy

Support: NSERC; Project #RT690332

Title: Unraveling Cannabidiol's Antiepileptic Potential: A Microelectrode Array-Based Approach

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Abstract: Epilepsy is a chronic neurological disorder that affects approximately 50 million people worldwide, and with no cure, patients are left with few options and a compromised quality of life. Anti-epileptic drugs (AEDs) are the first treatment option, but have side-effects of their own, and fail approximately 30% of patients. Thus, it is imperative that we characterize better AED combinations for safer and more effective long-term treatments. Cannabidiol (CBD) is one drug of interest and has recently been approved for adjuvant epilepsy treatment, although its exact mechanisms in preventing seizures are unknown. Additionally, little is understood about how it affects long-term network activity in the presence and absence of seizures. Fortunately, microelectrode arrays enable long-term, non-invasive recordings of neuronal activity, and provide the potential for a drug screening platform to monitor the long-term impact of different AEDs. We used this approach to assess the role of CBD in both preventing and arresting ongoing seizure-like activity in primary rat hippocampal neuron cultures. Cells were pre-treated with CBD, followed by perfusion with a low Magnesium salt solution (Low-Mg^{2+}) to induce epileptiform activity, before recovering in control media. The long-term effect of CBD and Low-Mg^{2+} on network activity was characterized over several days. In sperate experiments, baseline activity was monitored for 5min, followed by Low-Mg^{2+} induction for 10min. This was immediately followed by CBD perfusion and activity monitoring for 15min before recovering in control media. We observed that CBD both prevented and arrested ongoing seizure-like activity via unique changes in activity patterns. This included a return to baseline spike rate, and a decrease in burst duration as compared to the epileptiform induction period. Spike clustering also returned to baseline values, alongside burst frequency. Moreover, we observed a decrease in the number of spikes per burst as compared to seizure activity. To validate the impact on both treatments on neuronal health, we conducted a viability assay and found that CBD prevented neuronal death following the induction of epileptiform activity. Finally, we verified our findings in defined hippocampal networks using young adult rat brain slices and short-term recordings. To our knowledge, this work provides the first long-term characterization of the effects of low-Mg^{2+} and CBD on neuronal network activity and development in dissociated hippocampal neurons. This opens the door for further comparisons with other AED combinations to identify their interactions and effectiveness in preserving network integrity.

Disclosures: F. Iqbal: None. **M. Yacoub:** None. **Z. Khan:** None. **C. Jazieh:** None. **N. Al Shaer:** None. **L. Wei:** None. **S. Alsuwaileh:** None. **K. Yusuf:** None. **N.I. Syed:** None.

Poster

PSTR054: Epilepsy Models: Network Effects, Cellular Mechanisms, and Post-Seizure Modifications

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR054.12/A65

Topic: B.08. Epilepsy

Support: University of Michigan Research Scouts Award
CURE Epilepsy Taking Flight Award

Title: Quantification of cholinergic cell number in the pedunculopontine nucleus and medial septum of an Scn1a$^{+/-}$ mouse model of Dravet Syndrome

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Abstract: Epilepsy is a common neurological disorder characterized by recurrent seizures. Patients with epilepsy also frequently suffer from quality of life-limiting comorbidities including depression, anxiety, sleep disturbances, and inattention. The mechanistic link between seizures - which are paroxysmal and typically brief periods of uncontrolled electrical activity in the brain - and the development of chronic comorbidities - which persist on a much longer timescale - is not well understood. Converging evidence has associated epilepsy with dysregulation in arousal-promoting neuromodulatory networks, including cholinergic circuits known to be crucial for mood, attention, and sleep regulation. We hypothesize that seizures reduce cholinergic expression within and neurotransmission from cholinergic nuclei including the pedunculopontine nucleus (PPN) in the brainstem and the medial septum (MS) in the basal forebrain. We are testing this hypothesis in the well-validated preclinical *Scn1a*$^{+/-}$ mouse model of Dravet Syndrome, a developmental and epileptic encephalopathy. Mice were subjected to three heat-induced seizures at postnatal day (P)19, P21, and P23. We then quantified cholinergic cell density in the caudal PPN and the MS with gold-standard stereology and additionally measured single-cell features such as cell size. Our findings revealed that *Scn1a*$^{+/-}$ mice have a significant ~20% reduction in cholinergic cell numbers within the PPN and a preliminary similar finding in the MS relative to wild-type littermate controls (which also were exposed to hyperthermia but did not have behavioral seizures). To ascertain whether this reduction is attributable to the induced seizures, we are additionally testing a parallel cohort of mice that were not subjected to hyperthermia. Additional future directions of the project will be to elucidate the mechanism and the circuit- and behavioral-level consequences of these findings, with the ultimate goal of identifying a novel therapeutic strategy for comorbidities in epilepsy.

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Poster

PSTR054: Epilepsy Models: Network Effects, Cellular Mechanisms, and Post-Seizure Modifications

Location: MCP Hall A

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Topic: B.08. Epilepsy

Support: NIH NINDS R01 NS110869
R25 NS065745
Louis H Castor, M.D., Undergraduate Research Grant from Penn CURF
Frances Velay Fellowship from Penn CURF

Title: Dysregulation of inhibitory-serotoninergic pathways in the dorsal raphe-prefrontal cortex circuit in an animal model of Dravet syndrome

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Abstract: Dravet Syndrome (DS) is a neurodevelopmental syndrome that includes treatment-resistant epilepsy and features of autism spectrum disorder, caused by mutations in *SCN1A* gene encoding the Nav1.1 sodium channel subunit. Recently, the serotonin (5HT) boosting agent fenfluramine demonstrated anti-seizure effects in clinical trials, implicating the serotonergic system as a potential therapeutic target. Despite this, the exact role of serotonin in DS circuitry, and the mechanism whereby fenfluramine can impact DS-associated cognitive and behavioral deficits, remains to be elucidated. Here, we examine the role of serotonin in the bidirectional projection between dorsal raphe nucleus (DRN) and the medial prefrontal cortex (mPFC). Immunostaining analysis in the DRN of Dravet syndrome (*Scn1a+/-*) mice and wild-type littermate controls reveals medial expression of 5HT and lateral expression of parvalbumin (PV) interneurons, with a subset of PV and 5HT co-expressing cells located at the medial-lateral junction. Electrophysiological recordings from the DRN demonstrate distinct passive and active electrophysiological properties in 5HT and PV neurons. *Scn1a+/-* mice exhibit profound impairment in PV firing, with no effect on 5HT firing. Future tests aim to elucidate if loss of Nav1.1 modulates endogenous serotonin release and the mechanism of fenfluramine effects on behavioral comorbidities of DS assessed via behavioral, learning and memory, and sociability testing.

Disclosures: C. Wang: None. **E. Rosenberg:** None. **E. Frimpong:** None. **E.M. Goldberg:** None.

Poster

PSTR054: Epilepsy Models: Network Effects, Cellular Mechanisms, and Post-Seizure Modifications

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR054.14/A67

Topic: B.08. Epilepsy

Support: NIH Grant NS088358
NSF Grant NCS ECCS 1835278

Title: Localized network hyperconnectivity leads to hyperexcitability after injury

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Abstract: Brain injury increases the risk of epilepsy. Axonal sprouting and synaptogenesis are homeostatically mediated responses by neurons to injury-induced deafferentation and deefferentation. Rewiring that occurs due to axonal sprouting and synaptogenesis may alter network excitability and lead to epilepsy. However, seizures themselves may induce axon sprouting and synaptogenesis. Establishment of a causal relationship between re-wiring and epilepsy is not straightforward due to lack of experimental methods to manipulate circuit rewiring. In this work, development of organotypic hippocampal co-cultures with controllable wiring at microcircuit level is reported. Organotypic hippocampal cultures develop extensive axon sprouting and excessive functional connectivity within and between sub-regions. This is accompanied by appearance of spontaneous electrographic seizures. In this work, organotypic cultures of hippocampus, hippocampus+cortex, hippocampus lacking subiculum, and hippocampus lacking CA3c-DG were used. In these cultures, increased morphological connectivity was found in a 100 - 200 µm region near the lesion site. This was correlated with an increase in functional connectivity, and increase in excitatory and inhibitory synaptic responses. Seizure initiation in these cultures shifted significantly toward the hyperconnected region. Then, 'healed' cultures were created were organotypic hippocampal cultures lacking CA3c-DG were placed into close contact with the missing sub-region. This resulted in fusion of the two culture fragments. 'Healed' cultures exhibited strong functional connectivity between fused culture fragments. There was a lack of an increase in morphological and functional connectivity in the region near the lesion site. Seizure initiation in 'healed' cultures no longer occurred in the perilesional region. Lesioned and 'healed' cultures experienced the same injury, controlling for effects of other epileptogenic mechanisms, and isolating effects of re-wiring. These findings suggest that axon sprouting and increase in functional caused the shift in seizure initiation. The small size of the affected region, containing < 1000 neurons, suggests that microcircuit-level changes may be sufficient to alter epileptogenesis.

Disclosures: Y. Berdichevsky: None. **L. Dalir:** None. **S. Ghiasvand:** None.

Poster

PSTR054: Epilepsy Models: Network Effects, Cellular Mechanisms, and Post-Seizure Modifications

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR054.15/A68

Topic: B.08. Epilepsy

Support: CIHR Canada Graduate Scholarship - Master's Program

Title: A loss of intrinsic biophysical diversity and changes in excitability of deep subiculum pyramidal neurons accompanies seizure activity

Authors: *M. FALBY[1,2], H. MORADI CHAMEH[3], M. MOVAHED[3], K. IRELAND[5], B. BAZRGAR[6], D. ZHANG[7], T. THILLAINADARAJAH[8], S. TRIPATHY[9,10], L. ZHANG[4], T. A. VALIANTE[3,2,11,12,13];
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Abstract: Hypothesis/Research Question: Intrinsic biophysical diversity within neuronal populations is important to the physiological functioning of the brain. In its absence, pathological synchronizations and decreased resilience of network activity may emerge. We hypothesized that epileptogenic neuronal networks experience a loss of intrinsic biophysical diversity, rendering them vulnerable to volatility and excessive synchrony that characterizes seizures.
Materials and Methods: Using the kainic acid mouse model of epilepsy, we investigated the diversity of intrinsic biophysical properties of deep subiculum pyramidal neurons, an essential participant in the propagation of seizure activity.
Results: By comparing whole-cell patch clamp recordings between epileptogenic and non-epileptogenic conditions, we observed a significant loss of variability in the spike threshold property of subiculum neurons that coincided with seizure activity. Alongside this epilepsy-related change, we also found a dynamic shift in excitability phenotype, wherein deep subiculum pyramidal neurons from the epileptogenic condition demonstrated a trend toward higher sag voltage amplitude values potentially driven by increases in Ih-current.
Conclusion: Taken together, these results provide a compelling narrative behind how a loss of threshold diversity in the subiculum may play a role in seizure dynamics.

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Poster

PSTR054: Epilepsy Models: Network Effects, Cellular Mechanisms, and Post-Seizure Modifications

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR054.16/A69

Topic: B.08. Epilepsy

Title: Deciphering the Path to Seizure Activity The Loss of Intrinsic Biophysical Diversity in Human Cortical Slice Cultured Neurons and Mouse Model of Temporal Lobe Epilepsy

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Abstract: Background: Epilepsy, a complex neurological disorder marked by synchronized electrical activity in the brain, has remained an intricate puzzle despite a decade of research. The challenge is heightened by the fact that approximately 30% of patients do not respond to anti-epileptic medications affecting on E/I balance, emphasizing the necessity to explore epilepsy beyond the conventional excitatory/inhibitory (E/I) balance paradigm. In the context of this ongoing challenge, we hypothesis that the occurrence and spread of seizures may be accompanied by the loss of intrinsic biophysical diversity. To elucidate this, we suggest that placing cortical neurons in an environment characterized by highly synchronized input, resembling the conditions in epilepsy, can induce a homogenizing effect over time through intrinsic plasticity. **Methods:** To test our hypothesis, the kainic acid model of epilepsy and human cortical slice culture were used to investigate the diversity of intrinsic biophysical properties among cortical neurons. **Results:** Preliminary findings reveal a significant reduction in intrinsic biophysical diversity among neuronal cells in both KA and slice culture conditions models. The study delves into the role of intrinsic plasticity mechanisms as potential contributors to this observed decrease in cellular diversity. **Conclusion:** Our research sheds light on how shared environments, whether induced through synchronized activity or within slice culture conditions, lead to a decrease in intrinsic biophysical diversity **Keywords:** Intrinsic Plasticity, Epileptic Activity, Slice Culture, Neural Diversity.

Disclosures: H. Moradi Chameh: None. **M. Falby:** None. **M. Movahed:** None. **B. Bazrgar:** None. **D. Zhang:** None. **K. Ireland:** None. **T. Thillainadarajah:** None. **T.A. Valiante:** None.

Poster

PSTR054: Epilepsy Models: Network Effects, Cellular Mechanisms, and Post-Seizure Modifications

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR054.17/A70

Topic: B.08. Epilepsy

Support: NIH NS050229

Title: Tau phosphorylation changes in human and rat model epilepsy surveyed with mass spectrometry

Authors: O. O. ESTES[1], N. A. EKSTROM[1], F. A. CONCEPCION[2], M. N. KHAN[1], A. L. KO[1], B. L. GRANNAN[3], N. L. MAHER[1], ***N. P. POOLOS**[1];
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Abstract: Tau is an intracellular protein known to undergo increased phosphorylation (hyperphosphorylation) and subsequent neurotoxic aggregation in Alzheimer's Disease (AD). It is unclear whether tau undergoes similar changes in animal model or human epilepsy. We used the pilocarpine rat model of temporal lobe epilepsy (TLE) to study changes in tau phosphorylation in the hippocampus 4 months post-status epilepticus, and in hippocampal and neocortical tissue resected from patients undergoing surgery for refractory epilepsy. Previously (Concepcion et al., 2023) we found that at tau loci recognized by the AT8 antibody and known to be hyperphosphorylated in AD, there was a 45% reduction in phosphorylation in hippocampus where seizures arise. There was no change in AT8 levels in the somatosensory cortex, outside of the seizure onset zone. These findings suggest that tau in the epileptogenic hippocampus is not hyperphosphorylated at the canonical AD AT8 loci but instead is dephosphorylated. However, tau has many phosphosites, not all associated with AD pathogenesis. We surveyed tau phosphosites using mass spectrometry. We were able to detect phosphorylation at 43 tau phosphosites in rat hippocampus. Significant changes in phosphorylation state in chronic epilepsy compared to age-matched naïve animals were identified at T58 (32% increase), T167 (13% decrease), S189 (28% decrease), T203 (22% decrease) and S253 (39% decrease). We also identified 32 tau methylation sites but found no significant changes in methylation state in epilepsy. These data show that specific tau phosphosites are dysregulated in an animal model of chronic epilepsy, with 4 of the 5 sites showing dephosphorylation, not hyperphosphorylation as seen in AD. We then used mass spectrometry to analyze epileptogenic brain tissue resected from patients with refractory epilepsy, and compared levels of tau phosphorylation to data from our animal model. We were able to detect 39 tau phosphosites in human brain, with 30 orthologous to rat tau. Comparing to those phosphosites undergoing phosphorylation change in our animal model of TLE, we found similar levels of tau phosphorylation in human tissue, including: S198 (9.0% in human and 9.9% at rat S189), T212 (3.2% human and 6.7% at rat T203), and S262 (10.2% and 10.2% S253). (Note T167 has no human ortholog.) These data indicate that tau phosphorylation is highly conserved in rat and human brain, and that sites significantly

dysregulated in rat epilepsy are phosphorylated at similar levels in human epilepsy. Further study is needed to understand the functional impacts of tau dephosphorylation in chronic epilepsy.

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Poster

PSTR054: Epilepsy Models: Network Effects, Cellular Mechanisms, and Post-Seizure Modifications

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR054.18/A71

Topic: B.08. Epilepsy

Support: National Institutes of Health (NIH)
Class of '59 Grace Hopper Award
CG Swebilius Trust

Title: Approximate Entropy Measured during Single Pulse Electrical Stimulation is a Potential Biomarker for Seizure Onset Zone

Authors: *C. W. MEI[1], H. P. ZAVERI[2], K. PU[3], D. D. SPENCER[4], A. SIVARAJU[5];
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Abstract: Rationale: Approximately one-third patients with epilepsy are refractory to antiseizure medications. Visual analysis of ictal intracranial EEG (ICEEG) onsets may not be enough for accurate localization information prior to resective surgery. Single pulse electrical stimulation (SPES) and evoked responses may help identify epileptogenic cortex. With this study we aim to explore broadband ICEEG features induced by SPES that may be unique to the epileptogenic cortex.
Methods: Ten patients who underwent ICEEG monitoring for seizure onset localization at Yale New Haven Hospital between November 2020 and December 2021 were included in this study. All or most gray matter contacts (identified using post implant MRI and reconstruction images) were stimulated with 1 Hz, starting with the non-epileptiform contacts and marching towards the seizure-onset zone. Stimulation was bipolar, biphasic, and pulse width of 0.3 milliseconds. Each pair of contacts was stimulated at an amperage of 1 mA, 5 mA, and 10 mA for a duration of 30 seconds at each amperage.
We calculated total power, Teager energy and approximate entropy (ApEn), a measure of signal regularity. ICEEG electrodes were binarized as 'seizure onset' or 'distant' based on visual analysis. For each stimulation, analysis measures were plotted as a function of distance from the site of stimulation to the site of observed response. Thirty samples at each amperage (1, 5, 10) were averaged and responses in 'seizure contacts' were compared to those in 'distant contacts'

using the Student t-test with p <0.05 considered to be significant.
Results: ApEn measured in the seizure onset zone was significantly lower (p<0.001) at 1, 5, and 10 mA when compared to the 'distant' contacts (Figure 1). Conclusions: The response of the seizure onset area to stimulation in the seizure onset area or in response to stimulation in distant areas evoked signals with lower signal complexity in comparison to corresponding observations at distant areas. The lower signal complexity expressed in response to 1 Hz stimulation may be a biomarker of the seizure onset area.

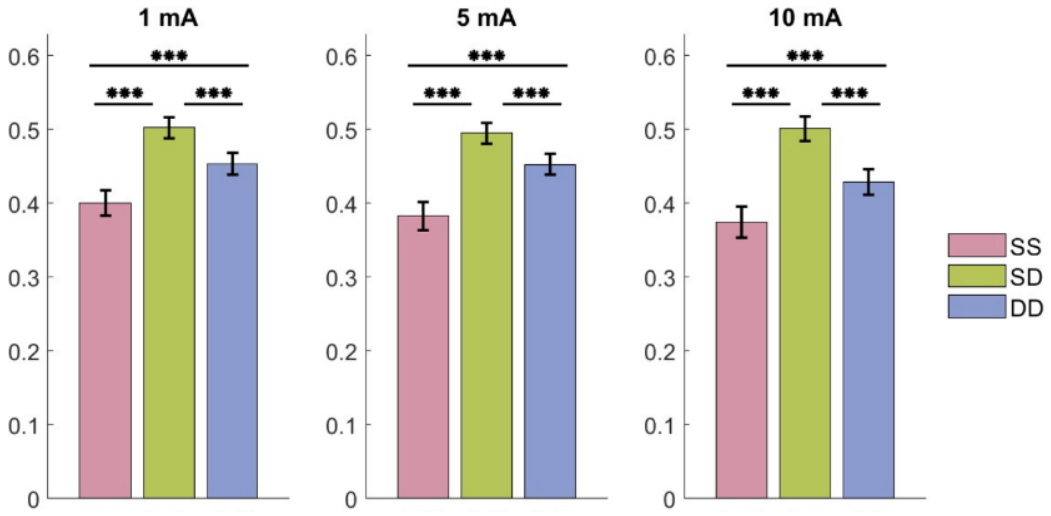

Figure 1. Mean approximate entropy of when comparing stimulations in seizure onset contacts vs. distant contacts at current strengths of 1, 5, and 10 mA. SS = stimulating in seizure onset contacts and measuring in seizure onset contacts, SD = stimulating in seizure onset contacts and measuring in distant contacts, DD = stimulating in distant contacts and measuring in distant contacts. Error bars represent 95% confidence intervals. ***p<0.001

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Poster

PSTR054: Epilepsy Models: Network Effects, Cellular Mechanisms, and Post-Seizure Modifications

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR054.19/A72

Topic: B.08. Epilepsy

Support: SNF197766

Title: Interictal Thalamic Connectivity as a Predictor for Neuromodulatory Treatments

Authors: *G. AIELLO[1,2,3,4], D. SOPER[3], A. C. PAULK[3], R. POLANIA[5], S. S. CASH[3,6], L. IMBACH[4], P. SALAMI[3];
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Abstract: Patients suffering from pharmacoresistant epilepsy can be eligible for thalamic neuromodulation. Different nuclei may be targeted: clinicians have tried anterior (ANT) for temporal, centromedian (CM) for broad, pulvinar (PLV) for posterior and dorsomedial (MD) for frontal epilepsies. However, it remains unclear which nucleus is the best target for individual patients and there is no quantitative data supporting one nucleus over the other. Moreover, current therapeutic approaches are advancing towards the identification of a biomarker that can be used for targeted neuromodulation, which is yet to be determined. Multi-day interictal recordings (at least 30' away from a seizure) during the presurgical evaluation of 38 patients implanted with sEEG were analyzed. Thalamic functional connectivity (phase lag index) to the rest of the brain was measured for different frequencies. Within each region, we measured nucleus-specific thalamic connectivity to epileptogenic zone (EZ) locations, normalizing it against thalamic connectivity to non-EZ locations. We correlated this measure to (i) the number of seizures in a 24h-period, (ii) time to the next seizure (iii) time from the previous seizure, which we refer to as "ictal measures" hereafter. We found significant, frequency-dependent correlations between thalamic connectivity to the EZ and each of the ictal measures. Even more interestingly, each thalamic nucleus exhibited distinct patterns of connectivity with certain brain regions associated with seizure occurrence: mesial temporal, parietal for ANT; occipital, parietal for PLV; frontal, subcortical for MD and all regions except mesial temporal and occipital for CM. Connectivity to the cingulate and lateral temporal areas was correlated to ictal measures in all the 4 nuclei. Intriguingly, we found that only connectivity in specific frequency bands correlated to the ictal measures, further narrowing the possible definition of a biomarker which can be used to tailor personalized neurostimulation.
This study is of key clinical importance as it provides a new perspective into thalamic nucleus selection based on a patient's specific EZ, while suggesting that biomarkers able to predict epileptogenicity can be defined during inter-ictal periods. Indeed, we found that connectivity of different nuclei to certain brain regions vary when considering EZ and non-EZ, with this variability being frequency dependent. Upon further validation in a bigger cohort, this could permit the resolution of two outstanding issues: 1) selection of the best neuromodulation target 2) implementation of closed-loop stimulation upon the detection of a pathological biomarker.

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Poster

PSTR054: Epilepsy Models: Network Effects, Cellular Mechanisms, and Post-Seizure Modifications

Location: MCP Hall A

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Program #/Poster #: PSTR054.20/A73

Topic: B.08. Epilepsy

Support: Supported by the Blue Brain Project, a research center of the École Polytechnique Fédérale de Lausanne, from the Swiss government's ETH Board of the Swiss Federal Institutes of Technology

Title: Seizure and redox rescue in a model of glucose transport deficiency

Authors: *J. COGGAN[1], H. MARKRAM[2], D. X. KELLER[3];
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Abstract: Disruptions of energy supply to the brain are associated with many neurodegenerative pathologies and are difficult to study due to numerous interlinked metabolic pathways. We explored the effects of diminished energy supply on brain metabolism using a computational model of the neuro-glia-vasculature ensemble, in the form of a neuron, an astrocyte and local blood supply. As a case study, we investigated the glucose transporter type-1 deficiency syndrome (GLUT1-DS), a childhood affliction characterized by impaired glucose utilization and associated with phenotypes including seizures. Compared to neurons, astrocytes exhibited markedly higher metabolite concentration variabilities for all but a few redox species. This effect could signal a role for astrocytes in absorbing the shock of blood nutrient fluctuations. Redox balances were disrupted during GLUT1-DS with lower levels of reducing equivalent carriers NADH and ATP. The best non-glucose nutrient or pharmacotherapies for re-establishing redox normalcy involved lactate, the keto-diet (β-hydroxybutyrate), NAD and Q10 supplementation. The model also predicts that seizures during GLUT1-DS result from after-discharge neuronal firing caused by post-stimulus ATP reductions and impaired Na^+/K^+-ATPase, which can be rescued by restoring either normal glucose or by relatively small increases in neuronal ATP.

Disclosures: J. Coggan: None. **H. Markram:** None. **D.X. Keller:** None.

Poster

PSTR054: Epilepsy Models: Network Effects, Cellular Mechanisms, and Post-Seizure Modifications

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Topic: B.11. Neuro-Oncology

Support: NIH Brain SPORE CEP P50CA221747
Starzi Academy Scholar Award

ASTRO Resident/Fellows Biology Seed Grant
Northwestern Radiation Oncology

Title: Extrinsic electrical modulation impacts glioblastoma tumor growth by disrupting its intercellular communication

Authors: *Y. ESHAC, I. PALACIN ALIANA, T. SITA;
Radiation Oncology, Neurolog. Surgery, and Malnati Brain Tumor Inst., Northwestern Univ., Chicago, IL

Abstract: Glioblastoma (GBM) is the most prevalent and fatal primary neoplasm of the central nervous system (CNS) in adults. GBM is an electrically active neoplasm that diffusely colonizes healthy brain tissues, disrupting the inhibitory/excitatory neurotransmission balance and causing glioma-related epilepsy (GRE) in up to 50% of patients. Interestingly, GRE is an independent favorable prognostic factor for survival in GBM with a doubling of survival in retrospective studies. The clinical induction of seizure, utilized frequently in psychiatric patients as electroconvulsive therapy, may have a previously unexplored oncologic value in GBM. For that purpose, GBM-bearing mice (CT-2A cells xenografted into 5 to 7 weeks old C57BL/6 female mice, n=5/group) were subjected to a single Extrinsic Electrical Modulation (EEM) of 2.0 millicoulombs (mC) or sham treatment. The mice were euthanized at 3 hours, 24 hours, 4 days, 7 days, and 10 days post-EEM, and tumors and contralateral brain cortex were harvested and analyzed using bulk RNA-seq, qPCRs, and Western Blotting. At 3 hours post-EEM, RNA-seq revealed that EEM induces the overexpression of several tumor-tumor and tumor-neuron connectivity markers, including growth-associated protein 43 (GAP43), neuroligin-3 (NLGN3), glutamate ionotropic receptor AMPA type subunit 4 (GRIA4), glutamate ionotropic receptor NMDA type subunit 1 (GRIN1), glutamate receptor ionotropic, kainate 1 (GRIK1), and metabotropic glutamate receptor 4 (GRM4). However, the expression of these markers diminishes at later time points, as observed by qPCR and Western Blotting. Furthermore, our results demonstrate that EEM slows tumor progression and improves overall survival in mice. EEM inhibits electrical integration with neuronal circuits by down regulating glutamatergic receptor expression, blocking the synapse-forming protein NLGN3, and silencing the network-connecting and radioresistance protein GAP43. Taken together, our findings reveal that EEM impacts GBM growth via the disruption of intercellular communication pathways. By targeting these critical interactions within the tumor microenvironment, EEM disrupts GBM intercellular communication and may enhance the efficacy of other therapeutic interventions.

Disclosures: Y. Eshac: None. **I. Palacin Aliana:** None. **T. Sita:** None.

Poster

PSTR055: Epilepsy Therapeutics and Screening: Animal Models

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR055.01/A75

Topic: B.08. Epilepsy

Support: Indian Council of Medical Research, New Delhi, India [Grant No: 45/01/2019-PHA/BMS]

Title: Bioinformatics guided rotenone adjuvant kindling in mice as a new animal model of drug resistant epilepsy.

Authors: *S. KUMAR;
Maharishi Markandeshwar (Deemed to be University), Ambala, India

Abstract: Drug-resistant epilepsy results from multiple mechanisms which are difficult to fully acquire in animal models. Technological advances, that allow transformation of big data into novel therapies, are now assisting in identification a disease targets for animal modeling. Our goal was to transform the available genomic and proteomic data related to drug-resistant epilepsy into ubiquitous disease target using system biology and network pharmacology approaches, followed by animal modeling and assess its validity. We used a dataset of 42 antiseizure drugs, 175 drug targets, and 601 epilepsy-gene associations to create interactome of 543 diseased proteins linked to drug-resistant epilepsy. DIAMOnD algorithm and DAVID web-services were used to identify 35 disease pathways whereby mitochondrial complex-I was selected for animal modeling. Albino mice were treated with specific inhibitor of mitochondrial complex-I (i.e., rotenone 2.5 mg/kg, i.p on daily basis) along with chemical and electric kindling stimulus for 35 days and 15 days, respectively. According to our results, the rotenone kindling model with inhibited complex-I activity showed significant ($P < 0.001$) resistance to lamotrigine (15 mg/kg), levetiracetam (40 mg/kg), carbamazepine (40 mg/kg), zonisamide (100 mg/kg), gabapentin (224 mg/ kg), pregabalin (30 mg/kg), phenytoin (35 mg/kg), topiramate (300 mg/kg), valproate (200 mg/kg), and drug combinations at doses that had significantly ($P < 0.001$) controlled seizure severity in lamotrigine- pentylenetetrazole and corneal kindling models. In conclusion, rotenone kindling model is more advantageous than earlier described lamotrigine and corneal kindling models which respond to drug combinations. As a result, pre-clinical drug screening through rotenone kindling may uncover broad spectrum drugs with novel antiseizure mechanisms which is a pressing issue to deal with drug-resistant epilepsy.

Disclosures: S. Kumar: None.

Poster

PSTR055: Epilepsy Therapeutics and Screening: Animal Models

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR055.02/A76

Topic: B.08. Epilepsy

Support: NIH R01NS038572
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Jonathan and Bonnie Rothberg
Neil and Barbara Smit
Mirowski Family Foundation

Title: Effective screening of anticonvulsants in chronically epileptic mice using on-demand seizures

Authors: *Y. CHEN[1], B. LITT[1], F. VITALE[1], H. TAKANO[2];
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Abstract: Screening of pharmacologics in chronically epileptic animals is a critical part of the drug development pipeline for anti-seizure medications (ASM). This is because epileptic brains differ significantly from healthy brains. Changes occur at all levels, ranging from the molecular composition of membrane bound receptors to network level perturbances in the dendritic arbor. The different landscape of the epileptic brain means that candidate medications that control seizures induced in naïve animals may be ineffective in epileptic animals. Unfortunately, screening drugs in epileptic animals is challenging, as spontaneous seizures are rare. In this study, we overcome this challenge by precipitating seizures "on-demand" in chronically epileptic animals. By selectively activating CA1 principal cells, we induce on-demand behavioral seizures in freely moving, epileptic animals. We then show that these seizures are influenced by several known anticonvulsants. Introduction of levetiracetam or diazepam significantly reduced the rate at which electrographic ($p < 0.016$) and behavioral ($p < 0.008$) seizures were evoked. We further show that the efficacy of the anticonvulsants decreases with time after injection. Finally, we use this model to compare ASM efficacy between evoked seizures in freely-moving, chronically epileptic animals and to acute seizures induced in naive animals .Our results indicate that the on-demand seizure model is capable of accelerating efficacy and kinetic evaluations of pharmacologics in chronically epileptic animals. We envision that this approach could reduce the time needed for drug discovery and therapeutic evaluation, and may identify promising ASM candidates not identified by current screening methods .

Disclosures: Y. Chen: None. **B. Litt:** None. **F. Vitale:** None. **H. Takano:** None.

Poster

PSTR055: Epilepsy Therapeutics and Screening: Animal Models

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR055.03/A77

Topic: B.08. Epilepsy

Title: Utilizing Planaria as a High Throughput Model for Epilepsy Research: A Convulsant Screening Approach

Authors: J. LONGO[1], M. SCOTTO[2], M. SPINLER[1], *S. GUARIGLIA[1];
[1]New York State Inst. for Basic Res., Staten Island, NY; [2]NYS IBR, Staten Island, NY

Abstract: Introduction: High throughput testing for epilepsy research is crucial for identifying potential therapeutic targets. Planaria (Dugesia dorotocephalata) present an inexpensive and easily manipulable invertebrate model suitable for such screening due to their capacity for simple compound dosing and rapid absorption, lack of blood-brain barrier and liver, and easy behavior quantification. Methods: We aimed to determine the utility of planaria as a high throughput model for epilepsy research by assessing the convulsant activity of known agents. Concentration-response relationships were established for Kainic Acid (100-500 μM), pilocarpine (1-100 mM), pentrazole (PTZ; 1 - 10 mM), bicuculine (100- 500 μM), and 4 Aminopyridine (4-AP) to identify threshold concentrations for convulsant-like activity. We classified convulsant-like activity as the number of rotations made by the animal when it is not moving in any direction. This was quantified using ANYMaze tracking software. Locomotor activity was also measured. Confirmation of central nervous system (CNS) activation by chemical exposure was achieved through quantitative Western Blot and c-Fos immunohistochemistry 3 hours post-exposure to the respective convulsant compounds.Results: 200 μM of Kainic Acid and bicuculine, as well as 10 mM of pilocarpine and 4AP, were determined as sufficient to induce convulsant-like activity in planaria. However, the effective concentration of PTZ remains to be specified. Quantitative c-Fos immunohistochemistry revealed increased expression in groups exhibiting convulsant-like or enhanced locomotor-like activity post-exposure, indicating widespread CNS activation.Conclusion: Our findings establish planaria as a promising high-throughput screening tool for epilepsy research. This model offers a valuable platform for testing potential anticonvulsant agents targeting specific molecular pathways underlying epileptiform activity by delineating threshold concentrations of convulsant agents and confirming CNS activation.

Disclosures: J. Longo: None. **M. Scotto:** None. **M. Spinler:** None. **S. Guariglia:** None.

Poster

PSTR055: Epilepsy Therapeutics and Screening: Animal Models

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR055.04/A78

Topic: B.08. Epilepsy

Support: R01NS129722 (GFB)
F31NS113479 (ANP)

Title: Peri-ictal activation of dorsomedial dorsal raphe serotonin neurons reduces mortality associated with maximal electroshock seizures

Authors: A. JONES[1], A. PETRUCCI[2], B. KREITLOW[2], *G. BUCHANAN[1];
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Abstract: *Rationale:* Sudden unexpected death in epilepsy (SUDEP) is the leading cause of death in patients with refractory epilepsy. The mechanisms underlying SUDEP are unknown, but EEG suppression and arousal deficits following a seizure may be involved. Serotonin (5-HT) is

protective against seizures and SUDEP as it modulates sleep/wake regulation, breathing, and arousal. The dorsal raphe nucleus (DRN) contains 5-HT neurons and is a component of the ascending arousal system. Our lab has previously shown that activating DRN 5-HT neurons decreases the period of unresponsiveness following seizures. We hypothesized that the same activation would also decrease mortality following a maximal electroshock seizure. *Methods:* *TPH2-ChR2-YFP* (n = 26) mice and wild-type (n = 27) littermates were implanted with EEG/EMG electrodes and an optic fiber in the DRN. 5-HT neurons in the DRN were activated with 473 nm light (4 Hz, 10 mW) for 300 seconds before a maximal electroshock seizure was induced with a 50 mA current. The light stimulation continued until recovery or death. Video and EEG were utilized to determine mortality, seizure duration, and seizure severity. *Results:* Pre-seizure activation of dorsomedial dorsal raphe (DRD) 5-HT neurons reduced mortality in *TPH2-ChR2-YFP* mice without affecting seizure severity or duration. *Conclusions:* These results suggest that the DRD plays a role in preventing seizure induced mortality. Future experiments will aim to characterize the DRD circuits and downstream targets most relevant to SUDEP.

Disclosures: A. Jones: None. **A. Petrucci:** None. **B. Kreitlow:** None. **G. Buchanan:** None.

Poster

PSTR055: Epilepsy Therapeutics and Screening: Animal Models

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR055.05/A79

Topic: B.08. Epilepsy

Support: CONAHCYT CF-2023-I-539
CONAHCYT CF-G-597

Title: Cannabidiol reduces seizures and modifies glial markers in rats with pentylenetetrazol

Authors: *A. PATRICIO-MARTÍNEZ[1,2], N. TZOMPANTZI JUAREZ[1,2], E. MARTINEZ JUAREZ[1], F. PATRICIO MARTÍNEZ[1,3], I. D. LIMON PEREZ DE LEON[1];
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Abstract: Epilepsy is a disorder characterized by hyperstimulation of the central nervous system that manifests itself with symptoms such as seizures. In refractory epilepsy, there is a constant state of neuroinflammation in addition to modifications in the cytoarchitecture of the cerebral cortex and the hippocampus, which is why great interest has been generated in the search for drugs that control the symptoms of epilepsy and provide neuronal protection. Cannabidiol (CBD) is the main non-psychotropic component of marijuana, the first reports of the properties of cannabidiol proposed it as an anticonvulsant agent, later many pharmacological effects were reported, including anti-inflammatory and neuroprotective. This variety of effects caused by CBD is due to its pleiotropic action since the actions are mediated by cannabinoid 1 (CB1) and 2 (CB2) receptors, also involving receptors 18 and 55 coupled to G protein (GPR18 and GPR55).

CBD is a non-psychoactive substance that is involved in the modulation of different receptors outside the endocannabinoid system and these interactions highlight its antiepileptic, and anti-inflammatory. For this reason, this study aimed to determine the effect of Cannabidiol on seizures and microgliosis in rats with pentylenetetrazole (PTZ). In the present work, an epilepsy model induced with PTZ (35mg/kg, i.p) was established in male rats of the Wistar strain, weighing 260-330g. CBD was administered at a dose of 15mg/kg and the CBD vehicle was ethanol: tween-20:SSI. Three experimental groups were formed (n=12): CBD vehicle+ PTZ vehicle (vehicle+vehicle); Vehicle + PTZ and CBD + PTZ. The administration of the drugs or the vehicle was carried out for fourteen days, seven days before and seven days after the administration of PTZ. On days 0, 2, 4, and 6, PTZ was administered, immediately after administration, the animals were videotaped to subsequently quantify seizures using the Racine scale. At the end of the treatment days, the animals were euthanized to remove the brains and evaluate GFAP and Iba-1 protein, markers of astrocytes and microglia. The expression of each protein was assessed by fluorescence microscopy in the cortex and hippocampus. The results show that the administration of CBD+PTZ significantly reduces the intensity of seizures compared to the group administered only with PTZ. Furthermore, the administration of CBD+PTZ induces changes in the expression of GFAP and Iba-1 in the motor cortex and hippocampus of rats treated only with PTZ. These results suggest that CBD administration may have a regulatory role in the toxic effect of PTZ at subconvulsive doses.

Disclosures: A. Patricio-Martínez: None. **N. Tzompantzi Juarez:** None. **E. Martinez Juarez:** None. **F. Patricio Martínez:** None. **I.D. Limon Perez De Leon:** None.

Poster

PSTR055: Epilepsy Therapeutics and Screening: Animal Models

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR055.06/B1

Topic: B.08. Epilepsy

Support: MHC-202402-003
HRF-202405-001

Title: Neuroprotective effect of C1q/TNF-Related Protein 9 (CTRP9) after pilocarpine induced seizures

Authors: *H. YANG[1], M. PARK[2], W. YANG[3,4,5], B. CHOI[6,7], S. SUH[8,9];
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Physiol., Hallym Univ., Chuncheon, Kang Won Do, Korea, Republic of; [9]Hallym Institute of Epilepsy Research, Chuncheon, Korea, Republic of

Abstract: Epilepsy, a prevalent neurological disorder, is characterized by severe or recurrent seizures that often lead to hippocampal neuronal death and cognitive impairments. Despite extensive research, definitive treatments for these debilitating effects remain elusive. C1q/TNF-Related Protein 9 (CTRP9), structurally similar to adiponectin, has shown anti-inflammatory and pro-angiogenic properties in vascular research through the AMP-activated protein kinase (AMPK) pathway. While extensively studied in cardiovascular diseases, the role of CTRP9 in neurological disorders, beyond global cerebral ischemia (GCI), remains largely unexplored. This study investigates the potential of CTRP9 in mitigating epilepsy-induced neuronal death. Using an animal model with pilocarpine-induced epilepsy, CTRP9 was administered intravenously at a dose of 1 mg/kg. Brain tissue was collected at various intervals for histological and biochemical analysis. Results showed that CTRP9 administration reduced neuronal death by decreasing glial cell activity and pro-inflammatory markers. Furthermore, angiogenic effects and pericyte functionality during chronic seizures were examined, revealing that post-seizure CTRP9 treatment enhances angiogenesis and pericyte function. Neurological and cognitive evaluations further affirmed CTRP9's neuroprotective benefits, as evidenced by improved cognitive and neurological outcomes in treated animals. These findings underscore CTRP9's therapeutic potential in addressing epilepsy-related neurological complications, driven by its neuroprotective, anti-inflammatory, and angiogenic properties. These effects are primarily mediated through endothelial cell restoration and pericyte-enhanced angiogenesis. Further research is crucial to validate these preliminary findings and explore CTRP9's clinical implications in developing treatments to mitigate neuron death and cognitive impairments in epilepsy.

Disclosures: H. Yang: None. **M. Park:** None. **W. Yang:** None. **B. Choi:** None. **S. Suh:** None.

Poster

PSTR055: Epilepsy Therapeutics and Screening: Animal Models

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR055.07/B2

Topic: B.08. Epilepsy

Support: BUAP-CA-288
PRONACES-CONACYT 194171

Title: Effect of medroxyprogesterone acetate on absence seizures in taiep rat: a model of h-abc leukodystrophy

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Univ. Autonoma de Puebla, Puebla, Mexico; [3]Behavioral Neurophysiol., Benemerita Univ. Autonoma De Puebla, Puebla, Mexico

Abstract: Effect of medroxyprogesterone acetate on absence seizures in *taiep* rat: a model of H-ABC leukodystrophy

Authors Karla Vazquez, Cortes Carmen, Jose R. Eguibar.
Behavioral Neurophysiology Laboratory, Physiology Institute International OfficeBenemérita Universidad Autónoma de Puebla, Pue. México The *taiep* rat is a tubulin mutant and its name is the acronym of the progressive motor signs tremor, ataxia, immobility, epilepsy and hindlimb paralysis. The *taiep* rat was described as a leukodystrophy with a mutation in the tubulin β 4A gene causing hypomyelination with atrophy of the basal ganglia and cerebellum (H-ABC). *Taiep* rats had spike-wave discharges (SWDs) in EEG recordings with a sexual dimorphism being the males more affected than females. It has been reported that progesterone reduced the incidence of seizures. The aim of this study was to evaluate the effect of medroxyprogesterone acetate (MPA), a long-lasting analog of progesterone, in spike-wave discharges in female *taiep* rats.We evaluate 6-month-old female rats that were bilaterally ovariectomized and implanted with electrodes in the cerebral cortex for EEG recording, in neck muscles for electromyography (EMG), and right eye´s orbit for electrooculography (EOG). We performed three 24 h EEG recordings one control, and the others after intramuscular administration with 5 and 10 mg/Kg dose of MPA, respectively with an interval of 72 h between them. Our results shown that the administration of 5 mg/Kg of MPA decreased the incidence of SWDS by 52.7%, and 10 mg/Kg dose only decreased 25.6% SWDs with respect to control conditions. The mean duration of SWDs increased 11.3% with the lower dose of MPA, but there is not change with the higher dose used. In conclusion, medroxyprogesterone acetate induced only slight changers in SWDs on absences seizures in *taiep* rat.
Partially supported by a grant from VIEP-BUAP 2022-2023 to CA in Neuroendocrinología (BUAP-CA-288). KEV is student of MSc on Physiological Sciences fellowship from CONAHCYT No. 1268024.

Disclosures: K. Vazquez Olaya: None. **C. Cortes:** None. **J.R. Eguibar:** None.

Poster

PSTR055: Epilepsy Therapeutics and Screening: Animal Models

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR055.08/Web Only

Topic: B.08. Epilepsy

Title: Anticonvulsant activity of Bocconia arborea S. Watson and its bioactive metabolite dihydrosanguinarine in mice

Authors: *D. MARTINEZ-VARGAS[1], M. GONZÁLEZ-TRUJANO[2];
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Mexico, Mexico; [2]Lab. de Neurofarmacología de Productos Naturales, Inst. Nacional de Psiquiatria Ramon de la Fuente Muniz, Mexico, D.F., Mexico

Abstract: Background: Epilepsy is a chronic disease characterized by spontaneous and recurrent seizures. Despite the availability of many antiepileptic drugs, any of them are efficacious enough to completely control epileptic seizures. The use of medicinal plants or their metabolites represents an option in the search for new drugs. In traditional Mexican medicine, the *Bocconia arborea* S. Watson (Papaveraceae) tree (*B. arborea*) is used to treat skin, kidney, and infectious diseases. Furthermore, it has been reported that extracts of different polarities of *B. arborea* cause central nervous system (CNS) depressant effects such as anxiolytics and analgesics involving the opioid and $GABA_A$ receptors. The above information suggests that this species could possess anticonvulsant activity. **Aim:** To evaluate the anticonvulsant activity of extracts of different polarity of *B. arborea* and one of its secondary metabolites called dihydrosanguinarine (DHS) on tonic-clonic seizures induced with pentylenetetrazole (PTZ) and maximum electroshock tests in mice. **Methods:** The study consisted of two experiments. In the first, thirty-six male Swiss Webster mice were implanted for electroencephalographic recording and divided into six groups: vehicle, diazepam (1 mg/kg), hexane (HEX), dichloromethane (DCM), methanol (MeOH), and the metabolite DHS (100 mg/kg). The treatments were intraperitoneally administered with an acute dose 30 min before the convulsant PTZ (85 mg/kg). For the second experiment, sixty-nine mice were used, and subjected to the maximum electroshock test 30 min after the administration of each treatment. **Results:** Animals treated with the HEX extract presented a decrease in the incidence ($p < 0.005$) and an increase in the latency ($p < 0.005$) of tonic-clonic seizures induced with PTZ. In addition, a lower rate of mortality ($p<0.005$) was observed. These results were similar to those obtained with the reference drug diazepam. Animals treated with the MeOH extract and DHS also showed significant responses, although to a lesser extent than HEX ($p<0.05$ for both). In the second experiment, animals treated with diazepam, the extracts (HEX and DCM) or DHS presented a protective effect on tonic-clonic seizures induced with the maximum electroshock test, as well as a shorter duration of seizures ($p<0.0001$). **Conclusion**: Our study provides evidence that constituents of HEX and MeOH extracts (low and high polarity, respectively) are involved in the anticonvulsant properties of *B. arborea*, where the DHS metabolite was partially responsible, and the modulation of the GABAergic system could mediate its effect.

Disclosures: D. Martinez-Vargas: None. **M. González-Trujano:** None.

Poster

PSTR055: Epilepsy Therapeutics and Screening: Animal Models

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR055.09/B3

Topic: B.08. Epilepsy

Support: 5/4-5/4GIA/Trauma/2020-NCD-I

Title: Anti-seizure effect of dietary curcumin in post-traumatic epilepsy: A pre-clinical study on electrophysiological and behavioural observations

Authors: *J. TYAGI[1], D. SHARMA[2], S. SARAN[3];
[2]Schhol of Life Sci., [1]Jawaharlal Nehru Univ., New Delhi, India; [3]Schhol of Life Sci., Jawaharlal Nehru University, New Delhi, New Delhi, India

Abstract: Post-traumatic epilepsy is a form of epilepsy that occurs after a brain trauma and is characterised by prevalence of spontaneous and recurrent seizures. Curcumin is a bioactive compound highly abundant on *curcumin longa* (turmeric) and is known for its several medicinal properties e.g., anti-oxidant, anti-inflammatory and neuroprotective properties. The present study was carried to evaluate anti-seizure effect of dietary curcumin by electrophysiological (EEG) and behavioural observations in an experimental model of PTE. To execute the study animals were divided into divided into four groups; (1) Control rats, (2) Epileptic rats, (3) curcumin-fed epileptic rats, and (4) curcumin-fed rats. Curcumin was fed at the dose of 1000 ppm for 3 months. EEG results of epileptic rats as compare to control rats were significantly elevated along with MUA counts, however curcumin-fed epileptic animals showed reduced epileptiform seizure activity, cortical MUA counts with respect to epileptic rat, suggesting anti-seizure activity of dietary curcumin. Morris Water Maze (MWM) test in epileptic rats displayed significantly prolonged escape latency to find the hidden platform. However, curcumin fed epileptic rats did not show any significant difference when compared with epileptic rats. Open-field test was performed to test the anxiety like behaviour by analysing locomotory activity, rearing, and defecation index. Curcumin fed epileptic rats exhibited significant increase in locomotory activity as compare to epileptic rats. whereas, no significant difference was observed in rearing, and defecation index. Our research indicates that curcumin have anti-seizure effect and increase locomotor activity in epileptic rats.

Disclosures: J. Tyagi: None. **D. Sharma:** None. **S. Saran:** None.

Poster

PSTR055: Epilepsy Therapeutics and Screening: Animal Models

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR055.10/B4

Topic: B.08. Epilepsy

Support: NIH Grant T32 MH082174

Title: Sleep enhancement to treat epilepsy and its comorbidities

Authors: *D. LASKY[1], L. ROSENBERG[2], B. HARVEY[1], C. ANACLET[3], N. P. PEDERSEN[2];
[1]Univ. of California, Davis, Davis, CA; [2]Neurol., Univ. of California, Davis, Davis, CA; [3]Neurolog. Surgery, Univ. of California, Davis, Davis, CA

Abstract: Epilepsy is a debilitating neurological disorder that affects over 70 million people worldwide. Temporal lobe epilepsy is the most common focal epilepsy and is typically refractory to treatment. People with epilepsy experience substantial sleep loss and fragmentation, which may worsen seizure control and negatively impact cognitive processes. Critically, improving sleep quality promotes seizure control, producing the modern view that epilepsy treatment must improve both for long-term well-being and cognitive function. We investigated, for the first time to our knowledge, the direct manipulation of sleep circuits as a treatment for epilepsy. Vgat-Cre C57BL/6J mice were injected bilaterally with an AAV to express the excitatory designer receptor hM3Dq in the GABAergic neurons of the medullary parafacial zone (PZ). Activation of these projections induces robust and prolonged non-rapid eye movement (NREM) sleep in healthy mice. Once recovered, mice underwent an optimized headplate surgery that measures electrocorticography, hippocampal field potentials, and electromyography. Temporal lobe epilepsy was induced using the intra-amygdala kainate model shown to have reduced and fragmented sleep. Mice were continually recorded to determine sleep-wake states, seizures, and electrophysiological effects. A crossover design was used with mice performing three weeks of voluntary oral drug administration to activate the inhibitory PZ projections followed by three weeks of vehicle. Effects on cognition were assessed at the end of each treatment condition through novel object recognition, object location, and tail suspension tests. Through sleep scoring, we found that activation of inhibitory PZ projections in epileptic mice induces prolonged NREM sleep. The success of this methodology provides the first circuit mechanism for exploring sleep enhancement in epilepsy. Next, we will use a machine-learning-based classifier to simultaneously identify sleep-wake states and seizures. We will assess both the behavioral and electrophysiological effects of sleep enhancement through behavioral task performance and quantification of epileptiform activity. We are particularly interested in alterations to interictal epileptiform activity as it has been associated with arousals, possibly underlying sleep fragmentation. This project will provide fundamental insights into the role of NREM sleep in seizure control and cognitive well-being, from behavioral and electrophysiological standpoints. This novel treatment can also be expanded to treating human epilepsy through the present use of AAV-based approaches in human subjects.

Disclosures: D. Lasky: None. **L. Rosenberg:** None. **B. Harvey:** None. **C. Anaclet:** None. **N.P. Pedersen:** None.

Poster

PSTR055: Epilepsy Therapeutics and Screening: Animal Models

Location: MCP Hall A

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Program #/Poster #: PSTR055.11/B5

Topic: B.08. Epilepsy

Support: R.12014/41/2022-HR

Title: Activation of sirtuin 1 (SIRT1) attenuates epileptic seizures and behavioural changes in the experimental model of post-traumatic epilepsy

Authors: *C. PRAKASH[1], S. SARAN[2], D. SHARMA[2];
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Abstract: The etiopathology of epilepsy is very complex with polygenic origins. Sirtuin 1 (SIRT1) is a NAD-dependent deacetylase of the sirtuin family intracellular regulatory proteins linked with energy homeostasis, and survival of neurons. Till now no published results have demonstrated the role of SIRT1 on post-traumatic epilepsy. Hence, we evaluated the role of SIRT1 in post-traumatic epilepsy in light of electrophysiological and behavioural observations. Rats were made epileptic by injecting $FeCl_3$ in the somatosensory cortex, resveratrol (SIRT1 activator; orally for 15 days) and Ex-527 (SIRT1 inhibitor; i.p. 4 doses two days apart) were given 15 days later. The results showed spontaneous and recurrent episodes of epileptic seizures in the cortex and hippocampus of epileptic rats which were concomitant to multiple unit activity (MUA) counts. Whereas, epileptic rats administered with resveratrol showed reduced epileptiform episodes and MUA counts. The MWM test demonstrated higher escape latency and resveratrol administration significantly lowered it without changes in swimming speed. The total distance moved in OFT and time spent in the central zone by epileptic rats was less than that of controls. Resveratrol administration to epileptic rats attenuated these changes. Contrary to this, epileptic rats administered with Ex-527 did not show any significant change in EEG and behavioural indices. The control rats treated with resveratrol or Ex-527 did not show significant changes in these parameters. Overall, findings indicate that activation of SIRT1 exerts an antiepileptic effect as evident from the alleviation of epileptiform seizure activity, learning and memory, and locomotor activity in the epileptic rats.

Disclosures: C. Prakash: None. **S. Saran:** None. **D. Sharma:** None.

Poster

PSTR055: Epilepsy Therapeutics and Screening: Animal Models

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR055.12/B6

Topic: B.08. Epilepsy

Support: NIH Grant NS120916-01
W.E. Lloyd Endowment Fund SG2200008

Title: The effects of NADPH oxidase inhibitor, Mitoapocynin, in a diisopropylfuorophosphate (DFP)-induced long-term neurotoxicity model

Authors: *C. MEYER[1], E. GREGO[1], S. SUNDARA VASANTHI[2], N. RAO[2], N. MASSEY[1], C. HOLTKAMP[1], T. THIPPESWAMY[2];
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Abstract: **Rationale**Acute exposure to diisopropylfluorophosphate (DFP) induces cholinergic crisis that leads to behavioral deficits, seizures, and neurodegeneration in the long term. A critical underlying mechanism of the chronic effects of DFP exposure is oxidative stress, or the

overproduction of reactive oxygen species, mediated by NADPH oxidase (NOX). In the DFP model, we discovered that NOX inhibitor, mitoapocynin (MPO), reduces astrogliosis in the brain in the short term. In this study, we investigate the long-term efficacy of MPO on DFP-induced seizures, epileptiform spikes, and behavioral abnormalities.
MethodsA mixed-sex cohort of Sprague Dawley rats was randomized into control, Veh+MPO, DFP+Veh, and DFP+MPO. To induce *status epilepticus* (SE), DFP (4mg/kg, s.c.) was administered, immediately followed by 2-PAM (25mg/kg, i.m.) and atropine sulfate (2mg/kg, i.m). SE severity was monitored and scored for an hour, and midazolam (3mg/kg, i.m.) was given to terminate SE. Animals were given 1 dose of blank or MPO-encapsulated nanoparticles (NP) (3.5mg-males, 3mg-females; i.m.) and 3 doses of oral MPO (30mg/kg) or vehicle. Behavioral tests were performed to measure brain dysfunction, and telemetry devices implanted to detect seizures and spikes for 4 weeks post-DFP. Serum biochemistry was conducted to detect kidney and liver function.
ResultsMortality rates were elevated post-DFP, which was exacerbated by MPO treatment. In the elevated zero maze, a significant increase in distance traveled was observed in DFP-exposed rats. In NOR, animals in the DFP+Veh group held no object preference, whereas control and DFP+MPO
preferred the familiar over the novel object. DFP-induced pathology was not observed in the object location, rotarod, and fear conditioning tests. Seizures and spikes were increased in DFP+MPO compared to DFP+Veh. There was a significant increase in aspartate aminotransferase (AST) and alanine aminotransferase (ALT) in DFP+MPO. **Conclusions**While MPO rescued memory and learning deficits, as observed in the novel object replacement test, mortality rates and elevated seizures suggest MPO toxicity in the current dosing regimen post-DFP. Interestingly, toxicity was not observed in the control+MPO or DFP+Veh group, indicating that the combination of DFP, MPO-NP, and oral MPO treatment together may have caused the adverse effects. Optimized oral or nasal dosing of MPO, without NPs (i.m.), should be considered in the future studies.

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Poster

PSTR055: Epilepsy Therapeutics and Screening: Animal Models

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR055.13/B7

Topic: B.08. Epilepsy

Support: Directorate of Research, Innovation and Consultancy (DRIC) Group-led Grant, 2022, University of Cape Coast

Title: Anticonvulsant potential of Ziziphus abyssinica extract and its bioactive constituent, β-amyrin: possible mechanisms

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Abstract: Natural products are invaluable in the development of new therapeutic options for medical disorders such as epilepsy. This study evaluated the hydro-ethanolic root bark extract of Ziziphus abyssinica (ZAE) and its isolated compound, β-amyrin (BA), for their anticonvulsant effects. The potential mechanism of action of BA was assessed in silico using a reverse docking approach. Established in vivo experimental models adopted to assess the anticonvulsant effect of the test agents were the pentylenetetrazol-induced seizures (PTZIS) and pilocarpine-induced seizures (PILIS) in mice. In the PTZIS, 10 groups of mice (n=7) were pretreated with a single dose of either ZAE (30, 100, and 300 mg/kg, p.o.), β-amyrin (10, 30, and 100 mg/kg, p.o.), or normal saline (10 mL/kg, p.o.). Experimental seizures were induced with PTZ (85 mg/kg, s.c.), and the onset, duration, and frequency of tonic and myoclonic convulsions determined. Brain homogenates of the mice were then assayed for total antioxidant capacity (TAC), catalase (CAT), total thiols (TT), and glutathione (GSH) levels. ZAE and BA were also assessed in the PILIS using pilocarpine (85 mg/kg, s.c.). After observations for the onset and severity of convulsions, the mice were humanely sacrificed, and their hippocampi were removed for histological assessment. In the in silico assay, human protein implicated in convulsions were prepared using Schrödinger Suites for docking with BA. Molecular dynamics simulation, MDS (Desmong module) was used to further evaluate the docking poses of BA in the selected proteins. Both ZAE and β-amyrin exhibited significant ($p<0.05$) anticonvulsant effects in PILIS and PTZIS. Additionally, ZAE and BA significantly elevated TAC, CAT, TT, and GSH levels in the PTZIS model while also offering hippocampal neuroprotection in the PILIS model. It was found from docking assay that BA has high binding affinities to three important proteins associated with epilepsy: ATP-binding cassette sub-family A member 13 (ACA13), GPI ethanolamine phosphate transferase 3 (GEPT3), and neuronal calcium sensor 1 (NCS1). The MDS revealed that BA remains stable with the three proteins throughout the 200ns simulation. Binding affinity estimation calculated by MM/GBSA was found to be -73.23 kcal/mol, -62.31 kcal/mol, and -72.05 kcal/mol for ACA13, GEPT3, and NCS1, respectively, suggesting a strong binding affinity of β-amyrin with these proteins. Further studies to validate these mechanisms in vitro and in vivo are recommended.

Disclosures: I. Henneh: None. **R.P. Biney:** None.

Poster

PSTR055: Epilepsy Therapeutics and Screening: Animal Models

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR055.14/B8

Topic: B.08. Epilepsy

Support: NIH grants NS085171
NIH grants AG065290
Neurodegeneration Consortium at MD Anderson

Title: The role of Bach1 in modulating oxidative stress response and neuroinflammation in seizure conditions

Authors: *P.-Y. CHUANG, C.-H. FU, W. YU, J. CHIN;
Neurosci., Baylor Col. of Med., Houston, TX

Abstract: Recurrent seizures are hallmark features of various neurological disorders, including Alzheimer's disease (AD) and epilepsy, which are often accompanied by oxidative stress and neuroinflammation. In human amyloid precursor protein (APP) transgenic mice that are used to model AD amyloidosis, the severity of memory deficits corresponds to seizure activity, implicating that seizures worsen cognitive impairment. Utilizing RNA sequencing (RNA-seq) in APP mice, we identified an upregulation of Bach1, a transcriptional repressor of oxidative stress-related pathways, in mice with greater susceptibility to seizures and cognitive impairment. Bach1 expression increased with both age and seizure activity. Using pharmacological mouse models of epilepsy, we demonstrated that seizure activity alone is sufficient to induce Bach1 expression. Notably, Bach1 has previously been implicated in neurological disorders; it is increased in Parkinson’s disease patients and is suggested to contribute to oxidative stress dysregulation and AD development in Down Syndrome patients. To investigate whether the ablation of Bach1 could confer neuroprotection in neurological conditions accompanied by oxidative stress, we generated Bach1 knockout (BKO) mice and induced seizures using a chemoconvulsant kainic acid (KA). Both BKO mice and wildtype (WT) control mice exhibited similar seizures within the first two hours post-KA. However, the anti-oxidative stress gene, Hmox1 (HO-1), typically repressed by Bach1, showed increased expression in BKO mice at 4 and 24 hours post-KA, suggesting an augmented antioxidant response. Moreover, in 72 hours post-KA treatment, glial fibrillary acidic protein (GFAP) expression, an indicator of astrocytic activation and neuroinflammation, was reduced in BKO mice compared to WT mice. This finding supports the notion that Bach1 ablation upregulates oxidative stress responses and reduces neuroinflammation in a pharmacological seizure mouse model. Our results provide evidence that targeting the Bach1 pathway may offer a novel therapeutic strategy to mitigate the oxidative and inflammatory consequences of seizures, potentially reducing downstream cognitive decline in both epilepsy and in AD.

Disclosures: P. Chuang: None. **C. Fu:** None. **W. Yu:** None. **J. Chin:** None.

Poster

PSTR055: Epilepsy Therapeutics and Screening: Animal Models

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

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Topic: B.08. Epilepsy

Support: Grant from the European Union's Horizon 2020 Work Programme (call H2020-FETOPEN-2018-2020) under grant agreement 964712 (PRIME; to M. Simonato).

Title: Role of tRNA-derived fragments in the rat pilocarpine model of epilepsy

Authors: *M. SOUKUPOVA[1], A. GUARINO[2], P. MARINO[2], L. ASTH[2], S. ZUCCHINI[2], E. PEREZ MORRISSEY[3], S. ZAHEER[3], J. H. PREHN[3], M. SIMONATO[2];
[1]Univ. of Ferrara, Ferrara, Italy; [2]Neurosci. and Rehabil., Univ. of Ferrara, Ferrara, Italy; [3]Physiol. and Med. Physics, Royal Col. of Surgeons In Ireland, Dublin, Ireland

Abstract: Around 50 million people worldwide have epilepsy and about 5 million people are newly diagnosed each year. Temporal lobe epilepsy (TLE) is one of the most frequent forms of epilepsy. Unfortunately, its current therapy is only symptomatic, and preventive treatments in at-risk individuals are not available. Despite advances in imaging, electroencephalography (EEG) remains an essential diagnostic and disease monitoring tool for epileptic patients while biomarkers of tissue transformation from normal to epileptic or progression of established epilepsy are still lacking. Some tRNA-derived fragments (tRFs) have recently been identified as potential biomarkers of seizure in patients with epilepsy. tRFs are non-coding RNAs that post-transcriptionally regulate protein expression. To validate selected tRFs (5'AlaTGC, 5'GluCTC,5'GlyGCC) as biomarkers of seizure occurrence, we performed qPCR analyses on liquor and plasma samples withdrawn from Li-pilocarpine-treated rats in the chronic phase of TLE (i.e. 50-64 days post status epilepticus, dpSE) and correlated the expression of these 3 tRFs with spontaneous recurrent seizures (SRS) and EEG interictal activity (IA) in individual epileptic rats. We further compared tRFs expression levels in epileptic vs. naïve rats. In total, 8 naïve and 14 epileptic, 6-weeks-old male rats were sampled 5 times every 72 h for liquor and plasma, such that 220 samples were assayed for tRFs. We did not identify significant differences in the median dCT values of 5'AlaTGC, 5'GluCTC, and 5'GlyGCC in CSF or plasma between baseline, pre-seizure, and post-seizure samples in epileptic animals, neither in pooled nor in single animal paired analysis. However, a tendency towards increased 5'tRF levels was observed in post-seizure samples compared to baseline and pre-seizure samples when analyzing pooled data. Similarly, we did not reveal any significant differences in epileptic rats while examining the medians of the 5'tRFs sampled when interictal activity was present or absent in the 2 hours before/after sampling. When comparing the pooled samples of epileptic and non-epileptic rats, the epileptic animals trended to display higher baseline levels of all 3 tRFs compared to naive controls in liquor and plasma. In conclusion, the available data results suggest that, in the Li-pilocarpine epilepsy model in male rats, 5'AlaTGC, 5'GluCTC, and 5'GlyGCC levels may not be directly linked to seizure occurrence nor to interictal activity.

Disclosures: M. Soukupova: None. **A. Guarino:** None. **P. Marino:** None. **L. Asth:** None. **S. Zucchini:** None. **E. Perez Morrissey:** None. **S. Zaheer:** None. **J.H. Prehn:** None. **M. Simonato:** None.

Poster

PSTR055: Epilepsy Therapeutics and Screening: Animal Models

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR055.16/B10

Topic: B.01. Transmitters, Transporters, and Other Signaling Molecules

Support: National Research Foundation of Korea (NRF-2023R1A2C100524811)

Title: Cxcl5/cxcr2 regulates seizure susceptibility with altered gat1 activity in the hippocampus

Authors: *S. YANG, R. SHARMA, Y. SEO, S. LEE, J. PARK;
Seoul Natl. Univ., Seoul, Korea, Republic of

Abstract: γ-Aminobutyric acid (GABA)-generated persistent tonic inhibitory currents (tonic $GABA_A$ current or I_{tonic}), is crucial for maintaining excitatory and inhibitory (E/I) balance in CNS. The GABA concentration may be regulated by three factors: GABA release, $GABA_A$ receptor composition, and clearance of GABA from both extracellular and synaptic cleft which predominantly depends on the GABA transporters (GATs). Compared to the $GABA_A$ receptor and vesicular GABA release, the mechanistic study underlying the expression and activity of GATs remains elucidated. Here, we report the absence of C-X-C motif chemokine ligand5 (CXCL5), a key inflammatory mediator, plays an important role in modulating the activity of GABA transporter 1 (GAT1) in dentate gyrus granule cells (DGGCs). Using a whole-cell patch clamp, we found that the I_{tonic} of DGGCs was significantly less in *Cxcl5* knock-out (KO) mice, 7-8 weeks old male with C57BL/6N background, than corresponding wild-type (WT) control. In contrast, the GAT1 inhibitor (NO-711) induced a larger inward shift of $I_{holding}$ in *Cxcl5* KO mice than in WT mice. As a result, the total tonic $GABA_A$ current in the presence of NO-711 was equalized in the two groups. Interestingly, presynaptic GABA release and the protein expression of GAT1 remained the same, suggesting that CXCL5 intrinsically suppresses the activity of GAT1 in the hippocampal circuit. Along with diminished I_{tonic}, the pharmacological inhibition of CXCL5 (SB 225002) mimicked the effect of genetic deletion of CXCL5. Overall, our results show that the CXCL5/CXCR2 axis constitutively restraining GAT1 activity to maintain the tonic $GABA_A$ inhibition could be a novel therapeutic target against the seizure-prone state.

Disclosures: S. Yang: None. **R. Sharma:** None. **Y. Seo:** None. **S. Lee:** None. **J. Park:** None.

Poster

PSTR056: Anticonvulsant and Antiepileptic Therapies

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR056.01/B11

Topic: B.08. Epilepsy

Support: FP7- HEALTH Project 602102 [EPITARGET]

Title: Combinatorial gene therapy for epilepsy based on Neuropeptide Y and its Y2 receptor

Authors: *S. CATTANEO[1,2], B. BETTEGAZZI[3], L. CRIPPA[3], M. BONFANTI[1], L. ASTH[4], M. REGONI[3], M. SOUKUPOVA[4], S. ZUCCHINI[4], F. CODAZZI[3], A. CANTORE[5], F.

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Abstract: About a third of epilepsy patients are drug-resistant, i.e., refractory to currently available anti-seizure drugs. Gene therapy is recently emerging as a feasible option for these patients. Here, we explored the potential of a novel gene therapy enhancing the therapeutic effects on Neuropeptide Y (NPY), a well-known endogenous anticonvulsant. To potentiate the effect of Neuropeptide Y, we developed a combinatorial gene therapy based on a lentiviral vector inducing the co-expression of Neuropeptide Y with its inhibitory receptor Y2. Both transgenes were put together under the control of the minimal CamKIIa(0.4) promoter, thereby biasing expression toward excitatory neurons and allowing autoregulation of neuronal excitability by Y2 receptor-mediated Neuropeptide Y inhibition. We assessed vector-induced Neuropeptide Y and Y2 receptor expression by using biochemical and immunocytochemical techniques in cultures of hippocampal neurons. In addition, we obtained efficient overexpression of both transgenes in the mossy fiber terminals of granule cells in vivo, after vector injection in the dentate gyrus. We then employed telemetry video-EEG monitoring to assess the effect of Neuropeptide Y and Y2 receptor overexpression on the epileptic phenotype of a genetic mouse model (the synapsin triple KO). Injection of the vector before the onset of spontaneous recurrent seizures dramatically reduced their frequency and duration. These data support the hypothesis that strategies aimed at the delivery of NPY and Y2 may be successful for the treatment of epilepsy, particularly for pharmaco-resistant and genetic forms of the disease.

Disclosures: S. Cattaneo: None. **B. Bettegazzi:** None. **L. Crippa:** None. **M. bonfanti:** None. **L. Asth:** None. **M. Regoni:** None. **M. Soukupova:** None. **S. Zucchini:** None. **F. Codazzi:** None. **A. Cantore:** None. **F. Valtorta:** None. **M. Simonato:** None.

Poster

PSTR056: Anticonvulsant and Antiepileptic Therapies

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR056.02/B12

Topic: B.08. Epilepsy

Title: Developing a localised GDNF-based gene therapy to treat neurodegenerative diseases

Authors: *L. CRIPPA[1], B. BETTEGAZZI[1], S. CATTANEO[2], A. GUARINO[3], M. REGONI[2], C. PORCARI[2], I. GIUPPONI[2], M. BONFANTI[2], M. SIMONATO[3];
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Abstract: The glial cell line-derived neurotrophic factor (GDNF) is a neurotrophic factor widely produced and secreted in the nervous system by glial cells and neurons. Upon release, GDNF

binds to the RET receptor, activating several intracellular pathways involved in neuronal development and survival. The neuroprotective properties of GDNF have garnered significant interest for potential applications in neurodegenerative disorders. In this research project, we aim to develop a novel gene therapy-based approach to drive a localized and sustained release of GDNF to treat two different diseases associated with neurodegeneration: Parkinson's Disease (PD) and Temporal Lobe Epilepsy (TLE). We developed an integrating lentiviral vector (LV) to achieve overexpression of GDNF from astrocytes *in vivo*, exploiting the GFABC1D promoter. We first performed *in vitro* experiments to determine the optimal LV design for enhanced GDNF expression and secretion from astrocytes. These experiments revealed strong expression and secretion of GDNF in primary astrocyte cultures. Subsequently, we confirmed specific GDNF expression in astrocytes in the rat *hippocampus* and mouse *striatum* by injecting either the therapeutic or control LVs into the target sites (*striatum* for PD and *hippocampus* for TLE). To test the therapeutic efficacy, we treated relevant animal models of the diseases with the GDNF or control LVs. For PD, we employed a genetic mouse model of Juvenile Parkinsonism, the R275W mice, that was treated in a prophylactic setting. For TLE, we used the pilocarpine-induced rat model, and we monitored the epileptic activity through video-EEG recordings upon treatment with either the GDNF or control LV. A trend towards a reduction in the spontaneous recurrent seizures was observed in the GDNF-treated group. The evidence gathered thus far is encouraging and holds promise for the development of a novel gene-therapy strategy to provide neuroprotection in PD and TLE.

Disclosures: L. Crippa: None. **B. Bettegazzi:** None. **S. Cattaneo:** None. **A. Guarino:** None. **M. Regoni:** None. **C. Porcari:** None. **I. Giupponi:** None. **M. bonfanti:** None. **M. Simonato:** None.

Poster

PSTR056: Anticonvulsant and Antiepileptic Therapies

Location: MCP Hall A

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Program #/Poster #: PSTR056.03/B13

Topic: B.08. Epilepsy

Support: PNRR-MAD-2022-12376434
PRIN 2022NWJ9N

Title: A gene therapy approach for focal epilepsy based on $GABA_A$receptor overexpression

Authors: *M. BONFANTI[1,2,3], S. CATTANEO[1], G. RUFFOLO[4], E. PALMA[4], B. BETTEGAZZI[5], M. SIMONATO[6];
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Abstract: Epilepsy is a chronic neurological disorder characterized by recurrent seizures. Despite the availability of many antiepileptic drugs (AEDs), 30% of the patients are resistant to standard therapies. In this context, gene therapy is emerging as a potential therapeutic approach. $GABA_A$ receptor ($GABA_AR$) expression and function are altered in the epileptic tissue, resulting in impaired inhibition and reduced sensitivity to GABAergic AEDs like barbiturates. We are developing a gene therapy strategy for focal drug-resistant epilepsy based on the overexpression of specific $GABA_AR$ subunits in hippocampal excitatory neurons, aiming at increasing network inhibition and enhancing the effectiveness of GABAergic AEDs. We developed lentiviral vectors (LVs) encoding $GABA_AR$ subunits, under the control of the neuron-specific minimal CamKII(0.4) promoter. *In vitro* experiments demonstrated co-expression and correct subunit processing in primary neurons transduced with these LVs. Further, patch clamp analysis indicated increased GABA-induced chloride conductance in transduced neurons, suggesting formation of functional $GABA_ARs$. Preliminary *in vivo* experiments showed that vectors induce overexpression of both receptor subunits when injected in the hippocampal parenchyma. Analysis of GABA-evoked currents in *Xenopus* oocytes, microtransplanted with hippocampal membranes obtained from LV-injected mice, showed that the upregulation of $GABA_A$ subunits induced an enhanced potentiation of currents after treatment with phenobarbital. Further experiments are ongoing to assess the synaptic localization of the overexpressed subunits and the modified $GABA_ARs$ composition. The already available findings demonstrate the feasibility of obtaining neuron-specific functional $GABA_AR$ overexpression by using our gene therapy approach, a first step to develop a therapeutic strategy for the treatment of drug-resistant epilepsy.

Disclosures: M. Bonfanti: None. **S. Cattaneo:** None. **G. Ruffolo:** None. **E. Palma:** None. **B. Bettegazzi:** None. **M. Simonato:** None.

Poster

PSTR056: Anticonvulsant and Antiepileptic Therapies

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR056.04/B14

Topic: B.08. Epilepsy

Support: PRIN-PNRR Prot. P20225E59W

Title: Trkb activation as a novel target for drug resistant temporal lobe epilepsy: from animal models to the human epileptic brain

Authors: *A. GUARINO[1], M. SOUKUPOVA[1], B. BETTEGAZZI[2], L. CRIPPA[2], S. ZUCCHINI[1], G. RUFFOLO[3], E. PALMA[3], M. SIMONATO[1,2];
[1]Neurosci. and Rehabil., Univ. of Ferrara, Ferrara, Italy; [2]Neurosci., Vita Salute San Raffaele Univ., Milan, Italy; [3]Univ. of Rome, Rome, Italy

Abstract: Epilepsy is one of the most common chronic neurological disorders. All pharmacological agents that are currently in use are merely symptomatic, as they do not target the causes of the disease. Furthermore, 30% of patients do not respond to any of these drugs. Thus, it is urgently needed to identify new treatment options capable of changing the natural history of the disease (i.e., disease-modifying). The brain derived neurotrophic factor (BDNF), through the activation of its high-affinity receptor TrkB, may play a kay role in epilepsy development as well as in the generation and recurrence of seizures. However, BDNF cannot be used as a regular drug because of its poor bioavailability. The aim of this study was to test the effects of an antioxidant agent and TrkB receptor agonist, 7,8-dihydroxyflavone (7,8-DHF) as a putative anti-epileptogenic and/or anti-epileptic drug. Firstly, we found that low- (5 mg/kg i.p.), but not high-dose 7, 8-DHF (10 mg/kg i.p.) can exert strong anti-epileptogenic effects in the rat lithium-pilocarpine model. We observed highly significant reduction in the frequency of spontaneous seizures and in the time to first seizure after status epilepticus (SE). Animals treated with low dose of 7, 8-DHF also showed an attenuation of epileptic cognitive co-morbidities. These different effects appear to correlate with differences in TrkB phosphorylation patterns and activation of specific TrkB-dependent signalling pathways. We are now investigating 7, 8-DHF and another TrkB receptor agonist, LM22A-4, as putative anti-epileptic drugs. Therefore, we are testing them in the rat pilocarpine model and in human mesial temporal lobe epilepsy (mTLE) tissue surgically resected from drug-resistant patients. The animal study provides information on efficacy against seizures, epilepsy-associated comorbidities and induced pathological traits (such as hippocampal sclerosis and gliosis), as well as on the safety of these drugs. Electrophysiological recordings on both rodent and human hippocampal slices aim to determine if 7, 8-DHF and LM22A-4 can enhance GABAergic function and control hyperexcitability, as we have previously shown for BDNF. This unique combination of in vivo and ex vivo preclinical data with ex vivo human data will set the ground for future translational and clinical studies. In fact, 7, 8-DHF, a flavonoid with antioxidant effects found in several plants, is already approved as a diet integrator in several countries.

Disclosures: A. Guarino: None. **M. Soukupova:** None. **B. Bettegazzi:** None. **L. Crippa:** None. **S. Zucchini:** None. **G. Ruffolo:** None. **E. Palma:** None. **M. Simonato:** None.

Poster

PSTR056: Anticonvulsant and Antiepileptic Therapies

Location: MCP Hall A

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Program #/Poster #: PSTR056.05/B15

Topic: B.08. Epilepsy

Title: Ncc-3490 ia a unique persistent sodium current blocker with potent antiepileptic activities and favorable safety properties

Authors: *O. NOZAWA[1], T. NANYA[1], Y. SHIMAZAWA[1], T. NOMURA[1], M. NIWA[2], Y. KONDO[2], J. KAMON[1];
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Abstract: Background/ It is widely known that enhanced persistent sodium currents are involved in the pathogenesis of epilepsy, while inhibition of peak sodium currents has been associated with adverse effects of standard antiepileptic drugs. To deal with these limitations, we evaluate the efficacy and tolerability of NCC-3490, a pharmacological inhibitor that we originally developed to preferentially target persistent sodium currents. **Methods/** The anti-convulsant efficacy of NCC-3490 was evaluated in the mouse maximal electroshock seizure (MES) model, rat MES model, mouse 6 Hz seizure model, and mouse corneal kindling model. Motor impairment was assessed in rota-rod test. Therapeutic index (TI) was defined as the ratio of the plasma concentration in Rota-rod test to MES model. Ames tests and 3T3 NRU tests were conducted for the genotoxicity and phototoxicity of NCC-3490. Arrhythmogenic effect of NCC-3490 was assessed in canine model. **Results/** In acute seizure models, orally administered NCC-3490 showed dose-dependent seizure protection (mouse/rat MES: ED_{50} = 5 mg/kg, mouse 6Hz: ED_{50} = 5 mg/kg). In the corneal kindling model, ED_{50} value of NCC-3490 was 23 mg/kg. TI of NCC-3490 was 19.1, while standard drug carbamazepine and lamotrigine was 5.2 and 10.6, respectively. Genotoxicities and phototoxicities of NCC-3490 were negative, and there were no concerns regarding the proarrhythmic effects and cardiovascular system of NCC-3490. **Conclusions/** These studies demonstrated that NCC-3490 exhibits a wide safety margin compared to standard antiepileptic drugs, and favorable preclinical safety profile. NCC-3490 could be a promising candidate to provide new treatment for epilepsy with pathogenic persistent sodium currents.

Disclosures: O. Nozawa: A. Employment/Salary (full or part-time):; Nissan Chemical Corporation. **T. Nanya:** A. Employment/Salary (full or part-time):; Nissan Chemical Corporation. **Y. Shimazawa:** A. Employment/Salary (full or part-time):; Nissan Chemical Corporation. **T. Nomura:** A. Employment/Salary (full or part-time):; Nissan Chemical Corporation. **M. Niwa:** A. Employment/Salary (full or part-time):; Nissan Chemical Corporation. **Y. Kondo:** A. Employment/Salary (full or part-time):; Nissan Chemical Corporation. **J. Kamon:** A. Employment/Salary (full or part-time):; Nissan Chemical Corporation.

Poster

PSTR056: Anticonvulsant and Antiepileptic Therapies

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR056.06/B16

Topic: B.08. Epilepsy

Title: Polyunsaturated fatty acids-enriched oil composite reduces epileptic seizures in an acute zebrafish larvae (Danio rerio) model of epilepsy

Authors: *A. KUMAR[1,2], S. K. SAINI[3], D. SINGH[4];
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Academy of Scientific and Innovative Research (AcSIR),, Ghaziabad-201002, India; [3]Pharmacol. and Toxicology Lab., Dietetics and Nutr. Technol. Div., CSIR- Inst. of Himalayan Bioresource Technol., Palampur 176061, Himachal Pradesh, India Acad. of Scientific and Innovative Res. (AcSIR),, Ghaziabad-201002, India; [4]Pharmacol. and Toxicology Lab., Dietetics and Nutr. Technol. Div., CSIR- Inst. of Himalayan Bioresource Technol., Palampur 176061, Himachal Pradesh, Palampur, India

Abstract: Epilepsy is a severe brain disorder that affects ~70 million of individuals worldwide (Li *et al*., 2024), with the highest risk seen in infants and older age groups. The pathophysiological link to epileptic seizures is multifaceted and strongly associated with genetic predisposition. Lipids and fatty acids play crucial roles in neuronal structure and function, particularly in neurotransmission and membrane composition during developmental stages. Essential fatty acids, including plant-based polyunsaturated fatty acids (PUFAs) like omega-3 fatty acids, are vital for maintaining the integrity of the blood-brain barrier (BBB) and preventing epileptogenesis. The current study aimed to explore the antiepileptic mechanism of a plant-based oil extract (ω-3) (a mixture majorly containing omega-3 fatty acids) in a Pentylenetetrazol (PTZ) acute seizure model using zebrafish larvae. Results revealed that 15 minutes' exposure of PTZ increased the locomotion and velocity of larvae in the diseased group (epi^{+}/epl^{+}) compared to the normal control (epi^{-}/epl^{-}) on the 7th day post-fertilization (*dpf*). Embryonic exposure of the oil extract ω-3 (ω*-3/epl*$^{+}$) for 7 *dpf* decreased PTZ-mediated hyperactivity and velocity, and also increased the latency to clonus-like seizure compared to the epi^{+}/epl^{+} group. Moreover, gene expression of *c-fos* as a marker for neuronal activity was found to be increased in the epi^{+}/epl^{+} group, while the ω*-3/epl*$^{+}$ group showed a significant reduction in *c-fos* gene expression. Similar trends were observed in the protein expression of c-Fos using whole-mount larvae protein expression, quantified by confocal microscopy. The pretreated group ω*-3/epl*$^{+}$ exhibited a significant reduction in *c-fos* gene and protein expression, maintaining BBB integrity by upregulating the gene expression of *mfsd2aa* and normalizing the gene expression of *ntrk2b*. Additionally, a significant increase in gene expression of *bdnf,* and $GABA_A$ subunits *gabrg2, gabrd* was found in ω*-3/epl*$^{+}$ as compared to the epi^{+}/epl^{+} group. The oil extract (ω-3) possibly interacts with *mfsd2aa, c-fos, gabrg2, gabrd, bdnf,* and *ntrk2b* genes. These findings indicate that the oil has the potential to regulate multiple pathways involved in controlling seizures, thereby offering therapeutic advantages in the management of epilepsy.

Disclosures: A. Kumar: None. **S.K. Saini:** None. **D. Singh:** None.

Poster

PSTR056: Anticonvulsant and Antiepileptic Therapies

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR056.07/B17

Topic: B.08. Epilepsy

Support: NIH Grant R01NS100947

Title: Siglec-E is required for the generation of seizures

Authors: *N. YASMEN, M. RAKIB, Y. YU, J. JIANG;
Pharmaceut. Sci., Univ. of Tennessee Hlth. Sci. Ctr., Memphis, TN

Abstract: As a key immunosuppressive molecule, the sialic acid-binding immunoglobulin-like lectin E (Siglec-E) functions to regulate immune cell signals via interacting with sialic acids, particularly the $\alpha_{2,8}$-linked disialyl glycans. This interaction causes activation of the intracellular immunoreceptor tyrosine-based inhibitory motif (ITIM) of Siglec-E, which inhibits subsequent cellular activation signals. Siglec-E is expressed in mice, while its functional ortholog in humans is named Siglec-9. Siglec-E is mostly found in myeloid cells, dendritic cells, and brain microglia. Previous studies reveal that Siglec-E in the CNS might be involved in the regulation of neurotoxicity, brain inflammation, and neuronal excitability. However, the role of Siglec-E in neurological disorders largely remains elusive. Herein, we utilized several well-characterized animal seizure models to determine the contributions of Siglec-E signaling to acute seizures. These animal models are recommended by the NIH/NINDS Epilepsy Therapy Screening Program (ETSP) and include models of generalized seizures induced by chemoconvulsants, such as pentylenetetrazole (PTZ), flurothyl, kainic acid, and pilocarpine, as well as a model of focal seizures triggered by the 6 Hz electrical stimulation. Electroencephalography (EEG) was utilized to monitor the electrographic seizures and validate the behavioral seizures. We first observed that genetic deletion of Siglec-E in mice (Siglec-$E^{-/-}$) increased the latencies to both myoclonic jerks (MJ) and generalized tonic-clonic seizures (GTCS) after administration of flurothyl or PTZ when compared to wild-type control mice. Surface EEG recording also revealed an increase in latency to electrographic seizures among Siglec-$E^{-/-}$ mice. In line with these findings, mice lacking Siglec-E generally showed less severe behavioral seizures (intensity and duration) than control animals after treatment with kainic acid or pilocarpine. Moreover, in the 6 Hz electrical stimulation test, Siglec-E knock-out mice demonstrated substantially lower behavioral seizure scores than the wild-type littermates. Importantly, the reduced seizure susceptibility observed in Siglec-$E^{-/-}$ mice appears highly consistent across different seizure models and thus is unlikely contingent on a specific model. Together, our findings support an important role of Siglec-E in setting seizure thresholds and generating acute seizures. Therefore, inhibition of Siglec-E-mediated signaling might represent a novel therapeutic strategy to manage seizures.

Disclosures: N. Yasmen: None. **M. Rakib:** None. **Y. Yu:** None. **J. Jiang:** None.

Poster

PSTR056: Anticonvulsant and Antiepileptic Therapies

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR056.08/B18

Topic: B.08. Epilepsy

Title: The gabaergic effects of ethanolic extract of synedrella nodiflora (asteraceae) in modulating seizure intensities.

Authors: *V. ABOAGYE, T. TAGOE;
Physiol., Univ. of Ghana, Accra, Ghana

Abstract: Introduction: Seizure is a neurological disorder which manifests as abnormal cortical nerve cell activity. This is predisposed by synchronous neuronal activity in the brain with some effects manifesting as uncontrolled jerky movements involving much of the body with loss of consciousness. Treatment of this neurological condition has also been linked to drug resistance and side effects. This has fueled the need to identify new compounds with properties which can be developed into drugs. Compounds from plant extracts such as *Synedrella nodiflora* (SNE) have previously been shown to exhibit anti-convulsive properties, making them worthy of further investigations. The aim of this study therefore is to explore the potential pathways with which the extract mediates via in decreasing seizure intensities. Methods: The anti-convulsant effect of ethanolic extract of *Synedrella nodiflora* was investigated using two animal seizure models; Acute Pentylenetetrazole (PTZ) and Chronic PTZ. Liver and Renal function test was assessed after Chronic PTZ induced seizures. Brain tissues were resected for histological studies. Flumazenil, a GABA receptor blocker was used to determine whether the extract reduce seizures via the GABAergic pathway. Results: SNE (1000 mg/kg/body weight) reduced PTZ induced kindling significantly (∗∗∗$P<0.05$). Also, SNE (100, 300, 1000 mg/kg/body weight) reduced the latency and frequency of acute PTZ induced seizures. SNE treated mice Hippocampal histology revealed normal neuronal cell count compared to control. There were no significant differences observed in serum determinants for Renal and Hepatic Function test and lastly SNE had no significant effect after the mice were pretreated with Flumazenil (GABA receptor Blocker). Conclusion: The result of this study provides evidence that the ethanolic extract of the whole plant of *S. nodiflora* possesses anti-seizure activity and mediates possibly through GABAergic pathway in murine experimental models.

Disclosures: V. Aboagye: None. **T. Tagoe:** None.

Poster

PSTR056: Anticonvulsant and Antiepileptic Therapies

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR056.09/B19

Topic: B.08. Epilepsy

Support: The Health and Medical Research Fund (HMRF), Food and Health Bureau, Hong Kong Special Administrative Region Government (Ref. No.: 08193956).

Title: Low-frequency deep brain stimulation attenuates epileptic seizure and restores neural firing in two mouse models of epilepsy.

Authors: *S. CHAN, V. CHU, G. KUMAR, C. H. MA;
Neurosci., City Univ. of Hong Kong, Kowloon Tong, Hong Kong

Abstract: Epilepsy, characterized by abnormal activity of excitatory and inhibitory neurons, affects over 50 million people globally with 1/3 of patients ultimately developing drug resistance epilepsy (DRE). Deep brain stimulation (DBS) of the anterior thalamic nucleus is often prescribed to DRE patients, with depression and memory impairment as common side effects. Our previous findings showed efficacy of the novel DBS target, located in the midbrain with stimulation parameters of 60Hz, 100μA, 80μs in the acute mouse model of pentylenetetrazol (PTZ)-induced epilepsy (single dose of 60mg/kg, i.p.). To evaluate long-term efficacy of novel DBS target with optimized DBS parameters, we performed 21-day DBS on chronic mouse model of PTZ-induced epilepsy (35 mg/kg, i.p.). Video behavioral analysis revealed latency of myoclonic jerks increased, and duration of clonic seizure and generalized tonic-clonic seizure decreased by 67% and 80%, respectively. Cortical electroencephalogram (EEG) power spectral analysis (PSA) revealed novel DBS target can suppress PTZ-induced hyperactivity in delta (1-4Hz) and theta (4-8Hz) range. Local field potential (LFP) PSA of the target region also shows DBS efficacy in modulating the PTZ-induced hyperactivity. Investigation of molecular mechanisms involved in epileptogenesis of PTZ-induced epilepsy revealed expression levels of immediate early gene (IEG) and epilepsy-associated gene such as c-Fos, FosB and Erg1, Gad67, vGLut1, Crocc and Mapt were altered and DBS treatment can restore control levels of IEG expression. Immunohistochemical staining revealed PTZ reduces fluorescent intensity of vGLUT1 and GAD67 by 30.2% and 31.1% respectively. But DBS can restore control levels of fluorescent intensity. To validate the novel DBS target in a mouse model of temporal lope epilepsy, a chronic model of kainic acid (KA)-induced epilepsy was used. DBS significantly reduced the duration of tonic-clonic seizures and episodes of neck jerking by 50%. EEG PSA showed DBS can modulate KA-induced hyperactivities in delta, theta, alpha (8-13Hz) and beta (13-30Hz) bands EEGs, returning to control levels by day 21 post-KA injection. LFP PSA showed similar beneficial effects. Immunohistochemical staining results shows KA-induced epilepsy results in the loss of vGLUT1 and GAD67 by 43.8% and 37.5% respectively. But DBS can return the fluorescent intensity back to control levels. In summary, our study demonstrates the therapeutic efficacy of low-frequency DBS at novel DBS site in chronic models of drug-induced epilepsy. Further studies will be conducted to decipher the molecular mechanisms that orchestrate the epileptogenesis and development of DRE.

Disclosures: S. Chan: None. **V. Chu:** None. **G. Kumar:** None. **C.H. Ma:** None.

Poster

PSTR056: Anticonvulsant and Antiepileptic Therapies

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR056.10/B20

Topic: B.08. Epilepsy

Support: Collaborative Research Program 2023-2025

Title: Antimicrobial, antiproliferative, and potential anticonvulsive properties of Artemisia root extracts from Kazakhstan

Authors: *A. TROFIMOV[1], *A. TROFIMOV[2], O. KARAPINA[1], B. SAILIKE[1], Y. YERMAGAMBETOV[1], G. MAMYTBEKOVA[3], D. BIRIMZHANOVA[3], Y. SULEIMEN[3], B. AKBAY[1], T. TOKAY[1];
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Abstract: This pilot study evaluates the antimicrobial, cytotoxic, and antiproliferative capabilities of root extracts from *Artemisia glauca* (AG) and *Artemisia vulgaris* (AV), which were harvested in Kazakhstan's Akmola region, for their potential use in epilepsy treatment. Given the resistance of many epilepsy forms to drugs, there's a critical demand for new alternatives that can mitigate neuroinflammatory responses, minimize oxidative stress, and improve GABAergic transmission. We hypothesize that the extensive pharmacological properties of these *Artemisia* species might help diminish brain susceptibility to seizures. The extracts' neuro- and cytotoxic effects were tested by observing their impact on brine shrimp (*Artemia salina*). Antimicrobial activity was determined by exposing clinical strains of *Escherichia coli*, *Staphylococcus aureus*, *Serratia marcescens*, *Candida albicans*, and *Aspergillus flavus* to the extracts. The antiproliferative effects were assessed using the alamarBlue cell viability reagent *in vitro*. The evaluation of antiepileptic properties began with the development of a chronic seizure model in 8 w.o. CD-1 mice (30 males and 30 females), involving a series of i.p. injections of pentylenetetrazole (PTZ) (5 x 40 mg/kg/day every other day + 1 x 60 mg/kg), followed by behavioral assessments in the Open Field (1 x 30 min), Elevated Zero-Maze (1 x 5 min), and Barnes maze (6 training days, 2 trials per day, inter-trial 90 min; 1 probe test 90 s) tests. The AV root ethanol extract shows low cytotoxicity and lacks neurotoxicity, while the extract from AG displays both cytotoxic and neurotoxic properties. The antimicrobial assessment indicates potential activity against numerous clinical strains for both extracts. Cell viability assays demonstrate that both AG and AV extracts induce a dose-dependent decrease in the proliferation of astroglial and astroglioma cells. In behavioral tests involving adult mice, i.p. injections of the AV extract (50 to 500 mg/kg) administered 30 minutes before PTZ injections had no impact on seizure measures, as scored by Racine's scale, nor did the positive control (naringin, 80 mg/kg/day). With no observed delayed behavioral effects, our future research will modify the seizure model by increasing the number of lower-dose PTZ injections to achieve chronic seizures and better determine the antiepileptic potential of these extracts.

Disclosures: A. Trofimov: None. **A. Trofimov:** None. **O. Karapina:** None. **B. Sailike:** None. **Y. Yermagambetov:** None. **G. Mamytbekova:** None. **D. Birimzhanova:** None. **Y. Suleimen:** None. **B. Akbay:** None. **T. Tokay:** None.

Poster

PSTR056: Anticonvulsant and Antiepileptic Therapies

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR056.11/B21

Topic: B.08. Epilepsy

Support: SIP 20231827

Title: Assessment of anticonvulsant and antiepileptic effect of DL-3-hydroxy-3-phenyl-3-propionamide with window-pentylenetetrazole kindling method in rats.

Authors: *J. PACHECO-ROSADO[1], B. VASQUEZ MOLINA[2], L. VALDES LUIS[2], S. E. MEZA TOLEDO[3];
[1]Fisiología, Inst. Politécnico Nacional, Ciudad de Mexico, Mexico; [2]Fisiología, Inst. Politécnico Nacional, Ciudad de México, Mexico; [3]Bioquímica, Inst. Politécnico Nacional, Esc.Nac.Cien.Biol, Ciudad DE Mexico, Mexico

Abstract: Currently, several drugs are used for the treatment of epilepsy; however, about30% of patients show resistance to existing drugs. In the present work, weinvestigated the anticonvulsant and antiepileptic activity of the HEPP molecule (DL-3-hydroxy-3-phenyl-3-propionamide), a phenyl alcoholamide that is a metabotropicGABAB receptor antagonist and protective against absence seizures. To induceseizures, we used the novel window pentylenetetrazole (win-PTZ) kindling model.Male Wistar rats (250-320 g) were used. To analyze the anticonvulsant effect, PTZ(35 mg/kg, ip) was administered on days 1, 3, 5, 7, 27, and 29. On day 29, HEPP(50 mg/kg, ip) was administered 30 min before PTZ. To evaluate the antiepilepticeffect, three groups of rats were formed: control, AE1, and AE2. Seizures wereinduced by administration of PTZ according to the previously described protocol inall three groups. In addition, the AE1 group was administered HEPP (50 mg/kg, ip)30 min before PTZ administration, while the AE2 group was administered HEPP 30min after PTZ administration. In both experiments, the latency, duration, andmaximum phase of seizures classified by the modified Racine scale weremeasured. The results show that in both anticonvulsant and antiepileptic protocols,the administration of HEPP increased the latency time and decreased the intensityand duration of seizures, so we can conclude that the HEPP molecule hasanticonvulsant and antiepileptic effect against the window-PTZ kindling model.

Disclosures: J. Pacheco-Rosado: None. **B. Vasquez Molina:** None. **L. Valdes Luis:** None. **S.E. Meza Toledo:** None.

Poster

PSTR056: Anticonvulsant and Antiepileptic Therapies

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR056.12/

Topic: B.08. Epilepsy

Title: Cholecystokinin 2 receptor antagonists alleviate drug resistant epilepsy in animal models

Authors: *A. WARIS;
Biomed. Sci., City Univ. of Hong Kong, Kowloon Tong, Hong Kong

Abstract: <Epilepsy is the most common, chronic, and severe neurological disease that affects more than 70 million individuals globally. Despite the pharmacological armamentarium and plethora of drugs in the market and other treatment options, 30-35% of individuals still show resistance to the current medication, termed drug resistance epilepsy (DRE), which contributes to 50% of the mortalities due to epilepsy. Therefore, there is still a need for effective drugs that have better effects on DRE and fewer side effects. We previously found that cholecystokinin (CCK) plays a significant role in the initiation and propagation of epilepsy. This study was designed to investigate the effect of YF476, which is a CCK 2 receptor antagonist, on the intensity, severity, and attenuation of seizures in DRE animal models. We first developed a strategy for the development of the DRE mice model and achieved a 50% success rate. These DRE mice were then treated with various doses of YF476, and the number, intensity, severity, stages, and other behaviors of the mice were compared with baseline and control groups. We found that YF476 decreased the average number of seizures per week, intensity of seizures, and behavior of DRE mice. Overall, we concluded that CCK plays a significant role in epilepsy, and YF476 is a potential pharmacological agent that leads to the alleviation of DRE in mouse models.>

Disclosures: A. Waris: None.

Poster

PSTR056: Anticonvulsant and Antiepileptic Therapies

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR056.13/B22

Topic: B.08. Epilepsy

Support: CONAHCyT grant A3-S-26782 (scholarship 1009939)
HempMeds Mexico SA de CV

Title: Gabaergic antiseizure medications combined with cannabidiol reduce the induction of drug resistance seizures in a rat model.

Authors: *M. FUENTES MEJIA[1], S. OROZCO-SUAREZ[2], L. L. ROCHA[3];
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Abstract: Drug resistance affects 30% of patients with epilepsy. Cannabidiol (CBD) decreases the expression of drug-resistant seizures in specific syndromes. However, it is unknown if CBD prevents the development of the drug-resistant condition in epilepsy. This study was designed to investigate if the repetitive administration of CBD alone or in combination with GABAergic antiseizure medications (ASMs: phenobarbital (PB) or diazepam (DZP)), prevents the development of drug resistant seizures (DRS). Male Wistar rats (250-300 g) were used. The animals received one of the following treatments (n=10 per treatment): CBD+PB; CBD+DZP;

DZP; PB; CBD; VHE. The doses and route of administration of the drugs were as follows: CBD (200 mg/kg p.o.), DZP (1 mg/kg i.m.), PB (11 mg/kg i.p.) and VHE (coconut oil, 9.52 ml/kg p.o.). After the treatment (DZP, 2 h; PB, 1 h; CBD, 1 h), the animals received the administration of 3-mercaptopropionic acid (MP, 30 mg/kg i.p.) and the severity of seizures was estimated for 30 minutes. The procedure was repeated every 12 hours for 10 trials. Twelve hours after the last trial, the animals received an administration of DZP or PB and then submitted to MP (37.5 mg/kg, i.p.). Rats were classified as resistant if they presented severe seizures or responsive if they did not present seizures. Animals receiving VHE developed drug-resistant seizures to DZP (100%) and PB (70%). All rats receiving the repetitive administration of CBD developed resistance to DZP (100%, p=0.9 vs VHE treatment). However, these animals showed lower resistance to PB (20%, p=0.034 vs VHE treatment). Sixty percentage of animals receiving repetitive DZP alone developed drug-resistant seizures to this drug (p=0.251 vs VHE treatment). However, the repetitive administration of DZP combined with CBD reduced the prevalence of animals resistant to DZP (10%, p=0.005 vs VHE treatment; p= 0.028 vs DZP treatment). Sixty percentage of rats receiving repetitive PB developed resistance to this drug (p=0.198 vs VHE treatment). In contrast, PB combined with CBD avoided the resistance to PB (0%, p=0.003 vs VHE treatment; p=0.003 vs PB treatment). Our results indicate that the subchronic administration of CBD, DZP or PB alone does not prevent the drug resistant condition induced by the repetitive induction of severe seizures. However, the drug resistant condition is avoided when the subchronic administration of GABAergic ASMs is combined with CBD. The present study supports that CBD associated with GABAergic ASMs can be used in syndromes with severe generalized seizures to prevent the development of the drug resistant condition. Further combinations of CBD with ASMs should be investigated.

Disclosures: M. Fuentes Mejia: None. **S. Orozco-Suarez:** None. **L.L. Rocha:** None.

Poster

PSTR056: Anticonvulsant and Antiepileptic Therapies

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR056.14/Web Only

Topic: B.08. Epilepsy

Support: Section of Postgraduated Studies and Research, Academic Secretary of National polytechnic Institute, México

Title: Effect of nitric oxide on glutamic acid decarboxylase activity, an in vivo study

Authors: *L. A. VEGA RASGADO;
BIOQUIMICA, ESCUELA NACIONAL DE CIENCIAS Biológicas, Inst., CDMX, Mexico

Abstract: Effect of nitric oxide on glutamic acid decarboxylase activity, an in vivo study
Author:L.A. VEGA RASGADO; Lab. Neuroquímica, Depto. Bioquímica, Escuela Nacional de Ciencias Biológicas del Instituto Politécnico Nacional

Disclosures
L.A. Vega: None
Abstract
Nitric oxide (NO) is a neurotransmitter/neuromodulator synthesized in a reaction catalyzed by Nitric Oxide Synthase (NOS), enzyme which presents 3 different isoforms: endothelial (e-NOS), neuronal (n-NOS) and inducible (i-NOS). NO participation in epilepsy is widely demonstrated, but its role in epileptogenesis is still a matter of controversy, with reports showing either pro or anticonvulsant effects. Previous results lead us to propose that a possible explanation of these paradoxical properties could be on the NOS isoform involved and their effects on glutamic acid decarboxylase (DAG), a key enzyme on glutamate and/or gamma aminobutyric acid (GABA). Results of an in vitro study suggest that NO convulsant or anticonvulsant properties are related to its effect on GAD activity, which depend on isoform involved, concentration and time of treatment. To continue exploring this hypothesis the effects of the administration of different doses of Nω-Nitro-L-arginine (L-NAME), 7-Nitroindazole (7-NI) and S-methylisothiourea hemisulfate (SMT), specific inhibitors of eNOS, nNOS and iNOS respectively, on GAD activity from mouse brain (CD1 strain, 20-25 g of body mass) were investigated. With this aim a spectrophotometric method described by Sasaki et al (Eur. J. Pharmacol. 367, 165–173, 1999) was employed. Experiments were conducted accordingly with the Helsinki Guide for Laboratory animals (Results $\pm$ SEM, $n \geq 4$, $p < 0.05$). L-NAME increased GAD activity with a peak at the doses 40 mg/kg, however doses higher than 60 mg/Kg decreased it. In contrast, all doses of 7-NI decreased GAD activity between 30 and 40%. SMT also has a biphasic effect on GAD activity, with two valleys at 2.5 and 10 mg/kg and two peaks at 5 and 15 mg/kg. Together, results suggest that NO convulsant or anticonvulsant properties are related to its effect on GAD activity, which depend on isoform involved. Apparently, in vivo eNO seems to present anticonvulsant properties, whereas nNO and iNO have proconvulsant effects. These results contribute to understand the role of NO in epileptogenesis and represent a base to the development of new antiepileptic drugs.

Disclosures: L.A. Vega rasgado: None.

Poster

PSTR056: Anticonvulsant and Antiepileptic Therapies

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR056.15/B23

Topic: B.08. Epilepsy

Support: 13381-ksu-2023-KSU-R-3-1-HW-

Title: Tiagabine and Brivaracetam Combination Therapy Shows Promising Antiepileptogenic and Neuroprotective Effects in kainic acid model of Epilepsy

Authors: *F. ALQAHTANI;
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Abstract: Tiagabine and Brivaracetam Combination Therapy Shows Promising Antiepileptogenic andNeuroprotective Effects in kainic acid model of EpilepsyAbstractBackground: The kainic acid-induced status epilepticus is a well-known model of temporal lobeepilepsy. The present study explored a multitargeted approach to prevent epileptogenesis bycombining low doses of tiagabine (TGB) and brivaracetam (BRV) in kainic acid model of epilepsy.**Methods:** The BALB/c mice were intrahippocampally administered with kainic acid followed bytreatment with TGB (3.5 mg/kg) and BRV (35 mg/kg) and their combination for 6 days starting 6h after kainate injection and monitored for incidence of electrographic changes at 4th and12th weeks. The mice were tested for anxiety and cognitive deficit in an array of behavioralexperiments followed by real-time PCR and histopathological studies of isolated brains.**Results:** The intrahippocampal kainate administration led to epileptogenesis as mice had frequentelectrographic alterations which were accompanied by post-kainate anxiety and cognitiveimpairment. The isolated brains showed marked neuronal degeneration in hippocampi andoverexpression of apoptotic and inflammatory markers in the cortex and hippocampus. Thetreatment with TGB + BRV worked superior to mono-therapy, as mice were markedly protectedfrom hippocampal paroxysmal discharges and high-voltage sharp waves. The cocktail effectivelymitigated the TLE-associated anxiety-like behavior and cognitive deficit as mice preferredexposed and elevated zones in OFT and EPM and remembered the familiar places and objects inT-maze and NOR tests. Mice treated with TGB + BRV had increased neuronal counts ($P<0.05$) instained hippocampi, and upregulated apoptotic and inflammatory markers weremarkedly alleviated ($P< 0.05$).**Conclusion:** The findings support the use of a combination of TGB and BRV in the kainic acidmodel, which incredibly mitigated ictal events, reduced anxiety, retained cognition, and preventedneuronal degeneration in 14 weeks post-kainate insult.

Disclosures: F. Alqahtani: None.

Poster

PSTR056: Anticonvulsant and Antiepileptic Therapies

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR056.16/B24

Topic: B.08. Epilepsy

Support: PRIN 2009 2009HST9YF (Italian Ministry of University) (A.L.M.)
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PRIN PNRR 2022 P202224ZTX (C.S.)
PRIN 2022 2022WH9MEF (C.S.)
Fellowship 2017 from Fondazione Veronesi Milano to C.S.

Title: Age and sex difference in cannabidiol efficacy to mitigate acutely induced epileptic seizures in a mouse model

Authors: *C. SAGHEDDU[1], M. PISTIS[1], A. MUNTONI[2], M. MELIS[1];
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Abstract: Epileptic seizures affect up to 1% people worldwide. Several forms of epilepsy successfully respond to pharmacological compounds. However, about one-third of patients are drug-resistant to traditional therapies[1], whereas some patients develop long-term side conditions that lead to therapy discontinuation. Understanding individual clinical picture, as well as treatment success rate, represents an unmet medical need. Cannabis derivatives have been proposed against epilepsy, being cannabidiol (CBD) currently approved against severe forms[2]. CBD addresses multiple molecular targets[3], and side-effects following CBD-based therapies are also emerging[4], suggesting that further study is needed. In a preclinical model of acute epileptic seizure, we investigated the efficacy of CBD to mitigate clinical signs over different sex and age. We used young (<3 m/o) and old (>12 m/o) C57/Bl male and female mice. CBD 200 mg/kg, or vehicle as control, was ip administered 24, 12, and 2h before inducing seizures. According to our previous studies[5], seizures were acutely induced by 10 mg/kg sc injection of nicotine, and thereafter they were monitored for 5 min. Symptoms were scored by considering straub tail, tremors, tackypnea, back arching, rapid movements of the legs, wild running, loss of righting response, and clonic/tonic seizures. Number of jerks and latency to seizure onset were also recorded. In control animals, we found no difference in the epileptic score and in the number of jerks induced by nicotine. However, seizure latency was reduced in old females, suggesting an age*sex increased sensitivity. In young males, pretreatment with CBD significantly reduced the epileptic score and increased the seizure latency. In old females, CBD significantly reduced the epileptic score, the number of jerks, and increased the seizure latency. Altogether, our data show different sensitivity to acute epileptic seizures, and different efficacy of treatment with CBD, due to age and/or sex individual background. Further, we will characterize possible molecular mechanism underlying these conditions both singly and combined in an age*sex effect.[1]doi: 10.3389/fneur.2021.674483[2]doi: 10.1136/bmj.k2827[3]doi: 10.3390/molecules28073271[4]doi: 10.1001/jamanetworkopen.2023.9126[5]doi: 10.1111/epi.13863

Disclosures: C. Sagheddu: None. **M. Pistis:** None. **A. Muntoni:** None. **M. Melis:** None.

Poster

PSTR056: Anticonvulsant and Antiepileptic Therapies

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR056.17/B25

Topic: B.08. Epilepsy

Support: Forska Utan Djurförsök, 2023-0007

Title: High-capacity assessment of compound effects on modulating epileptiform local field potentials in human iPSC-brain cells

Authors: *N. JAISUPA[1], S. ILLES[1,2];
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Abstract: Human induced pluripotent stem cell (iPSC) brain models have emerged as invaluable tools in neuroscience research, particularly in the pharmaceutical industry. These models serve a dual purpose: to uncover potential epileptogenic effects of compounds on human brain function as part of neurotoxicty assessment and to evaluate the potency and efficacy of anti-seizure drugs (ASDs). While much emphasis has been placed on extracting spiking data from recorded extracellular signals, the significance of local field potentials (LFPs) in assessing drug effects remains underexplored.
Our study bridges this gap by investigating the impact of well-established anti-seizure drugs (ASDs) and novel compounds, such as cannabidiol, on human brain activity using functional iPSC-based brain cell platforms.
We demonstrate that analyzing LFPs alongside spiking activity provides valuable insights into compound potential mechanisms of action and their modulation of neuronal excitability, excitatory or inhibitory synaptic regulation. Furthermore, our findings shed light on distinct patterns of epileptiform activity induced by different commonly used epileptogenic conditions.
We introduce a validated assay designed to reveal potential epileptogenic adverse effects of compounds, providing a deeper understanding of newly developed anti-epileptic drugs and their impact on neuronal network dynamics.
Our human-brain cell functional assay offers significant implications for the pharmaceutical industry, facilitating lead optimization, pre-clinical risk assessment and the advancement of therapeutic interventions for epilepsy management.

Disclosures: N. Jaisupa: None. **S. Illes:** A. Employment/Salary (full or part-time):; Oscillution AB, Gothenburg, Sweden.

Poster

PSTR056: Anticonvulsant and Antiepileptic Therapies

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR056.18/B26

Topic: B.08. Epilepsy

Support: Future Neuro Grant: 22095A07

Title: Analysing the role of 5' tRF GluCTC in an iPSC-derived cortical neuronal model

Authors: *R. STEWART[1], H. DUSSMANN[2], J. H. PREHN[3];
[1]Physiol. and Med. Physics, Royal Col. of Surgeons in Ireland, Dublin, Ireland; [3]Dept. of Physiol. and Med. Physics, [2]Royal Col. of Surgeons In Ireland, Dublin, Ireland

Abstract: Temporal lobe epilepsy (TLE) is the most common form of focal epilepsy, affecting over 70 million people worldwide. There are currently no effective biomarkers for seizure prediction. In a recent study, 3 plasma tRNA fragments; 5’ GlyGCC, 5’ AlaTGC and 5’ GluCTC

were found to be upregulated in plasma samples of patients with focal epilepsy pre-seizure compared to post-seizure. In this study, we aim to perform a knockdown of 5' GluCTC expression in human iPSC-derived cortical neurons to analyse the effect of 5' GluCTC on RNA and protein expression. Furthermore, we seek to better understand how 'seizure-like' conditions affect the release of 5' tRFs from cortical neurons. h-iPSCs were differentiated into excitatory cortical neurons using dual SMAD inhibition with the small molecules SB431542 and LDN193189 over 100 days. Cortical neurons were characterised by immunocytochemistry, RT-qPCR analysis, and calcium imaging. Knockdown of 5' GluCTC was performed by treatment with custom designed Anti-Sense Oligonucleotides (ASOs) at 500nM for 24h for analysis by RNA sequencing and Mass Spectrometry. To determine the effect of 'seizure-like activity' on 5'tRF expression, neurons were treated with the seizure-inducing drugs; bicuculine, kainic acid and 0mg+. 5'tRF expression was measured by RT-qPCR using custom designed TaqMan primers with controls c.elegans miR-39-3p spike-in and U6. h-iPSC-derived cortical neurons were positive for cortical markers CTIP2 and SATB2, excitatory marker vGLUT1, and displayed spontaneous calcium transients using Fluo-4AM during calcium imaging. We found that the expression of 5' GluCTC and GlyGCC increased overtime as the cortical neurons matured in culture. Furthermore, we saw that treatment with these 'seizure-inducing' drugs caused a significant change in 5'tRF expression. Finally, RT-qPCR analysis revealed a successful knockdown of 5'GluCTC using our custom designed ASO. Our results confirm that release of these 5'TRF fragments are affected by 'seizure-like' activity in h-iPSC-derived cortical neurons, making them potential candidates for seizure biomarkers. Our RNA sequencing revealed that knockdown of 5' GluCTC had little effect on the transcriptome of cortical neurons between all 3 timepoints. Mass Spectrometry analysis is underway.

Disclosures: R. Stewart: None. **H. Dussmann:** None. **J.H. Prehn:** None.

Poster

PSTR056: Anticonvulsant and Antiepileptic Therapies

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR056.19/B27

Topic: B.08. Epilepsy

Title: The effect of deep brain stimulation on neurotransmitter systems in rodent models of epilepsy: A systematic review

Authors: *R. MATIN[1,2], K. ZHANG[5,1], C. GORODETSKY[3,2], F. VENETUCCI GOUVEIA[2], G. IBRAHIM[2,4,1];
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Abstract: Rationale. Approximately one-third of patients with epilepsy continue to experience debilitating seizures despite the best available medical treatments. Deep brain stimulation (DBS)

is a neuromodulation technique that involves surgically implanting electrodes to target deep brain regions and has been shown to influence neurotransmitter dynamics both locally and across networks. Despite promising clinical outcomes with DBS for refractory epilepsy, the specific mechanisms underlying its anti-seizure effects remain unclear, preventing the development of personalized treatments. Tightly controlled preclinical experiments in rodent models of epilepsy have provided valuable insight on the effects of DBS on neurotransmitter systems. Here, we conducted a systematic review to evaluate DBS in rodent models of epilepsy, synthesizing current knowledge to inform future studies. **Methods**. This systematic review was performed in accordance with PRISMA guidelines. A literature search was performed on PubMed MEDLINE (National Library of Medicine) database for original articles published in English using the following search terms: “epilepsy”, “DBS”, “deep brain stimulation”, “rat”, “mouse”. Following screening, a total of 33 articles were included for data extraction, focusing on the effects of DBS on neurotransmitter systems in rodent models of epilepsy. **Results**. The most targeted brain regions were the hippocampal formation (33% of studies), anterior thalamic nuclei (ANT) (18%), and amygdala (15%). The effects of DBS were studied most often on GABA (52% of studies), serotonin (5-HT)(15%), and adenosine (12%). DBS of the hippocampal formation was shown to have an inhibitory effect by increasing local GABA levels and the expression of GABAa receptors. Moreover, Hipp-DBS demonstrated enhanced anti-seizure effects when administered alongside GABAergic anti-seizure medications. When targeting the amygdala, DBS similarly augmented GABAergic signaling while also activating hippocampal 5-HT1A receptors. Additionally, the anti-seizure effects of ANT-DBS were associated with increased adenosinergic signaling, mediated by hippocampal adenosine A1 receptors. **Conclusions**. This review provides insight into the target-dependent effects of DBS on various neurotransmitter systems, highlighting specific modulatory effects that may underlie its ability to suppress seizures. Further studies investigating the interplay between DBS and neurotransmitters will guide efforts in optimizing stimulation parameters and target selection to improve seizure reduction and limit adverse effects.

Disclosures: R. Matin: None. **K. Zhang:** None. **C. Gorodetsky:** None. **F. Venetucci Gouveia:** None. **G. Ibrahim:** None.

Poster

PSTR056: Anticonvulsant and Antiepileptic Therapies

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR056.20/B28

Topic: B.08. Epilepsy

Support: CIRM Awards TRAN1-11611
CIRM Awards CLIN2-13355

Title: Establishing assays to support the development of inhibitory cell therapy, NRTX-1001, for drug-resistant mesial temporal lobe epilepsy (MTLE)

Authors: *G. SUBRAMANYAM[1], M. BERSHTEYN[1], Y. MAURY[1], J. SALVATIERRA[4,1], M. SEZAN[1,2], R. ZHOU[1,2], S. HAVLICEK[1], L. C. FUENTEALBA[3], P. HAMPEL[2], E. T. SEVILLA[3], M. B. PAREKH[5,1], S. KRIKS[1], A. BULFONE[3], C. A. PRIEST[6], C. NICHOLAS[2]; [1]Discovery Res., [2]Neurona Therapeut., South San Francisco, CA; [3]Neurona Therapeut., South San Francisco, CA, ; [4]Univ. of California, San Francisco Sch. of Med., San Francisco, CA, ; [5]Univ. Florida, South San Francisco, CA, ; [6]Neurona Therapeutics, Inc, South San Francisco, CA.

Abstract: Epilepsy, one of the most common neurological disorders, is characterized by hyperactive neuronal networks triggering seizure onset and propagation. With one-third of patients suffering from drug-resistant seizures, there is a significant unmet need for safe and effective therapeutic options. With this aim, we developed NRTX-1001 - an investigational cell therapy meant to provide a restorative alternative to resection or laser ablation surgeries that are destructive to brain tissue and can cause neurocognitive impairment. NRTX-1001 comprises post-mitotic medial ganglionic eminence-type pallial GABAergic interneurons (MGE-pIN), which persist long-term and significantly suppress mesiotemporal seizures and histopathology in a mouse model of drug-resistant MTLE (Bershteyn et al., 2023). Based on extensive preclinical safety and efficacy data, NRTX-1001 is currently being evaluated in a first-in-human phase I/II clinical trial for drug resistant MTLE (NCT05135091). To support the development of NRTX-1001, we established in vitro molecular and functional assays. Endogenous MGE-pINs are characterized by key functional properties, including their ability to migrate, secrete GABA, and regulate excitatory circuits. We performed single cell/nuclei RNA sequencing analyses, which demonstrated consistent derivation of highly pure MGE-pIN lots in vitro and maturation into SST- and PV-interneuron sub-lineages post-transplantation in vivo, with a transcriptional signature that is very similar to endogenous human MGE pallial interneurons. In vitro functional assays demonstrated that MGE-pINs secrete GABA and migrate. Furthermore, a seizure-in-a-dish co-culture model using multi electrode arrays (MEA) is being developed to assess the ability of the MGE-pINs to suppress network hyperexcitability. Preliminary results suggest that MGE-pINs modulate burst frequency, network activity, and synchrony of glutamatergic cultures. These data support the ongoing clinical investigation of NRTX-1001 and will help to elucidate interneuron cell therapy mechanism of action.

Disclosures: G. Subramanyam: A. Employment/Salary (full or part-time):; Neurona Therapeutics. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Neurona Therapeutics. **M. Bershteyn:** A. Employment/Salary (full or part-time):; Neurona Therapeutics. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Neurona Therapeutics. **Y. Maury:** A. Employment/Salary (full or part-time):; Neurona Therapeutics. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Neurona Therapeutics. **J. Salvatierra:** A. Employment/Salary (full or part-time):; Neurona Therapeutics. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Neurona Therapeutics. **M. Sezan:** A. Employment/Salary (full or part-time):; Neurona Therapeutics. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Neurona Therapeutics. **R. Zhou:** A. Employment/Salary (full or part-time):; Neurona Therapeutics. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent

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Poster

PSTR056: Anticonvulsant and Antiepileptic Therapies

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR056.21/B29

Topic: B.08. Epilepsy

Support: NIH Grant 5R25NS080687

Title: Development of novel inhibitors targeting Nav channels for Epilepsy treatment

Authors: *A. S. CRUZ CALDERÓN;
Chem., Univ. of Puerto Rico Río Piedras Campus, San Juan, Puerto Rico

Abstract: Title: Development of novel inhibitors targeting nav channels for epilepsy treatment

Authors*ANGÉLICA S. CRUZ-CALDERON[1], CORNELIS P. VLAAR[2]
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Puerto Rico; [2]University of Puerto Rico, Medical Sciences Campus, School of Pharmacy, San Juan, Puerto Rico.
AbstractBackground: Epilepsy is a disorder that affects the central nervous system and manifests as repeated seizures. Research has shown that numerous factors may induce this disorder including genetic mutations in ion channels. Voltage-gated sodium channels (VGSC) play a central role in the generation and propagation of action potentials. Limitations in current drug treatments due to long-term adverse effects and drug-resistant epilepsy highlight the necessity for novel therapies. Channelopathies resulting from mutations in VGSC, especially the α subunit of Nav 1.1, have been identified in patients with epilepsy. Rufinamide is an antiepileptic drug that has been FDA-approved in 2008 as an adjunctive treatment for seizures associated with Lennox-Gastaut syndrome. It is suggested to act by modulation of the sodium channels. Objective: The aim of this study is to design and synthesize novel derivatives of Rufinamide with improved anti-epileptic activities via selective Nav 1.1 channel inhibition. Methods: Site-specific docking with modeling software AutoDock Vina predicted that replacement of the difluorophenyl group of Rufinamide (binding energy of -6.3 kcal/mol) with bioisosteric indole, benzothiazole, imidazole, benzimidazole, and pyrazole groups (-7.5 kcal/mol) increased binding affinity to the VGSC Nav 1.1. Results: Novel indole, benzothiazole, imidazole, benzimidazole, and pyrazole rufinamide derivatives were synthesized via azide formation and subsequent copper-catalyzed click reaction to form the critical 1,2,3-triazole. The products were purified via Combiflash chromatography and analyzed with ^{1}H and ^{13}C NMR spectroscopy. Conclusion: Molecular modeling was used to propose new rufinamide derivatives with predicted increased activity. Further research is needed to test the anticonvulsant activity of the novel compounds and evaluate their modulation of VGSC Nav 1.1.

Disclosures: A.S. Cruz Calderón: None.

Poster

PSTR056: Anticonvulsant and Antiepileptic Therapies

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR056.22/B30

Topic: B.08. Epilepsy

Title: Sensorium's Natural Compound product engine generates novel drug discovery program for Epilepsy and Anxiety

Authors: *G. DAIGLE[1], J. M. BROWN[2];
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Abstract: CNS drug discovery is burdened with high failure rates and a lack of innovative approaches. To overcome these challenges, Sensorium has built a robust drug discovery platform which leverages the intersection of natural compounds, human exposure, Machine learning, and *in vivo* pharmacology to discover novel therapeutics. The Sensorium platform identifies natural compound starting points with novel chemical backbones and favorable CNS-drug properties.

Validation of the platform was achieved with nominating a drug discovery program focused on Anxiety and Epilepsy. Mood disorders such as Anxiety and depression are present in ~30% of patients with epilepsy. Effective treatments that can address both neuropsychiatric and anticonvulsant aspects of adult Focal onset seizures is of high unmet medical need. Data presented highlights the capabilities of our discovery platform with a focus on generating a differentiated CNS program targeting Epilepsy with Anxiety comorbidities

Disclosures: G. Daigle: None. **J.M. Brown:** None.

Poster

PSTR056: Anticonvulsant and Antiepileptic Therapies

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR056.23/B31

Topic: B.08. Epilepsy

Title: Towards clinical translation of optogenetic seizure inhibition

Authors: E. SWISSA[1], K. L. BAR-OR[1], C. R. AUERBACH-ASCH[1], *Y. KFIR[1], O. YIZHAR[2], O. LEVI[1], **Y. ELDAR**[1];
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Abstract: One-third of epilepsy patients are resistant to treatment with anti-seizure medications and live with drug-resistant epilepsy (DRE), a condition associated with increased mortality, cognitive deficits, and impaired quality of life. Although surgical options exist, many patients are not candidates for resection due to poorly localized focal epilepsy or seizures arising from eloquent cortex areas. A small fraction of patients are treated by electrical neurostimulation approaches, which are invasive, non-specific, and only partially effective. There is an urgent need for new treatments for DRE. We are developing a novel platform for precise and minimally invasive neuromodulation to treat DRE using optogenetic inhibition. Our approach leverages eOPN3, a Gi/o-coupled rhodopsin with unique ultrasensitive and red-shifted properties capable of robustly inhibiting both somatic activity and synaptic vesicle release. Due to its unique properties, eOPN3 overcomes many of the challenges associated with translating optogenetics to the clinic to treat neurological disorders characterized by hyperactivity. We conducted preclinical validation studies to test whether eOPN3 can be used to inhibit seizures in rodent models of epilepsy. To that end, we expressed eOPN3 in excitatory cells at the seizure onset zone. Our findings show that transcranial illumination of excitatory neurons expressing eOPN3 is sufficient to reduce seizure rate and/or duration in acute and chronic models of epilepsy. Furthermore, employing a combination of light penetration measurements in large-animal brains and computational modeling, we establish the feasibility of delivering safe light doses to human brain targets. Together, our results demonstrate the potential for an eOPN3-based optogenetic therapeutic platform to treat neurological disorders.

Disclosures: E. Swissa: A. Employment/Salary (full or part-time):; Modulight.Bio. **K.L. Bar-Or:** A. Employment/Salary (full or part-time):; Modulight.Bio. **C.R. Auerbach-Asch:** A. Employment/Salary (full or part-time):; Modulight.Bio. **Y. Kfir:** A. Employment/Salary (full or part-time):; Modulight.Bio. **O. Yizhar:** F. Consulting Fees (e.g., advisory boards); Modulight.Bio. **O. levi:** A. Employment/Salary (full or part-time):; Modulight.Bio. **Y. Eldar:** A. Employment/Salary (full or part-time):; Modulight.Bio.

Poster

PSTR056: Anticonvulsant and Antiepileptic Therapies

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR056.24/B32

Topic: B.08. Epilepsy

Title: Efficacy And Safety Of Transcranial Magnetic Stimulation (TMS) And Electroencephalogram (EEG) In Epilepsy: A Systematic Review & Meta-Analysis

Authors: *S. MIRMIRE[1], C. M. KADIPASAOGLU[1], K. DAHLBERG[2], R. RAMESH[3], K. RASHIDI[2], T. HODICS[4], B. MA[1], M. HOGAN[5];
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Abstract: Background: Epilepsy is a prevalent neurological disorder that impacts 70 million people worldwide, 30% of them classified as drug resistant epilepsy (DRE). Guideline directed therapy for such patients is invasive, ranging from surgical excision to neuromodulation with implantable devices. The use of Transcranial Magnetic Stimulator (TMS) has been studied in modulatory effects in the field of neurorehabilitation. Although there has been some evidence suggesting the use of TMS for DRE, variability in the study design and protocol has contributed to inconsistent results. Some studies suggest up to 50% reduction in seizure frequency, making it a potential novel non-invasive treatment. Meta-analysis using individual level data is a gold standard method to estimate intervention effects as it collects published and unpublished data, standardizes outcome definitions and analysis units, and evaluates intervention-participant interactions. Methods: A comprehensive literature search from the years 1995 to 2024 was performed, searching for keywords “TMS,” “EEG,” and “DBS,” with MeSH terms for epilepsy, which yielded 757 papers. Reviewers identified papers that specifically performed RCTs to evaluate the effect on seizure frequency. Of 757 studies, 8 met the inclusion criteria. Authors from these RCTs were contacted to participate. So far, we have procured data from 2 authors and are actively working with 2 more to finalize data-sharing agreements. Results: Review of literature from different studies and meta-analyses showed conflicting outcomes based on their inclusion and exclusion criteria. Data from 2 papers included a total of 20 in treatment and 11 in control arm. There was no statistically significant difference between control and treatment baseline groups (mean difference 4.03, 95% CI [-2.64, 10.72], $p = 0.22$) or between the pre-post sham group (mean difference 1.51, 95% CI [-1.99, 5.01], $p = 0.35$). There was a statistically

significant difference between pre-post treatment group (mean difference -3.79, 95% CI [-6.18, -0.77], p = 0.016). Conclusions: TMS shows benefits, which is promising in this difficult to treat cohort. Previous small sample sizes, study design differences, and differences in treatment methods have led to inconsistencies in reported benefits. The current study addresses this variability using an individual-level meta-analysis to control for study parameters and increase the power of our analysis. Our preliminary results show that this collaboration may clarify TMS treatment effect determinants for DRE.

Disclosures: S. Mirmire: None. **C.M. Kadipasaoglu:** None. **K. Dahlberg:** None. **R. Ramesh:** None. **K. Rashidi:** None. **T. Hodics:** None. **B. Ma:** None. **M. Hogan:** None.

Poster

PSTR056: Anticonvulsant and Antiepileptic Therapies

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR056.25/B33

Topic: B.08. Epilepsy

Title: Data Visualization Strategies to Enhance Outpatient Management in Patients with Chronic EEG Recordings

Authors: *R. RAMESH[1], K. DAHLBERG[2], S. MIRMIRE[3], K. RASHIDI[4], C. M. KADIPASAOGLU[4], B. MA[4], T. HODICS[5];
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Abstract: Between 3-4 million Americans are diagnosed with epilepsy, a neurologic disorder. Of these, 1.5-2 million cases are diagnosed as Drug-Resistant Epilepsy. In these cases, alternative treatments such as surgical interventions and neuromodulation therapies can be attempted. Responsive neurostimulation treats epilepsy by implanting a device to prevent seizures before they begin via electrical stimulation, much like a cardiac pacemaker. Despite proven efficacy and a lack of excisional surgery, there is underutilization due to the complexity of reading single-subject chronic intracranial EEG (icEEG) data. Making informed treatment decisions is complex due to patterns in time, circadian rhythms, precipitating factors, or other dimensions. We have developed a novel visualization platform to solve this problem.
Our work aims to address this challenge with a novel, enhanced data visualization approach for RNS icEEG recordings. This visualization platform makes identifying patterns easier, which leads to more effective seizure prevention. Patterns are highlighted and trended over multiple variables.
To assess the effect of such methods, we generated synthetic seizure data mimicking the variability and rrhythms of seizure data using a combination of Poisson distributions for stochastic variability and sinusoidal shifts to model daily and multidian rhythms. Then, performed a single-center evaluation by clinical neurologists, using Likert scales (1-5) and

usability metrics to assess ease of use, clarity, confidence in interpretation, clinical decision-making utility, and overall satisfaction. Our method performed highly with scores of 4.5-5 for ease of use, clarity, and interpretation confidence. Perceived utility in clinical decision-making was 5 for our approach and an overall satisfaction at 5. Qualitative input indicated that "color shading proved most beneficial in distinguishing frequencies."
Through structured follow-up interviews, our approach was reported to enhance clinical workflows by offering intuitive interpretability, reducing cognitive load on the practicing neurologist, and enabling personalized patient management. Improving the utilization of advanced visualization of complex patterns allows this technology to be used in more patients. Learning insights of how RNS can best be used for patients can also lead to better medicine dosage timing. Our next step is to utilize this visualization technology to more easily identify when to provide medications in one patient alongside neurostimulation to reduce seizure frequency.

Disclosures: R. Ramesh: None. **K. Dahlberg:** None. **S. Mirmire:** A. Employment/Salary (full or part-time):; Houston Methodist. **K. Rashidi:** None. **C.M. Kadipasaoglu:** A. Employment/Salary (full or part-time):; Houston Methodist. **B. Ma:** A. Employment/Salary (full or part-time):; Houston Methodist. **T. Hodics:** A. Employment/Salary (full or part-time):; Houston Methodist.

Poster

PSTR056: Anticonvulsant and Antiepileptic Therapies

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR056.26/B34

Topic: B.08. Epilepsy

Support: NS111389
NS126418
Citizens United for Research in Epilepsy
NS072179 (KAS)

Title: Ketogenic diet improves cardiorespiratory function and longevity in Kv1.1 KO mice, a model of sudden unexpected death in epilepsy (SUDEP)

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Abstract: Sudden unexpected death in epilepsy (SUDEP) is one of the leading causes of death in epilepsy. Clinical studies indicate that severe seizures and cardiorespiratory dysfunction

including bradycardia, apnea and severe hypoxia are major risk factors for SUDEP. **There is a critical need to identify treatments that target the overall cardiorespiratory dysfunction in SUDEP.** We have previously reported that the Kv1.1 KO (KO) mice, a model of SUDEP, have increased seizures, bradycardia, apnea and chronic intermittent hypoxia prior to death; thus, providing window for preventative therapeutic intervention. We have reported that the high fat, low carbohydrate ketogenic diet (KD) reduced severe seizures and increased longevity in the KO mice. Other studies in and outside of epilepsy have also reported that KD treatment reduced refractory seizures, apneas, hypoxia and cardiac dysfunction. Here, we hypothesize that chronic KD treatment will improve cardiorespiratory function and thereby increase longevity in the Kv1.1 KO model of SUDEP. Age-matched KO mice and wild-type (WT) littermates were weaned onto standard diet or KD, and cardiorespiratory parameters were measured starting postnatal day (P)21 until sudden death. Heart rate and blood O_2 saturation were determined noninvasively with ECGenie and pulse oximetry respectively. Respiration was measured with noninvasive airway mechanics. Frequency and severity of the seizures were recorded using EEG-video monitoring. Endpoints included survival, heart rate, incidence of bradycardia (heart rate<600 bpm), intermittent hypoxia (<90% blood O_2 saturation) and apnea. A 100% of the KO mice died by P56 ± 2.4 days. Compared to the WT controls, KO mice had a progressive decrease in heart rate, and experienced more bradycardia as these mice approached SUDEP age ($p<0.001$). KD treatment normalized the KO heart rates to control levels ($p<0.01$) and reduced the incidence of bradycardia. KO mice experienced higher incidence of apnea closer to SUDEP age ($p<0.001$). KD treatment reduced the incidence of apnea in the KO mice ($p <0.01$). We have previously reported that KO mice have increased episodes of intermittent hypoxia prior to death. Here we found that, KD treatment reduced the fraction of hypoxic episodes experienced by the KO mice from 25% to 6.8% ($p < 0.001$). KD treatment also significantly reduced their seizure burden ($p<0.01$) and increased their survival by ~35% ($p<0.0001$). These results indicate that KD ameliorated the progressive cardiorespiratory dysfunction and increased longevity in a preclinical SUDEP model. This presents ketogenic diet as a possible metabolic treatment to improve longevity in patients at risk for SUDEP.

Disclosures: S. Iyer: None. **S.A. Matthews:** A. Employment/Salary (full or part-time):; Creighton University School of Medicine. **L. Netzel:** None. **T.A. Simeone:** A. Employment/Salary (full or part-time):; Creighton University School of Medicine. 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 grants, GRants from CURE epilepsy foundation. **K.A. Simeone:** A. Employment/Salary (full or part-time):; Creighton University School of Medicine. 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 grants, GRants from CURE epilepsy foundation.

Poster

PSTR056: Anticonvulsant and Antiepileptic Therapies

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR056.27/B35

Topic: B.08. Epilepsy

Support: JHU Samata Therapeutics

Title: Glucose dendrimer-ketamine targets hyperactive neurons and protects against seizures in a rodent model of status epilepticus

Authors: *P. VYAS[1], W. LIYANAGE[2], K. LAC[3], J. ALLENDE LABASTIDA[3], M. P. AVALOS[3], N. KALE[2], J. LIU[3], V. ARUN[3], M. TRIVEDI[3], K. S. PARIKH[2], K. M. RANGARAMANUJAM[2], S. KANNAN[3];
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Abstract: *Status epilepticus* (SE) is a serious and life-threatening neurological emergency characterized by self-sustaining, unceasing or recurring seizures with no recovery in between. These ongoing seizures rapidly modify the neuronal activity and synaptic function resulting in neurodegeneration, neuroinflammation, and abnormal neurogenesis in the hippocampus depending on seizure severity and duration. This may lead to development of refractory epilepsy and failure of conventional anti-seizure medications. N-methyl-D-aspartate (NMDA) receptors play a critical role in sustaining SE by mediating plasticity of gamma-aminobutyric acid **(**GABA) and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors. Ketamine is a non-competitive NMDA antagonist that has been investigated for treatment of refractory SE, but requires invasive administration over long durations, and is associated with significant side effects, including respiratory depression, cardiac issues, hepatotoxicity, and drug-drug interactions. Delivering ketamine specifically to the hyperactive neurons may accelerate therapeutic efficacy, reduce dosage required, and prevent systemic side effects. Since hypermetabolism is associated with the acute ictal and post-ictal discharges, we leveraged increased glucose uptake during these phases to facilitate transport of ketamine specifically to hyperactive and excitable neurons *via* glucose-based dendrimer nanomedicine. We investigated effects of our novel glucose dendrimer ketamine conjugate (GD-ket) vs ketamine (ket) in a pilocarpine model of refractory SE in C57BL/6 mice. GD-ket (0.3mg/kg IP or IN) reduced seizures post pilocarpine-induced SE; 28% GD-ket (0.3mg/kg IN) treated animals did not experience seizure episodes of more than stage 3. GD-ket (0.3mg/kg IN) had the highest survival (91.70%) followed by 87.50% for GD-ket (0.3mg/kg IP), 81.25% for ket vs 64.70% for saline. Duration of medium and high grade seizures were significantly lower with GD-ket indicating a decrease in seizure severity with neuronal targeting. We assessed biodistribution of GD-ket conjugated with Cy5 fluorophore, GD co-localized primarily in Thy-1-YFP neurons in brain regions associated with refractory and super-refractory SE, including entorhinal cortex, thalamus, dorsal and ventral hippocampus and red nucleus. We next plan to quantify the electroencephalographic changes in animals treated with GD-ket vs vehicle, and the subsequent impact of therapy on neuronal pathology. We conclude that glucose dendrimer targets hyperactive neurons and GD-ket has potential for convenient, safe, and effective treatment of refractory SE.

Disclosures: P. Vyas: A. Employment/Salary (full or part-time):; Johns Hopkins. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Samata Therapeutics. **W. Liyanage:** A. Employment/Salary

(full or part-time):; Johns Hopkins. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Samata Therapeutics. **K. Lac:** None. **J. Allende Labastida:** None. **M.P. Avalos:** None. **N. Kale:** None. **J. Liu:** None. **V. Arun:** None. **M. Trivedi:** None. **K.S. Parikh:** A. Employment/Salary (full or part-time):; Johns Hopkins. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Samata Therapeutics. **K.M. Rangaramanujam:** A. Employment/Salary (full or part-time):; Johns Hopkins. 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.; Samata Therapeutics. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Samata Therapeutics. **S. Kannan:** A. Employment/Salary (full or part-time):; Johns Hopkins. 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.; Samata Therapeutics. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Samata Therapeutics.

Poster

PSTR057: Astrocytes in Aging, Neurodegenerative Diseases, and Mental Health Disorders

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR057.01/B36

Topic: B.09. Glial Mechanisms

Support: COBRE Grant 5P20GM103653
RISE Grant R25GM122722
HBGI Title III Grant 10003317

Title: Exploring the function of cortical astrocytes in the SMND7 mouse model for SMA.

Authors: *T. BAMFO[1], V. A. TALABATTULA[2], M. T. MOORE[1], J. SUN[3], M. A. HARRINGTON[4];
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Abstract: Spinal muscular atrophy (SMA) is a debilitating neurodegenerative disease caused by the deletion or mutation of the Survival Motor Neuron 1 (*SMN1*) gene, and has long been understood to be characterized by the loss of motor neurons in the spinal cord. However, more recent studies in mouse models expressing only SMN2 and SMNDelta7 have identified pathological changes in the brain due to lack of SMN protein, and indicated that restoration of the protein in motor neurons alone has little effect on SMA-related symptoms. Such findings

demonstrate that complete understanding of the pathological and molecular mechanisms of SMA must go beyond lower motor neurons to include non-neuronal cells and how these cells are impacted in the brain. In this study, we aim to characterize the physical and functional properties of cortical astrocytes derived from the SMNDelta7 mouse model. *In vitro* experiments were performed on brain tissue samples and cortical astrocytes cultured from SMNDelta7 mice.Brain tissue samples from P12 SMA mice in western blots showed reduced SMN protein expression in various brain regions, with levels comparable to those detected in the spinal cords. Wild-type (WT) and SMA astrocytes were isolated and cultured from the cortex of neonatal mice of the SMNDelta7 mouse model on post-natal days (P)1-2, and western blots were used to measure SMN protein expression in the cortical astrocytes. We found that, in comparison to WT astrocytes, relative SMN expression levels are significantly reduced in SMA astrocytes from SMNDelta7 mice. We also compared various measurements for morphometric analysis of WT and SMA cortical astrocytes to assess the effect of SMN-deficiency on the structure of these cells. To determine whether lack of SMN protein alters regulation of intrinsic cellular properties, we also examined differences in calcium signaling in the comparison of WT and SMA cortical astrocytes from SMNDelta7 mice. Results are compared to similar experiments done in spinal astrocytes where results suggested that the changes observed in intracellular calcium signaling of SMN-deficient cortical astrocytes may negatively impact interaction between astrocytes and motor neurons.The goal of this study is to provide a better understanding of how cortical astrocytes are affected by the pathology of SMA, as well as their role in supporting other neuronal cells in this SMA disease model. Such studies may aid in targeting new areas for further development of efficient therapeutic solutions for those diagnosed with SMA.

Disclosures: T. Bamfo: None. **V.A. Talabattula:** None. **M.T. Moore:** None. **J. Sun:** None. **M.A. Harrington:** None.

Poster

PSTR057: Astrocytes in Aging, Neurodegenerative Diseases, and Mental Health Disorders

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR057.02/B37

Topic: B.09. Glial Mechanisms

Support: AG078116
AG027297

Title: Regulation of microglia and oligodendrocyte transcriptional changes by astrocytes in a diet-based model of small cerebral vessel disease

Authors: *C. M. NORRIS[1], J. GOLLIHUE[2], P. SOMPOL[1], D. M. WILCOCK[3], J. M. MORGANTI[1];
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Abstract: Vitamin B6 and B12 deficient diets induce hyperhomocysteinemia (HHcy) and small cerebral vessel disease associated with vascular inflammation, synapse dysfunction, and cognitive decline. We recently showed that HHcy inducing diet leads to Ca2+ dysregulation in astrocytes and hyperactivation of the calcineurin/NFAT signaling pathway. Expression of the NFAT inhibitory peptide, VIVIT, in astrocytes using AAV-Gfa2 vectors, reduced neurovascular coupling deficits, improved synapse function, and stabilized cognition in HHcy diet mice. Here, we used scRNA-seq to further characterize the impact of astrocytic calcineurin/NFATs on multiple brain cell types in the context of HHcy. 7-8-week-old male C57Bl/6J mice recieved intrahippocampal injections of AAV-Gfa2-EGFP (control) or AAV-Gfa2-VIVIT. Mice were then fed control (CT) diet or HHcy diet for up to 15 weeks. Brains were then extracted and hippocampi processed for transcriptional analyses. scRNA-seq was used to identify diet and AAV-dependent cell specific gene expression changes. The results showed effects of diet and AAV treatment on microglial and oligodendrocyte cell populations. HHcy was associated with the upregulation of numerous microglial genes linked to disease-like phenotypes (e.g. Apoe, Il1b, Ccl5, Cebpb, Cybb). VIVIT treatment reversed these changes, and was characterized by a bias toward homeostatic microglial gene expression (e.g. P2ry12, Gpr34, Fcrls, Sparc). Similar HHcy and VIVIT trends were observed in oligodendrocytes. The results suggest that reactive astrocytes may govern the molecular phenotypes of other local glial cells, and as such, could provide a cellular target for preventing/resolving the detrimental inflammatory milieu that develops with Alzheimer's disease and related dementias.

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Poster

PSTR057: Astrocytes in Aging, Neurodegenerative Diseases, and Mental Health Disorders

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR057.03/B38

Topic: B.09. Glial Mechanisms

Support: NIH/NINDS R21 NS121959-01A1

Title: An adeno-associated (AAV)-based tool to specifically damage mtDNA in astrocytes within pre-specified regions of the adult mouse brain

Authors: *D. A. AYALA[1], A. J. MATARAZZO[2], B. SEABERG[2], C. MATTHEWS[1], M. PATEL[1], E. TIJERINA[2], M. RIMER[3], R. SRINIVASAN[4];
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Abstract: We have previously shown that astrocytes in live dorsolateral striatum (DLS) slices exhibit robust spontaneous Ca2+ influx events in their mitochondria, suggesting that astrocyte mitochondria actively participate in neuronal function. Based on this rationale, we hypothesize that the specific disruption of mitochondrial function in astrocytes within pre-specified brain regions would manifest as neuronal dysfunction in that brain region, while also accelerating neurodegeneration. To damage astrocytic mitochondria, we created an AAV expressing the restriction enzyme PstI (Mito-PstI) under the astrocyte GfaABC1D promoter and a Mito7 signal sequence. In principle, this AAV can direct PstI specifically to astrocytic mitochondria. We rationalized that since mice possess PstI restriction sites in their mitochondrial DNA (mtDNA), flanking genes involved in the mitochondrial oxidative phosphorylation cascade, the AAV-mediated expression of PstI only in astrocytic mitochondria would significantly damage mtDNA in astrocytes. Using this novel method, we found that mtDNA damage in striatal astrocytes results in profound changes in astrocytic mitochondrial morphology, function, reactivity, and neuroinflammation within the DLS. Having established a novel tool to damage astrocytic mtDNA in pre-specified brain regions, we are employing Mito-PstI to damage mtDNA in substantia nigra pars compacta (SNc) astrocytes. We are conducting behavioral assays as well as optogenetic readouts to assess changes in striatal dopamine release following specific disruption of mtDNA in the SNc of mice exposed to 6-hydroxydopamine (6-OHDA). Results from these experiments will enable a better understanding of the role of astrocytic mitochondria during SNc dopaminergic neuron loss and the progression of Parkinson's disease.

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Poster

PSTR057: Astrocytes in Aging, Neurodegenerative Diseases, and Mental Health Disorders

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR057.04/B39

Topic: B.09. Glial Mechanisms

Support: RF1AG027297
P01AG078116

Title: Longitudinal two photon imaging of astrocytes in young and aged intact mice reveals dynamic changes related to inflammation and pharmacological manipulation with tacrolimus

Authors: *J. GANT[1], C. B. ROGERS[2], E. B. RUCKER, III[3], P. HECKER[1], J. GOLLIHUE[4], C. M. NORRIS[2];
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Abstract: Astrocyte reactivity in the brain is a hallmark of deleterious conditions related to, but not limited to inflammation, neurodegenerative diseases and brain damage. Astrocyte reactivity

is often characterized by the physical state of astrocytes, with astrocyte hypertrophy commonly accepted as an indicator of immune response in the brain. In addition, the expression of glial fibrillary acidic protein (GFAP) is concomitant with astrocyte reactivity and immune response. The ability of astrocytes to alternate between reactivity states is not fully understood and is rarely observed, however, we have shown that inhibition of calcineurin-dependent transcription factors such as NFAT4 helps to maintain a healthy reactivity phenotype. Additionally, aging and/or neurodegenerative disease may impact the ability of astrocytes to recover from the hypertrophic state. Here we utilize longitudinal two-photon imaging and AAV.GFAP-dependent expression of eGFP to follow changes in astrocyte morphology and a number of other measures related to astrocyte hypertrophy for 5 weeks before and following insult with lipopolysaccharide (LPS) in young and aged C57BL/6 mice. Additionally, we utilize an inhibitor of calcineurin (Tacrolimus/FK506) to study its effects on astrocyte measures related to LPS-induced immunoreactivity. LPS significantly induced a hypertrophic phenotype in young and aged mice. In young mice, this was transient with astrocytes returning to pre-LPS trophic phenotype over time. In aged mice, the hypertrophic state was longer lasting. Interestingly, FK506 was able to reverse the persistence of the hypertrophic state in aged mice, but was detrimental to the hypertrophic state in young mice. We also observed a number of changes in other measures such as increases in the number of GFAP expressing astrocytes following LPS injections and a decrease in GFAP expressing astrocytes over time in young and following FK506 treatment. These findings suggest that astrocyte reactivity is a dynamic process that can resolve or persist depending on age and/or pharmacological manipulation. Treatment with inhibitors of calcineurin, or inhibitors of calcineurin-mediated processes, are an effective means by which to mediate the immunoreactivity of astrocytes *in vivo*.

Disclosures: J. Gant: A. Employment/Salary (full or part-time):; University of Kentucky. **C.B. Rogers:** A. Employment/Salary (full or part-time):; University of Kentucky. **E.B. Rucker:** A. Employment/Salary (full or part-time):; University of Kentucky. **P. Hecker:** A. Employment/Salary (full or part-time):; University of Kentucky. **J. Gollihue:** A. Employment/Salary (full or part-time):; University of Kentucky. **C.M. Norris:** A. Employment/Salary (full or part-time):; University of Kentucky.

Poster

PSTR057: Astrocytes in Aging, Neurodegenerative Diseases, and Mental Health Disorders

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR057.05/B40

Topic: B.09. Glial Mechanisms

Title: Attenuated Ca^{2+} Signalling in Dentate Gyrus Astrocytes Results in Cognitive Phenotypes

Authors: *M. WANG[1], M. KAMBALI[2], R. NAGARAJAN[2], J. LYU[1], X. YU[3], U. RUDOLPH[2]; [1]Univ. of Illinois Urbana-Champaign Neurosci. Grad. Program, Urbana, IL; [2]Comparative Biosci., Univ. of Illinois Urbana-Champaign, Urbana, IL; [3]Mol. and Integrative Physiol., Univ. of Illinois Urbana-Champaign, Urbana, IL

Abstract: Astrocytes are increasingly being recognized as having important roles in regulating the function of neuronal circuits. Many animal studies have shown behavioral phenotypes that are altered by astrocytic activation or inhibition. In the hippocampus, astrocytes have been found to modulate long-term potentiation in CA1 and dentate gyrus (DG). While the roles of astrocytes in CA1 have been investigated extensively, the behavioral consequences of manipulating astrocytes in the DG are largely unknown. To evaluate the functional significance of the astrocytes in the dentate gyrus, we expressed the calcium extrusion pump hPMCA2w/b (CalEx) in dentate gyrus astrocytes. CalEx removes calcium from the astrocytes and thus disrupts any calcium-dependent astrocytic functions. A viral construct expressing CalEx or tdTomato (for the control group) from the astrocyte-specific GfaABC1D promoter was stereotaxically injected into the DG hilus of adult C57BL/6J mice. After a recovery period of 3 weeks behavioral experiments were performed, including elevated plus maze, open field, light/dark box, Y-maze, and social interaction tests, as well as the Morris water maze, latent inhibition to conditioned freezing, pre-pulse inhibition / startle habituation, and pattern completion tests. When assessing spatial learning and reversal learning in the Morris water maze, mice injected with CalEx-expressing virus have so far shown an improved performance both in the learning phase and in the reversal learning phase compared to controls. Previous studies have shown that modulation of the activity of principal neurons in DG affects pattern completion. In a water maze-based object pattern completion test, our current data show that the performance of the CalEx-expressing mice was impaired. We are currently exploring pattern separation in object-based test and context-based test, as pattern separation and pattern completion are considered opposing but complementary functions of the hippocampus. In summary, our results so far show that functional inhibition of astrocytes may affect the performance in behavioral tasks linked to the function of DG principal neurons. Our results are consistent with astrocytes in dentate gyrus being an essential part of dentate gyrus neural circuits and being required for normal cognitive function.

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Poster

PSTR057: Astrocytes in Aging, Neurodegenerative Diseases, and Mental Health Disorders

Location: MCP Hall A

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Program #/Poster #: PSTR057.06/B41

Topic: B.09. Glial Mechanisms

Support: NIH/NIA grant P01AG026572 to RDB (Project 1 and Analytic Core to FY; Animal Core to TW)
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Arizona Alzheimer’s Consortium Pilot Project grants to FY

Title: Apoe4 Interacts with Perimenopausal Transition in Regulating Central and Peripheral Lipid Metabolism

Authors: *H. PAN[1,2], G. QI[3], Y. MI[3], T. WANG[4], R. D. BRINTON[5], F. YIN[4];
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Abstract: Age, hormone depletion at menopause and the APOE-ε4 (ApoE4) genotype are among the top risk factors for developing late-onset Alzheimer's disease (AD). Findings from our and other groups have suggested that ApoE4 interacts with perimenopause in regulating a neuroimmune cascade encompassing mitochondrial dysfunction, metabolic reprogramming, and neuroinflammation. Our recent work revealed that astrocytes maintain brain lipid homeostasis by performing fatty acid (FA) degradation, and ApoE4 diminishes such capacity and thus promotes astrocytic lipid droplet (LD) accumulation. It is thus intriguing to determine whether lipid metabolism is involved in ApoE4-perimenopause modulation of the neuroimmune system and AD risk. We first assessed mRNA levels of major metabolic processes in astrocytes acutely isolated from female humanized ApoE3 or ApoE4 mice before (6-month regular cycling), during (15-month irregular cycling), and post menopause (15-month acyclic). Astrocyte gene expression analysis suggested a trend towards increase in fatty acid synthase (*Fasn*) levels upon perimenopause, which was sustained through menopause in ApoE4, but not ApoE3 mice. In contrast to the changes in *Fasn*, a key FA β-oxidation (FAO) gene carnitine palmitoyl transferase 1a (*Cpt1a*) was decreased in astrocytes from post-menopause mice regardless of ApoE genotype. Moreover, ApoE4- and menopause-induced metabolic reprogramming in the brain was coupled with peripheral metabolic changes. In line with changes in body weight, an elevation in circulating leptin levels and a trend towards increase in leptin mRNA levels in inguinal white adipose tissue (iWAT) were found in ApoE4, but not ApoE3 mice upon perimenopause. Moreover, endocrine effect on plasma free FA levels was significant in ApoE4 mice only, whereas endocrine effect on iWAT free FA levels was significant in ApoE3 mice only. Analysis of key genes involved in FA metabolism also supported a lack of response of ApoE4 iWAT to endocrine transition. Collectively, adaptations in lipid metabolism across the brain and periphery during female menopausal transition were disrupted by ApoE4, which could interactively contribute to a metabolic-inflammatory cascade that predispose ApoE4-carrying post-menopausal women to a substantially higher AD risk. This work has been supported by the NIH/NIA grants P01AG026572 to RDB (Project 1 and Analytic Core to FY; Animal Core to TW), RF1AG068175 and RF1AG079157 to FY, and Arizona Alzheimer's Consortium Pilot Project grants to FY.

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Poster

PSTR057: Astrocytes in Aging, Neurodegenerative Diseases, and Mental Health Disorders

Location: MCP Hall A

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Program #/Poster #: PSTR057.07/B42

Topic: B.09. Glial Mechanisms

Support: NIH P01AG078116-01
NIH RF1AG027297

Title: Investigating the Dynamic Relationship Between Astrocyte Calcium Signaling and Cerebrovascular Functional Impairments in Alzheimer's Disease

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Abstract: Background: Astrocytes are a glial cell type responsible for many protective functions in the brain. While they are primarily recognized for regulating synaptic activity, they're also essential for maintaining the neurovascular unit, and cerebral hyperperfusion during metabolic demand. Calcium signaling has been identified as a regulatory process for these functions. Amyloid Beta deposits (Aβ) are a primary diagnostic marker of Alzheimer's disease, and are linked to synaptic degeneration, astrocyte reactivity, and cognitive decline. Alzheimer's disease also frequently presents with vascular damage and hypoperfusion, suggesting impaired astrocyte function. We investigated the impact of amyloid burden on stimulation-evoked vasoreactivity and astrocyte calcium signaling to determine potential patterns of physiological impairment that may contribute to Alzheimer's disease pathology.
Methods: Six-month-old 5XFAD and littermate control mice were injected with AAV2/5-Gfa104-jGCaMP8f into barrel cortex and imaged three weeks later, while awake, using two-photon microscopy. Neurovascular coupling experiments were conducted using timed air puff stimulation of whiskers, and calcium signals were recorded from activated astrocytes. Calcium transient properties were analyzed over different cellular compartments by custom developed Matlab applications. Vascular tone at rest, and in response to stimulation was also measured, and correlations calculated with endfeet signaling.
Results: Astrocytes from 5XFAD mice showed a significant reduction in calcium signaling amplitudes, ($F(1,53) = 8.735$, $p = 0.0047$, $n = 25,32$) compared to wild type controls with a significant deficit in female 5XFAD mice. Correlations between other signaling properties such as rise/decay kinetics, and network connectivity were also characterized between the 5XFAD and control mice. Astrocyte endfoot compartments also showed reduced transient amplitudes. ($F(1,30) = 3.226$, $p = 0.033$, $n = 17,15$) Neurovascular coupling in the 5XFAD mice was reduced ($F(1,39) = 2.511$, $p = 0.015$, $n=20,19$) despite no changes in arteriole elasticity. A correlation between astrocyte calcium signaling and the magnitude of stimulation-induced vasodilation was observed in wild-type mice but not in the 5XFAD group.
Conclusion: Amyloid induced pathology impairs the brain's adaptivity to neuronal stimuli at the neurovascular unit. The uncoupling between vasoreactivity and astrocyte signaling processes

implies that amyloid accumulation may render the brain vulnerable to conditions of neuronal hyperexcitability and metabolic dysregulation observed in Alzheimer's disease.

Disclosures: B.E. Weiss: None. **J.C. Gant:** Other; Panda Labs LLC. **R. Lin:** None. **S.D. Kraner:** None. **O. Thibault:** None. **P. Sompol:** None. **C.M. Norris:** None.

Poster

PSTR057: Astrocytes in Aging, Neurodegenerative Diseases, and Mental Health Disorders

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR057.08/B43

Topic: B.09. Glial Mechanisms

Support: NIH/NIA grant RF1AG068175 (FY)
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Packer-Wenz research endowment (FY)

Title: Apoe4 Exacerbates Astrocytic Mitochondrial Dysfunction-Induced Neuroinflammation and Neurodegeneration

Authors: *G. QI[1], Y. MI[2], F. YIN[2,3,4];
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Abstract: Abundant evidence has documented brain lipid dyshomeostasis as an early and persistent hallmark of Alzheimer's disease (AD). Moreover, a variety of AD risk factors are found directly involved in lipid trafficking and/or lipid metabolism. We previously reported that APOE-ε4 (ApoE4), the greatest genetic risk factor for AD, induces a metabolic shift in astrocytes towards diminished fatty acid (FA) oxidation and elevated lipid droplet (LD) accumulation. In addition, reduced capacity of ApoE4 astrocytes in eliminating and degrading neuronal lipids contribute to their compromised metabolic- and synaptic support to neurons. Our recent work further revealed that disrupted FA degradation by astrocytes is sufficient to trigger progressive neuroinflammation and neurodegeneration resembling human AD. However, whether and how compromised astrocytic FA degradation interacts with ApoE4 in promoting AD onset and progression remains unclear. Here, using a mouse model combining humanized ApoE3 or ApoE4 allele with astrocytic mitochondrial dysfunction (ApoE3-Tfam^{AKO} and ApoE4-Tfam^{AKO}), we demonstrated that cognitive impairments induced by astrocytic mitochondrial dysfunction was exacerbated by ApoE4. Consistently, ApoE4-Tfam^{AKO} showed reduced hippocampal long-term potentiation, synaptic density and dendrite complexity compared to ApoE3-Tfam^{AKO} mice. Moreover, ApoE4-Tfam^{AKO} mice exhibited stronger neuroinflammation in terms of microglial activation and reactive astrogliosis. Along with enhanced astrocyte

reactivity, ApoE4 also increased accumulations of free FA, triacylglycerol, and astrocytic LDs in the hippocampus and cortex of Tfam^{AKO} mice. Relative to ApoE3-Tfam^{AKO} mice, ApoE4-Tfam^{AKO} mice also manifested demyelination, suggested by diminished density and thickness of white matter tracts and lower expression of the myelin-basic protein (MBP). These findings support our hypothesis that ApoE4 converges with brain mitochondrial dysfunction at astrocytic FA oxidation in disrupting brain lipid homeostasis and driving neuroinflammation and neurodegeneration in AD.

Disclosures: G. Qi: None. **Y. Mi:** None. **F. Yin:** None.

Poster

PSTR057: Astrocytes in Aging, Neurodegenerative Diseases, and Mental Health Disorders

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR057.09/B44

Topic: B.09. Glial Mechanisms

Support: R01AG078728

Title: Investigating parenchymal dynamics and efflux of astroglial exosomes in Alzheimer's Disease (AD) mouse model: implications for CNS-to-periphery signaling

Authors: *C. REYNOLDS[1,2], J. HACKER[1], S. JIN[3], F. MOWRY[4], L. YE[5], S. SAJADI[6], M. PAUKERT[7], Y. YANG[8];
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Abstract: Alzheimer's disease (AD) pathology involves a cascade of events implicating glial cell dysfunction and neuroinflammation, yet the mechanisms underlying the communication between the central nervous system (CNS) and the periphery remains unclear. Here, we investigate the role of neuroinflammation on the dynamics and efflux of astroglial exosomes in the 5xFAD AD mouse model via in vivo 2-photon live imaging and high magnification confocal imaging of the neurovascular unit, focusing on their potential role in CNS-to-peripheral signaling and as biomarkers for neurodegeneration.It is known that chronically activated microglia in AD secrete proinflammatory cytokines, triggering astrocyte activation and subsequent release of astrocytic reactive exosomes. These exosomes undergo alterations in cargo composition within the challenged CNS environment. As astrocytes ensheath vessels in the parenchyma with their endfeet, they form a keystone in the neurovascular unit and provide a direct conduit to facilitate possible exosome entry to the glymphatic system.Our hypothesis posits that astrocytic exosomes can efflux from the CNS and enter peripheral circulation, potentially influencing immune cell

activation and serving as biomarkers for neurodegeneration.Through *in vivo* 2-photon live imaging, our results show a decrease in exosome dynamics within the parenchyma of our lab's generated 5xFAD-hCD63-GFP astrocytic exosome-reporting mice but not in age-matched wild-type mice. Confocal imaging of the neurovascular unit also reveals alterations in astrocytic exosomes within the cortex of AD models. Furthermore, confocal imaging of cervical lymph nodes from 5xFAD-hCD63-GFP astrocytic exosome-reporting mice and in age-matched wild-type mice show expression of hCD63-GFP suggesting efflux to the periphery via the glymphatic system in AD.Together, our results suggest that disease induced changes in neuroinflammatory pathways contribute to the alterations in astrocytic exosome secretion, dynamics and efflux from the CNS in 5xFAD AD models. These findings shed light on the intricate interplay between CNS-derived exosomes, neuroinflammation, and peripheral signaling in AD pathogenesis, opening avenues for novel diagnostic and therapeutic strategies.

Disclosures: C. Reynolds: None. **J. Hacker:** None. **S. Jin:** None. **F. Mowry:** None. **L. Ye:** None. **S. sajadi:** None. **M. Paukert:** None. **Y. Yang:** None.

Poster

PSTR057: Astrocytes in Aging, Neurodegenerative Diseases, and Mental Health Disorders

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR057.10/B45

Topic: B.09. Glial Mechanisms

Support: VA Career Development Award IK2BX003240
NIH Grant 1R01NS132778
NIH Grant T32GM113896

Title: Modulation of Neurotoxic Reactive Astrogliosis by LRP1

Authors: *M. WANG, Z. CHEN, K. DIETERT, S. AHMAD, P. REED, S. SPRAGUE, N. L. SAYRE;
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Abstract: BACKGROUND: Chronic brain inflammation, observed in traumatic brain injury (TBI) and aging, exacerbates cognitive decline and increases the risk of neurodegenerative diseases. Neurotoxic astrocyte reactivity is upregulated in this process. This study investigates the role of astrocyte low-density lipoprotein receptor-related protein 1 (LRP1) in modulating neurotoxic reactive astrogliosis in TBI and aging. Preliminary data suggest that loss of astrocyte-LRP1 worsens cognitive and motor decline with age. Targeting LRP1 may offer therapeutic potential in preserving brain function. **METHODS:** To test our hypothesis that LRP1 decreases age-related brain functional decline through reducing astrocyte susceptibility to neuroinflammatory stimulation, we proposed two aims: 1) investigate if neurotoxic reactive astrogliosis upregulates neuroinflammation and impairs brain health in TBI and aging using mouse models and human brain tissue; and 2) determine if LRP1 modulates astrocyte reactivity

to inflammatory stimulus using primary astrocyte cultures and an astrocyte-specific LRP1 knockout (KO) mouse model. Additionally, we will utilize single-cell RNA sequencing to study gene expression changes in neurotoxic reactive astrocytes and assess the impact of LRP1KO. **RESULTS:** Our analysis of human brain tissue reveals upregulation of neurotoxic reactive astrogliosis markers in tissue from patients diagnosed with chronic traumatic encephalopathy. In our *in vivo* studies, we observed increased neurotoxic reactive astrocytes in LRP1KO mice following neuroinflammatory stimulation. Ongoing experiments include further *in vivo* studies, additional *in vitro* experiments, and continued analysis of human brain samples. **CONCLUSIONS:** Our findings thus far suggest that astrocyte-LRP1 plays a protective role against age-related brain functional decline by decreasing astrocyte sensitivity to neuroinflammatory stimulation.

Disclosures: M. Wang: None. **Z. Chen:** None. **K. Dietert:** None. **S. Ahmad:** None. **P. Reed:** None. **S. Sprague:** None. **N.L. Sayre:** None.

Poster

PSTR057: Astrocytes in Aging, Neurodegenerative Diseases, and Mental Health Disorders

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR057.11/B46

Topic: B.09. Glial Mechanisms

Support: NIH Grant R21NS125861-01
NIH Grant R21NS125861-01S1

Title: Contribution of astrocytic SPARCL1 to cortical synaptic dysfunction in C9orf72-FTD/ALS

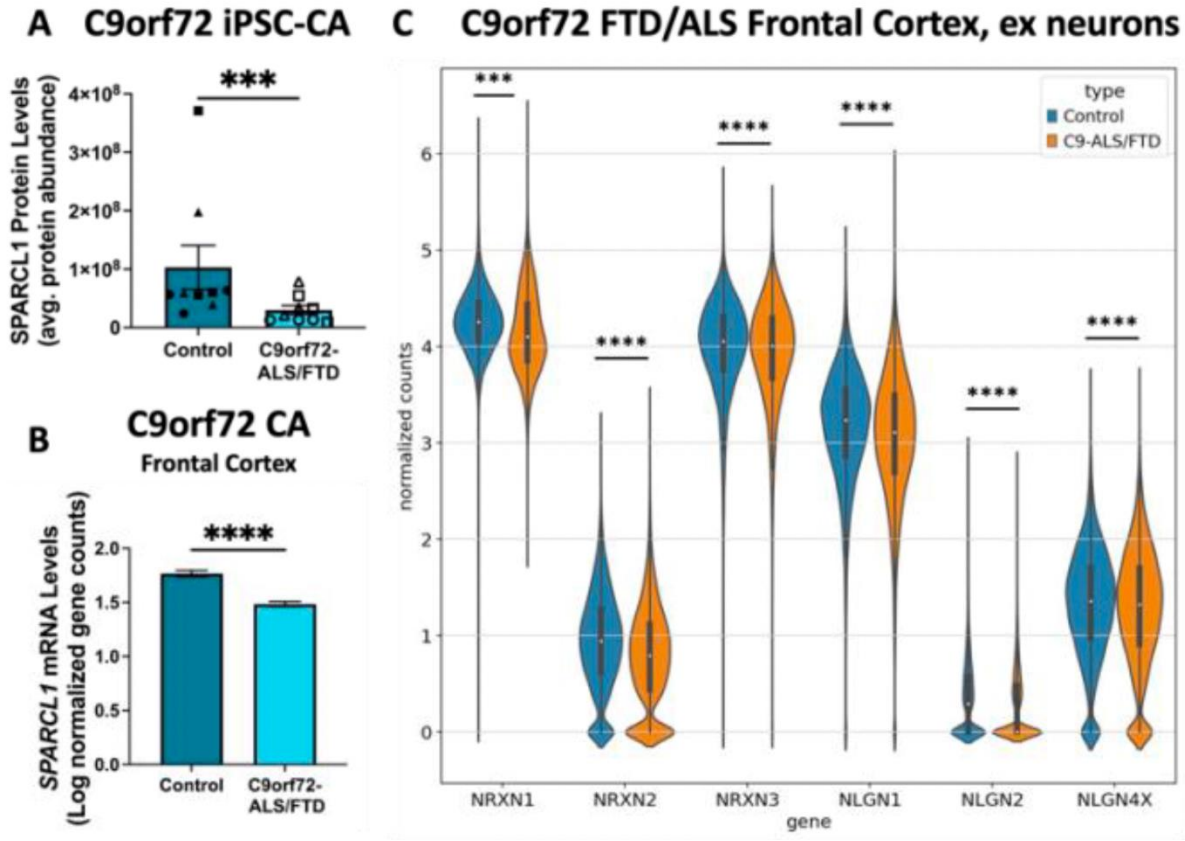
Authors: *R. A. CULIBRK[1], L. M. BUSTOS[1], L. M. GITTINGS[1], B. ONDATJE[1], D. JULIAN[1], N. P. HANSEN[2], R. SHARMA[2], J. ANTONE[3], P. PIRROTTE[2], R. G. SATTLER[1]; [1]Translational Neurosci., Barrow Neurolog. Inst., Phoenix, AZ; [2]Cancer and Cell Biol. Div., [3]Neurogenomics Div., Translational Genomics Res. Inst., Phoenix, AZ

Abstract: Background and Rationale. Reactive astrocytes have been implicated in the pathogenesis of *C9orf72*-FTD/ALS, the most common genetic form of this neurodegenerative disease spectrum. The astrocyte-secreted factor SPARCL1 - a key synaptogenic protein - has been shown to be pivotal to synapse maintenance and strength, yet no studies have carefully addressed whether SPARCL1 dysregulation may contribute to neurodegeneration. Interestingly, decreased SPARCL1 expression in CSF correlates with cognitive impairment in AD (Seddighi et al. *JAD* 2018, **61** 401-414). Our study therefore aimed to ascertain whether similar SPARCL1 perturbations occur in *C9orf72*-FTD/ALS and how SPARCL1 dysfunction contributes to cortical neurodegeneration.
Methods. iPSCs from *C9orf72*-FTD/ALS patients (n = 3) and matched controls (n = 3) were differentiated into cortical astrocytes and subjected to bulk RNA-Seq and proteomics analyses.

Postmortem frontal cortex tissues from *C9orf72*-FTD/ALS patients (n = 6) and non-neurological controls (n = 10) were analyzed using snRNA-Seq, with a focus on synaptic maintenance pathways.

Results. We observed a significant reduction of SPARCL1 protein in *C9orf72*-FTD/ALS patient-derived cortical astrocytes compared to controls (log2FC ≈ -1.11; p = 0.009; Figure A). In the frontal cortex of *C9orf72*-FTD/ALS patients, astrocytic *SPARCL1* mRNA levels were similarly diminished (log2FC ≈ -0.33; p < 0.0001; Figure B). Furthermore, mRNA levels of several synaptic adhesion molecules, including neurexin and neuroligin family members, were notably decreased in excitatory neurons (p < 0.0001; Figure C).

Conclusion. These data indicate that astrocytic SPARCL1 dysregulation is strongly associated with cortical synaptic dysfunction and neurodegeneration in *C9orf72*-FTD/ALS. Our ongoing experiments aim to characterize whether SPARCL1 loss directly impinges on synaptic maintenance, with a mechanistic focus on its presumed stabilization of neurexin/neuroligin interactions.



Disclosures: R.A. Culibrk: None. **L.M. Bustos:** None. **L.M. Gittings:** None. **B. Ondatje:** None. **D. Julian:** None. **N.P. Hansen:** None. **R. Sharma:** None. **J. Antone:** None. **P. Pirrotte:** None. **R.G. Sattler:** None.

Poster

PSTR057: Astrocytes in Aging, Neurodegenerative Diseases, and Mental Health Disorders

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR057.12/B47

Topic: B.09. Glial Mechanisms

Support: NIH R01NS115809

Title: Development of a novel non-secreted form of S100B and its relevance to Parkinson's disease

Authors: *C. RODRIGUEZ[1], E. A. BANCROFT[2], N. HARRISON[2], S. NALLURI[2], R. SRINIVASAN[3,4];
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Abstract: Parkinson's disease (PD) is a devastating neurodegenerative disorder with no known cure. Understanding pathogenic processes in early PD is therefore critical for developing neuroprotective treatments. Multiple reports point to a pathogenic role of secreted S100B in clinical PD, and we have previously shown that extracellularly applied recombinant human S100B peptide inhibits A-type voltage-gated potassium channels in primary cultured dopaminergic (DA) neurons thereby pathologically increasing L-type voltage-gated calcium channel-mediated calcium fluxes. As a next step, to assess if S100B secreted from astrocytes leads to similar effects on DA neurons, we develop and test a novel astrocyte-specific adeno-associated virus (AAV) that expresses a non-secreted form of S100B. We generated two AAV constructs expressing either a non-secreted (S100Bnon-sec) or a secreted form of S100B (S100Bsec). Both constructs contain the mCherry reporter followed by an internal ribosome entry sequence (IRES) at the N-terminus of S100B and are driven by the astrocyte-specific GfaABC1D promoter. Using primary DA neuron-astrocyte mouse co-cultures, we found that when compared to full-length S100B, non-secreted S100B decreased Sec13 labeled ER exit sites (ERES) in astrocytes. This decrease in Sec13-ERES corresponded with a significant increase of endogenous S100B protein, a decrease in S100B in culture media, changes in calcium signaling events in DA neurons and a decrease in the nuclear translocation of the phosphorylated cyclic-AMP response element binding (pCREB) in DA neurons. Together, these results successfully validate our non-secreted S100B construct. We are currently comparing the ability of S100Bnon-sec versus S100Bsec to accelerate DA loss in vivo, in a preclinical mouse model of PD.

Disclosures: C. Rodriguez: None. **E.A. Bancroft:** None. **N. Harrison:** None. **S. Nalluri:** None. **R. Srinivasan:** None.

Poster

PSTR057: Astrocytes in Aging, Neurodegenerative Diseases, and Mental Health Disorders

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR057.13/B48

Topic: B.09. Glial Mechanisms

Support: Lafayette Board of Regents Support Fund
Lafayette Parish Endowed Professorship
UL Lafayette GSO

Title: Amygdala transcriptome in a Non-Human Primate model of Self-Injurious Behaviors demonstrating astrocyte reactivity and gliosis.

Authors: *J. BARUA[1], R. KARIYAWASAM[2], J. YOUNG BROOKS[2], M. JACKSON[3], B. L. FORET[5], K. M. SMITH[4];
[1]Univ. of Louisiana Lafayette, Lafayette, LA; [3]Biol., [4]Dept. of Biol., [2]Univ. of Louisiana at Lafayette, Lafayette, LA; [5]Univ. of Louisiana At Lafayette, Lafayette, LA

Abstract: Self-injurious behavior (SIB) also known as Non-Suicidal Self-Injury (NSSI) in humans, is the act of destroying one's own bodily tissues without the intention of committing suicide but with a higher risk of suicide ideation and future attempt. SIB is a public health issue around the globe, affecting 1-4% of the adult population and having a lifetime prevalence of 5.9%. Individuals suffering from neuropsychiatric disorders such as Autism Spectrum Disorder (ASD) present higher frequencies of self-injury than the general population. SIB affects both humans and non-human primates (NHP) and is performed to alleviate emotional distress. SIB is thought to be linked with disruptions in the limbic system and is associated with alterations in endogenous opioid signaling and the hypothalamic pituitary axis (HPA). We are studying rhesus macaque (*Macaca mulatta*) NHP brain samples to acquire a thorough understanding of the neurobiology of SIB. NHPs experienced spontaneous SIB with wounds of mild-moderate severity and whose symptoms were not sufficiently alleviated by treatment with Diazepam or environmental enrichment. Control animals were healthy age and sex matched NHP euthanized following a terminal research protocol. Our current investigation is focused on male NHP's exhibiting SIB, since female NHP with SIB are rare. Our previous studies identified a reduction of expression of Mu opioid receptor (MOR, OPRM1 gene) messenger RNA (mRNA) in the amygdala and decreased prodynorphin in the hypothalamus of NHP with SIB. Here, we compare and analyze the gene expression profiles of the amygdala of NHP with SIB (9 males) to that of control NHP (3 males) via RNAseq. We identified 26 Differentially Expressed Genes (DEG) in the amygdala of animals with SIB based on log2 fold change and adjusted P-value. We used the DAVID and PANTHER bioinformatics tools to identify the pathways that are involved in SIB. Differentially expressed genes include Vimentin (VIM), HSD11B1 (11β-hydroxysteroid dehydrogenase type 1), CD44 (P-glycoprotein 1), RARRES2 (Chemerin), MB (Myoglobin), MIR675 (MicroRNA 675), and HBA1 (hemoglobin subunit alpha 1). Interestingly, Vimentin was independently studied in SIB as a marker of gliosis, and it was upregulated in the cingulate cortex of that SIB cohort. Vimentin immunoreactivity was evaluated by immunohistochemistry in five additional SIB samples showing increased Vimentin staining across the brain particularly in amygdala, hippocampus, and anterior cingulate cortex compared to five control NHP. Our studies support the hypothesis that variations in the glial cell physiology and stress hormone alterations contribute to the pathophysiology of SIB.

Disclosures: J. Barua: None. **R. Kariyawasam:** None. **J. Young Brooks:** None. **M. Jackson:** None. **B.L. Foret:** None. **K.M. Smith:** None.

Poster

PSTR057: Astrocytes in Aging, Neurodegenerative Diseases, and Mental Health Disorders

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR057.14/Web Only

Topic: B.09. Glial Mechanisms

Title: Glial glutamate transporter activator LDN-212320 ameliorates lipopolysaccharide-induced depressive-like behaviors and cognitive impairment in a comorbid inflammatory pain and MDD model

Authors: *A. KHAN, S. RAHMAN;
Pharmaceut. Sci., South Dakota State Univ., Brookings, SD

Abstract: Inflammatory pain and major depressive disorder (MDD) are two complex states that often coexist. Clinical observations have long recognized that individuals affected from inflammatory pain are more likely to experience symptoms of depression, anxiety, and cognitive deficits. Evidence indicates that increased inflammatory mediators including pro-inflammatory cytokines can induce excessive glutamatergic activity involving glutamate transporter in the hippocampus (HC) and prefrontal cortex (PFC) that is associated with comorbid pain and MDD. We have previously investigated that glial glutamate transporter type 1 (GLT-1) activator LDN-212320 reduces inflammatory pain and anxiety-like behavior in lipopolysaccharide (LPS)-induced comorbid pain-MDD model. The objective of the present study was to determine the effects of LDN-212320 on LPS-induced depressive-like behaviors and cognitive deficits in mice using tail suspension test (TST) and Y-maze test, respectively. In addition, we have measured the effects of LDN-212320 on GLT-1 expression in the HC and PFC using Western blot analysis. We also quantified the effects of LDN-212320 on pro-inflammatory cytokine interleukin-1β (IL-1β) level in the HC and PFC using the Enzyme-linked immunosorbent assay (ELISA). Experiments were conducted in C57BL6 male and female mice (7-9 weeks old). One-way ANOVA revealed that LDN-212320 (20 mg/kg, i.p.) significantly decreased the immobility time during TST in both male ($p < 0.0001$) and female ($p < 0.0001$) mice compared to LPS-treated group. Pretreatment with LDN-212320 significantly increased spontaneous alternation between arms during Y-maze test in male ($p < 0.05$) and female ($p < 0.01$) mice in comparison to LPS-treated group. Western blot analysis indicated that LDN-212320 significantly reversed the down regulation of GLT-1 expression in the HC and PFC of male ($p < 0.05$) and female ($p < 0.01$) mice. Pretreatment with LDN-212320 modestly reversed LPS-induced increased IL-1β level in the HC and PFC of male and female mice. Taken together, these results suggest that LDN-212320 ameliorates LPS-induced depressive-like behavior and cognitive impairment in both the male and female mice likely by upregulating glial GLT-1 expression in the HC and PFC.

Disclosures: A. Khan: None. **S. Rahman:** None.

Poster

PSTR057: Astrocytes in Aging, Neurodegenerative Diseases, and Mental Health Disorders

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR057.15/B49

Topic: B.09. Glial Mechanisms

Support: NSFC Grant 32371070
NSFC Grant 32100824
Shenzhen Science and Technology Program, Nos. RCBS20210609104606024

Title: Astrocytic EAAT2 in Basolateral Amygdala Regulates Stress-Induced Anxiety-like Behavior

Authors: *X. XU[1], Q. XIAO[2], J. TU[3];
[1]Shenzhen Inst. of Advanced Technol. Chinese Acad. of Sci., Shenzhen, China; [2]The Brain Cognition and Brain Dis. Inst., Shenzhen Inst. of Advanced Technol., CAS, Shenzhen, China; [3]Shenzhen Inst. of Advanced Technol., Guangdong, China

Abstract: The conventional perception of astrocytes solely as supportive cells within the brain has been recently challenged by empirical evidence, revealing their active involvement in regulating brain function and encoding behaviors associated with emotions. Specifically, astrocytes located in the basolateral amygdala (BLA) have been implicated in modulating anxiety-like behaviors induced by chronic stress. However, the precise molecular mechanisms underlying the involvement of BLA astrocytes in the regulation of chronic stress-induced anxiety-like behaviors remain unclear. In our investigation, we have discovered that in a model of anxiety induced by unpredictable chronic mild stress (UCMS), the expression of excitatory amino acid transporter 2 (EAAT2), a glutamate transporter primarily expressed on astrocytes, is up-regulated in the BLA. Notably, our observations indicate that targeted knockdown of EAAT2 specifically within BLA astrocytes rescues anxiety-like behavior in stressed mice. Intriguingly, the overexpression of EAAT2 in the BLA, achieved either through intracranial administration of EAAT2 agonists or through injection of EAAT2-overexpressing viruses with GfaABC1D promoters, elicits anxiety-like behavior in mice. Our single nucleus RNA sequencing (snRNA-seq) analysis further confirms that chronic stress induces an upregulation of EAAT2 specifically in astrocytes in the BLA. Moreover, through *in vivo* calcium signal recordings, we demonstrate that targeted EAAT2 knockdown exclusively within BLA astrocytes effectively mitigates anxiety-like behavior in stressed mice by modulating the activity of BLA glutamatergic neurons. Additionally, the administration of an EAAT2 inhibitor in the BLA yields a notable reduction in anxiety levels among stressed mice. These results suggest that BLA astrocytic EAAT2 are engaged in the regulation of UCMS-induced anxiety-like behavior by impacting the activity of local glutamatergic neurons, and targeting EAAT2 in the BLA holds therapeutic promise for addressing anxiety disorders.

Disclosures: X. Xu: None. **Q. Xiao:** None. **J. Tu:** None.

Poster

PSTR057: Astrocytes in Aging, Neurodegenerative Diseases, and Mental Health Disorders

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR057.16/B50

Topic: B.09. Glial Mechanisms

Support: FRQS

Title: Examining cerebellar astrocytes and Purkinje cells in depression and suicide

Authors: *C. HERCHER[1,2], G. ABAJIAN[2,3], M. DAVOLI[2], N. MECHAWAR[1,2];
[1]McGill Univ., Montreal, QC, Canada; [2]Douglas Mental Hlth. Univ. Inst., Verdun, QC, Canada; [3]Univ. of British Columbia, Vancouver, BC, Canada

Abstract: Accumulating evidence suggests that the cerebellum is involved in cognitive and emotional regulation; critical facets of brain activity that are disrupted in depression. However, little is known about depression-associated cellular and molecular alterations occurring in this brain region. Of interest are astrocytes, a heterogeneous population of glial cells involved in a variety of crucial biological functions. While post-mortem findings in the cerebral cortex indicate dysregulation of astrocytes in depressed individuals who died by suicide, the extent to which depression potentially alters cerebellar astrocytes remains a gap in the literature. Well-characterized post-mortem human cerebellar tissues from crus I were obtained from the Douglas-Bell Canada Brain Bank and included 16 neurologically healthy individuals (H) (9 male, 7 female) and 18 individuals who had a diagnosis of depression and died by suicide (DS) (9 male, 9 female). Stereology was performed counting glial fibrillary acidic protein (GFAP) immunoreactive (IR) and aldehyde Dehydrogenase-1 Family member L1 (ALDH1L1)-IR astrocytes in the Purkinje cell layer (PCL), the granule cell layer (GCL), and white matter (WM). Purkinje cells (PCs) were also quantified due to their tight connection with Bergmann glia. Stereological estimates are pending. We also investigated potential dysregulation of astrocyte communication by examining connexins, channel proteins essential in forming a functional network between astrocytes. Astrocyte connexins were visualized using in situ RNA detection (RNAscope) for connexin 30 (cx30) and connexin 43 (cx43) followed by immunolabelling for ALDH1L1. Cx43 and cx30 puncta densities within each layer were obtained. 5 ALDH1L1+ cell bodies were outlined per layer to obtain puncta densities specifically within these cells. Cx43 puncta densities were lower in DS in the PCL (29%) and GCL (36%). Cx30 puncta densities showed an overall decrease in DS irrespective of layer (41%). Cx43 puncta densities within ALDH1L+ astrocytes were slightly decreased in DS (23%). No group differences were observed for cx30 puncta densities within ALDH1L1+ astrocytes. This original study provides microscopy-based evidence for the downregulation of key astrocytic connexins in depression and suicide. Such observations support previous findings in the cerebral cortex and suggest that astrocytic dysfunction is widespread in depression. The stereology estimates of astrocytes and

PCs will determine if the observed connexin decreases are resulting from lower astrocyte densities in DS. Furthermore, it will provide seminal knowledge for potential alterations of PCs in depression.

Disclosures: C. hercher: None. **G. Abajian:** None. **M. Davoli:** None. **N. Mechawar:** None.

Poster

PSTR058: *In Vitro* Modeling of Neuroinflammation and Neurodegeneration

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR058.01/B51

Topic: C.02. Alzheimer's Disease and Other Dementias

Title: A high content imaging screening assay to identify novel neuroinflammation modulators using human patient iPSC derived microglia

Authors: *N. MIRZA[1], D. KUMAR[1], E. ROSETHORNE[1], D. SWIFT[1], P. GYASI-ANTWI[1], F. CAVALLO[1], H. SHARPLIN[2], J. TILMAN[2], D. WALLBANK[2], J. BHAGWAN[2], S. VYAS[2], T. PHILLIPS[1];
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Abstract: Neuroinflammation occurs in various chronic CNS disorders. Although novel targets that influence neuroinflammatory processes have been identified, translation to human based treatments has been slow. In Drug Discovery (DD) various tools including primary cell lines are often used to screen for new chemical matter. However, screening strategies utilising human induced pluripotent stem cells (iPSCs) can humanise early stages of DD improving translation compared to simple/reduced *in vitro cell* models. We used human iPSC-derived microglia (iMGL) from patients harbouring a loss of function mutation in triggering receptor expressed on myeloid cells 2 (TREM2) an Alzheimer's disease biomarker and developed/validated a high-content imaging-based *in vitro* phagocytosis assay to phenotypically screen for & identify novel neuroinflammation modulators. The iMGLs were phenotypically characterised by immunofluorescence, showing expression of human microglial markers Transmembrane protein (TMEM) 119, P2Y purinoceptor 12 (P2RY12), and distribution and expression of TREM2. The confocal imaging-based phagocytosis assay is a fixed timepoint, endpoint assay that allows the % of phagocytosing cells to be accurately quantified. We successfully miniaturised the assay to a 384-well format and used a pHrodo-labelled brain protein as a patho-physiologically relevant bait. Providing deeper insight into cellular mechanisms, up to five different parameters are measured in parallel: (i) total nuclei count, (ii) phagocytosis of pHrodo Amyloid-β bait, (iii) TREM2 expression/distribution, (iv) LAMP-1 co-localisation, and (v) cell morphology. We demonstrated that iMGL LoF TREM2 cells had a marked reduction in the level of basal phagocytosis compared to healthy iMGL cells. We screened 960 compounds from our in-house library using the high-content imaging assay to identify putative phagocytosis activators/enhancers. Compounds were tested at 10uM (N=3), pre-incubated with iMGL LoF

TREM cells for 60 min, after which phagocytosis was induced by adding the bait. After 2 hours, cells were fixed with 4% (v:v) paraformaldehyde and read on a Molecular Devices ImageXpress confocal instrument. Data analysis included both compound-induced cytotoxicity and % phagocytosis. We identified compounds that increased basal levels of phagocytosis in iMGL LoF TREM2 cells which are being further characterised to better understand pharmacology and define mechanism of action. Our goal has been to incorporate more predictive humanised screening assays into our DD programmes, deliver more successful projects, and identify neuroinflammation modulators to treat CNS diseases.

Disclosures: N. Mirza: None. **D. Kumar:** None. **E. Rosethorne:** None. **D. Swift:** None. **P. Gyasi-Antwi:** None. **F. Cavallo:** None. **H. Sharplin:** None. **J. Tilman:** None. **D. Wallbank:** None. **J. Bhagwan:** None. **S. Vyas:** None. **T. Phillips:** None.

Poster

PSTR058: *In Vitro* Modeling of Neuroinflammation and Neurodegeneration

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR058.02/B52

Topic: C.02. Alzheimer's Disease and Other Dementias

Title: Amyloid-beta induces toxicity and cell death in human IPSC derived neurons: Alzheimer disease in vitro model

Authors: M. BSIBSI[1], *M. DUDEK[3], C. GOMEZ-PUERTO[1], M. ZANELLA[1], S. KOSTENSE[1], M. VLAMING[1], D. F. FISCHER[2];
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Abstract: Alzheimer’s is a genetic chronic neurodegenerative disease that typically begins around the age of 60 and progressively impairs cognition and language. A key common hallmark is the accumulation of plaques containing β-amyloid that lead to synaptic failure and, eventually, neuronal death. In recent years, reproducing and studying the mechanisms behind Alzheimer’s disease’s (AD) pathology and β-amyloid plaques-dependent degeneration have been facilitated by the advent of induced pluripotent stem cells (iPSCs). We lately developed a robust AD *in vitro* model, based on the treatment of iPSC-derived glutamatergic neurons with commercially available β-amyloid aggregates. Compared to vehicle control and untreated cells, exposure of neurons to β-amyloid for 72 hours induced toxicity, as shown by the destruction of neuronal structures (stained for β-III tubulin) and the reduction of DAPI-positive healthy nuclei. In addition, neurodegeneration was further confirmed by a higher release of Neurofilament Light chain (NfL) in β-amyloid aggregate-treated neurons. Taken together, these preliminary results support the validity and strength of this model and open the path for future disease-relevant applications, including compound screening, with the goal of establishing effective treatments for AD.

Disclosures: M. Bsibsi: None. **M. Dudek:** None. **C. Gomez-Puerto:** None. **M. Zanella:** None. **S. Kostense:** None. **M. Vlaming:** None. **D.F. Fischer:** None.

Poster

PSTR058: *In Vitro* Modeling of Neuroinflammation and Neurodegeneration

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR058.03/B53

Topic: C.02. Alzheimer's Disease and Other Dementias

Title: Microglia-containing cerebral organoids model APOE4-driven Alzheimer's disease pathologies

Authors: *D. QUANG, B. DOOLING, R. A. SUMMERS, H. POTTER, N. JOHNSON; Univ. of Colorado Alzheimer's and Cognition Center, Linda Crnic Inst. for Down Syndrome Research, Dept. of Neurology, Univ. of Colorado Anschutz Med. Campus., Aurora, CO

Abstract: The *APOE* ε4 allele (APOE4) is the strongest genetic risk factor for Alzheimer's disease (AD) in the typical population and increases the risk for AD in people with Down syndrome (DS-AD) in comparison to the most common allele, APOE3. Data support the hypothesis that microglial-apoE interactions drive neuroinflammation and contribute to DS-AD progression, highlighting a valuable potential therapeutic target for improving cognition and longevity in people with DS-AD. However, little is known about the mechanisms underlying microglial-apoE interactions and their contributions to neuroinflammation and neurodegeneration in the human brain. Therefore, we developed a platform using human induced pluripotent stem cell (hiPSC)-based, microglia-containing cerebral organoids (MCOs) to: i) gain mechanistic insights into the contributions of APOE4 to DS-AD, and ii) determine whether novel drugs identified in our screen for inhibitors of the apoE4-amyloid-beta (Aβ) interaction prevent or delay DS-AD phenotypes. We used CRISPR-Cas9 gene editing to convert the genotype from APOE3/3 to APOE4/4 in an hiPSC line derived from a donor with DS, and in an isogenic control hiPSC line disomic for chromosome 21. We then developed MCOs and cerebral organoids without microglia (COs) to investigate how APOE4 affects the microglial contribution to AD pathologies in the DS brain. In our DS-AD models, we found that the microglia present in the MCOs, which were not present in the COs, expressed markers of microglial maturity, colocalized with amyloid plaques, and modulated plaque deposition and morphology at different stages of disease. APOE4/4 MCOs exhibited neurodevelopmental and/or neurodegenerative phenotypes resulting in reduced organoid size relative to APOE3/3 MCOs. We also tested compounds from the Spectrum Collection drug library that includes compounds in the U.S. and International Drug Collections and Natural Product and Discover libraries comprised of 50% FDA-approved drugs, 30% natural compounds, and 20% novel small molecule drugs. Our initial exploratory screen of 2,560 compounds identified 23 hit compounds that decreased apoE4-catalyzed Aβ fibrillization in a ThT-based amyloid assay. Three of the 23 lead drug candidates reduced intracellular Aβ neuropathology in iPSC-derived DS neurons, and we will evaluate them using our MCO models of DS-AD. Together, these studies will help delineate the molecular

pathways linking APOE4 to DS-AD and potentially identify a novel set of drugs that may prevent or delay the onset of DS-AD in APOE4 carriers in order to improve the quality of life for individuals with DS and possibly for the typical AD population as well.

Disclosures: D. Quang: None. **B. Dooling:** None. **R.A. Summers:** None. **H. Potter:** None. **N. Johnson:** None.

Poster

PSTR058: *In Vitro* Modeling of Neuroinflammation and Neurodegeneration

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR058.04/B54

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH AG084421
NIH AG068992

Title: Integration of microglia into 3D human iPSC-derived brain Microphysiological Systems for Disease Modeling

Authors: A. C. MURCHISON[1], N. BUTELET[1], M. NICHOLSON[1], *P. ZHOU[1], J. TCW[2], D. V. LESSARD[1], W. W. POON[1,3];
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Abstract: Microglia have been implicated in Alzheimer Disease Genome-wide Association Studies focused on late-onset Alzheimer Disease risk (LOAD) in which a number of human-specific genes are connected to modifying disease etiology. Because of this link between microglia and human disease, there is a growing need for a human source of microglia to model aspects of Alzheimer disease and to be utilized to identify AD/ADRD therapeutics. While human primary sources of microglia are difficult to obtain, induced pluripotent stem cell (iPSC)-derived microglia protocols have been developed to generate a renewable human microglia source, accelerating mechanistic studies on neuroinflammation and AD. These *in vitro* models recapitulate many of the salient features of *in vivo* microglia. Outside the context of a brain environment, microglia rapidly undergo transcriptomic changes and de-differentiation. Thus, recent chimera models have been developed to study microglia in a homeostatic CNS environment. While these models better recapitulate relevant disease-specific phenotypes, they are not amenable for high-throughput screening and drug discovery. Here, we describe our development of a 3D Microphysiological Systems (MPS) platform incorporating isogenic neurons, astrocytes, and microglia to recapitulate AD/ADRD neuropathological phenotypes. The ability of NeuCyte to generate these iPSC-derived cells from any genetic background enables identification of non-cell autonomous phenotypes and guides therapeutic drug discovery for AD. Importantly, this platform is scalable and translatable to high-throughput drug screening for AD/ADRD. Lastly, because this platform is modular, brain microvascular endothelial cells can be incorporated to recapitulate the CNS/BBB interface in order to study the role of BBB

dysfunction in disease, model ARIA (Amyloid-Related Imaging Abnormalities), and improve CNS drug delivery.

Disclosures: A.C. Murchison: A. Employment/Salary (full or part-time):; NeuCyte, Inc. **N. Butelet:** A. Employment/Salary (full or part-time):; NeuCyte, Inc. **M. Nicholson:** A. Employment/Salary (full or part-time):; NeuCyte, Inc. **P. Zhou:** A. Employment/Salary (full or part-time):; NeuCyte, Inc. **J. Tcw:** A. Employment/Salary (full or part-time):; Boston University. **D.V. Lessard:** A. Employment/Salary (full or part-time):; NeuCyte, Inc. **W.W. Poon:** A. Employment/Salary (full or part-time):; NeuCyte, Inc..

Poster

PSTR058: *In Vitro* Modeling of Neuroinflammation and Neurodegeneration

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR058.05/B55

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: NIH Grant R44ES029898

Title: Neural Organoids Incorporating Microglia for Interrogation of Neural Toxicity

Authors: W. RICHARDS[1], K. PARHAM[2], K. GREUEL[2], N. Y. YUAN[3], ***S. VISURI**[4], R. GORDON[2], C. LEBAKKEN[2];
[1]R&D, [3]Res. and Develop., [2]Stem Pharm, Inc., Madison, WI; [4]Stem Pharm, Inc, Madison, WI

Abstract: There is a critical need to develop multicellular human neural models that can complement and reduce the use of animals and accurately predict efficacy and toxicology in drug discovery and environmental toxicology. Most current *in vitro* models do not reflect the complexity and diversity of cell populations and cell-cell interactions found within neural tissue, particularly for neuro-immune interactions. Advances in differentiation of human induced pluripotent stem cells (hiPSCs) have allowed great strides in generating models with greater recapitulation of the multi-cellular components in the human brain. Stem Pharm's cerebral organoids contain neurons, astrocytes, endothelial cells, and microglia and leverage our proprietary synthetic hydrogel platform to form reproducible glia-containing organoids with responsive astrocytes and microglia. To demonstrate application for toxicology screening, we have developed a variety of assays using our organoids to probe acute and longer-term exposure to potential neurotoxins. These include transcriptional, cytokine, biomarker, cell viability and morphological analysis. In this study, organoids were subjected to known neurotoxins with diverse mechanisms of action and negative controls (including thalidomide, valproic acid, colchicine, benzo(a)pyrene, anthracene, rotenone, chlorpyrifos, permethrin, tricresyl phosphate, acrylamide, bisphenol A and lead acetate trihydrate). Concentrations for this screen were selected using the Developmental NeuroToxicity Data Integration and Visualization Enabling Resource (DNT-DIVER) maintained by the National Institute of Health and were 50-200 µM, depending upon compound. We performed an acute 24-hour treatment and harvested RNA for

transcriptional analysis using bulk RNASeq. We assessed differential expression (DE) (pAdj <0.05 and log2fold changes >1.2) between treatment groups and identified gene ontology (GO) sets affected by treatment. Compounds demonstrate differential effects based on mechanism of action. For example, colchicine and valproic acid transcriptional data sets demonstrate significant down-regulation of microglial specific genes, while thalidomide demonstrated expected downregulation of angiogenesis and lead acetate and chlorpyrifos demonstrated the most significant decreases in nervous system development. Our results demonstrate the importance of using multicellular systems to assess toxicities, the promising application of Stem Pharm's neural organoids for toxicology screening, and the potential for facilitating translation between pre-clinical and clinical development.

Disclosures: W. Richards: A. Employment/Salary (full or part-time):; Stem Pharm. **K. Parham:** A. Employment/Salary (full or part-time):; Stem Pharm. **K. Greuel:** A. Employment/Salary (full or part-time):; Stem Pharm. **N.Y. Yuan:** A. Employment/Salary (full or part-time):; Stem Pharm. **S. Visuri:** A. Employment/Salary (full or part-time):; Stem Pharm. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Stem Pharm. **R. Gordon:** A. Employment/Salary (full or part-time):; Stem Pharm. **C. Lebakken:** A. Employment/Salary (full or part-time):; Stem Pharm. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Stem Pharm.

Poster

PSTR058: *In Vitro* Modeling of Neuroinflammation and Neurodegeneration

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR058.06/B56

Topic: B.09. Glial Mechanisms

Title: Development of cytokine release assays for human iPSC-derived microglia

Authors: M. CURTIS, C. SAVIC, S. BURTON, M. GOEDLAND, R. FIENE, S. HILCOVE, S. SCHACHTELE, *C. B. CARLSON;
FUJIFILM Cell. Dynamics, Madison, WI

Abstract: OBECTIVE / RATIONALE: Microglia are the resident immune cells of the central nervous system (CNS) and are essential for maintenance of normal brain function. However, dysregulated microglia can contribute to a variety of neurodegenerative diseases. Thus, deciphering microglia functional states and understanding how they modulate inflammation during CNS infection holds great promise to identify key mechanisms of development, disease, and opportunities for therapeutic intervention. The differentiation of human induced pluripotent stem cells (iPSC) into microglia offers a reliable and functional source of cells for understanding microglia function in health and disease. METHODS / RESULTS: Human iPSC-derived microglia (iCell Microglia), medium, and supplements were from FUJIFILM Cellular Dynamics. These cells were differentiated from an apparently healthy normal (AHN) male donor following

the same protocol published by *Abud et al*. in 2017 (PMID: 28426964). Cytokine release and cell signaling assays were performed on iCell Microglia plated at either 30K cells/well (96w plate) or 10K cells/well (384w plate). Microglia were cultured for 3-days post-thaw to allow the cells to recover from cryopreservation. Various endpoint assays for microglia in mono-culture were developed. First, IL-6 secretion from microglia treated overnight with LPS (100 ng/mL) using an HTRF Kit (Revvity; 62HIL06PET). Stimulated microglia consistently yielded >1000 pg/mL of IL-6 with an EC50 value for LPS from 1-5 ng/mL. This assay was optimized and validated across multiple lots of iCell Microglia. Second, IL-1beta release was measured using the Lumit Immunoassay (Promega; W6030). To trigger processing and secretion of mature IL-1beta analyte, cells were sequentially treated with LPS (3 hours) and ATP (30 minutes). Third, a pSyk cellular assay was used to evaluate the TREM2-mediated signaling pathway using the THUNDER pSyk (Y525/Y526) TR-FRET Assay Kit (Bioauxilium; KIT-SYKP-100). Robust signal was achieved following exposure to pervanadate (100 uM for 30 minutes). CONCLUSIONS: These data establish a foundation for studying cytokine release and cell signaling following inflammatory activation of AHN human iPSC-derived microglia. This provides a baseline for future studies on neuroinflammation, co-culture with iPSC-derived neurons and astrocytes, and disease modeling (i.e. iPSC-microglia expressing Alzheimer's Disease-relevant TREM2 or APOE mutations). Additionally, these assays provide robust readouts for cell activation that will enable discovery of new microglia modulating compounds with more physiological relevance and therapeutic potential.

Disclosures: M. Curtis: A. Employment/Salary (full or part-time):; FUJIFILM Cellular Dynamics. **C. Savic:** A. Employment/Salary (full or part-time):; FUJIFILM Cellular Dynamics. **S. Burton:** A. Employment/Salary (full or part-time):; FUJIFILM Cellular Dynamics. **M. Goedland:** A. Employment/Salary (full or part-time):; FUJIFILM Cellular Dynamics. **R. Fiene:** A. Employment/Salary (full or part-time):; FUJIFILM Cellular Dynamics. **S. Hilcove:** A. Employment/Salary (full or part-time):; FUJIFILM Cellular Dynamics. **S. Schachtele:** A. Employment/Salary (full or part-time):; FUJIFILM Cellular Dynamics. **C.B. Carlson:** A. Employment/Salary (full or part-time):; FUJIFILM Cellular Dynamics.

Poster

PSTR058: *In Vitro* Modeling of Neuroinflammation and Neurodegeneration

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR058.07/B57

Topic: C.02. Alzheimer's Disease and Other Dementias

Title: Characterization of iPSC-derived human microglial activation using Automated, Multiplex Capillary Western blot analysis

Authors: *R. CHO[1], J. HIRSCHFELD[2], F. RAMIREZ[3], K. GARDNER[3], C. HEGER[4], M. CURTIS[5], S. SCHACHTELE[6], C. B. CARLSON[7];
[1]Develop., Cell Signaling Technol., Inc., Danvers, MA; [2]Cell Signaling Technol., Danvers, MA; [3]Bio-Techne, San Jose, CA; [4]Applications Sci., ProteinSimple, a Bio-Techne Brand, San Jose,

CA; [5]R&D Applications, FUJIFILM Cell. Dynamics, Madison, WI; [6]Product Mgmt., FUJIFILM Cell. Dynamics, Madison, WI; [7]FUJIFILM Cell. Dynamics, Madison, WI

Abstract: Microglia are the resident immune cells of the brain that have important roles in mediating inflammatory response in the central nervous system (CNS). Among other tasks, microglia are responsible for the recognition and elimination of foreign invaders and the repair of local damage to CNS tissue resulting from injury. Additionally, microglia likely play a role in Alzheimer's disease (AD) and neurodegenerative diseases. In particular, triggering receptor expressed on myeloid cells 2 (TREM2) is a receptor protein localized at the membrane of microglia that has been genetically-linked to AD and has gained significant attention as a potential therapeutic target. Investigating the role of microglial TREM2 and activation of downstream cell signaling cascades within human-relevant in vitro human models has been historically challenging. However, this is now possible through human induced pluripotent stem cell (iPSC) technology and protocols for differentiation into specialized microglia cells.
In this study, we used commercially available iPSC-derived microglia (iCell Microglia) to investigate mechanisms of TREM2 signaling using high-throughput capillary Western analysis (Simple Western). With specific TREM2 signaling antibodies that might reflect TREM2-dependent microglia functions, we compared apparently healthy normal (AHN) iPSC-derived microglia to a small panel of AD-relevant microglia, including cells that were differentiated from iPSC engineered with homozygous or heterozygous versions of a functional knockout of TREM2 or from patient-derived iPSC harboring the TREM2 R47H mutation. Cells were stimulated with lipopolysaccharide (LPS; 100 ng/mL), sodium pervanadate (100 uM), or other alternate agonists. By examining changes in cellular signaling pathways for activated microglia or TREM2 mutant cells, the different phosphorylation states (e.g. phospho-Syk) or varied levels of protein expression (e.g. YY1), may provide insight into how TREM2 mediates microglial activation, phagocytosis, cytokine release, or morphological changes that might directly contribute or ameliorate AD progression. Together, these data demonstrate how TREM2-mediated activation can vary with disease state and demonstrate how high-throughput, multiplexed capillary Western analysis on Simple Western combined with antibodies rigorously validated for Simple Western can be used on human iPSC-derived microglia to enable detailed interrogation of key cellular signaling pathways.

Disclosures: R. Cho: A. Employment/Salary (full or part-time):; Cell Signaling Technology. **J. Hirschfeld:** A. Employment/Salary (full or part-time):; Cell Signaling Technology. **F. Ramirez:** A. Employment/Salary (full or part-time):; Bio-Techne. **K. Gardner:** A. Employment/Salary (full or part-time):; Bio-Techne. **C. Heger:** A. Employment/Salary (full or part-time):; Bio-Techne. **M. Curtis:** A. Employment/Salary (full or part-time):; FUJIFILM Cellular Dynamics. **S. Schachtele:** A. Employment/Salary (full or part-time):; FUJIFILM Cellular Dynamics. **C.B. Carlson:** A. Employment/Salary (full or part-time):; FUJIFILM Cellular Dynamics.

Poster

PSTR058: *In Vitro* Modeling of Neuroinflammation and Neurodegeneration

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR058.08/B58

Topic: B.09. Glial Mechanisms

Title: Comparison of iPSC-derived and human primary primary astrocytes as an in vitro model for astrocyte activation

Authors: M. BSIBSI[1], G. VAN PUIJVELDE[1], L. GEERTS[1], S. KOSTENSE[1], *C. S. PERITORE[2], M. VLAMING[1], D. F. FISCHER[3];
[1]Charles River Labs, Leiden, Netherlands; [2]Charles River Labs, Wilmington, MA; [3]Charles River, Saffron Walden.

Abstract: Astrocytes are the most abundant glial cells in the human central nervous system. This subtype of glial cells has historically been attributed mostly a supportive function, but it is now evident that they perform many active and reactive functions in the healthy and diseased brain. Reactive astrocytes are observed in a variety of neurodegenerative diseases - ALS, Alzheimer's Disease, Huntington's Disease, Multiple Sclerosis, Parkinson's Disease and Prion Diseases - and their modulation may thus provide an avenue for mitigation of pathogenesis.As the availability of post-mortem human brain material for isolation of primary astrocytes limits the use of primary astrocytes in large drug development studies, the convenience of a robust and biologically relevant induced pluripotent stem cell (iPSC)-derived alternative is key to advance research towards actual treatment of neurodegenerative diseases. Therefore, we set out to compare and characterize these two model systems and gain a better understanding of their respective responsiveness to an inflammatory trigger.Using immunocytochemistry, the expression of key astrocyte markers (S100b, EAAT1, GFAP) and absence of microglia and neuronal markers was confirmed in primary human astrocytes isolated from brain tissue provided by the Netherlands Brain Bank and a culture of iPSC-derived astrocytes, indicative of a pure population in both model systems. Ongoing studies focus on the comparison of IL-6 and IL-8 cytokine release upon exposure to various concentrations of activating LPS and inhibition by dexamethasone.Our research sheds light on the overlap of biologically relevant properties of iPSC-derived versus human primary astrocytes. iPSC-derived astrocytes are suggested as a more accessible model that can be considered in larger target identification and compound screening studies. Subsequent downstream validation in (patient-derived) primary astrocytes and/or a co-culture model is still recommended to further enhance the chance of translational success.

Disclosures: M. Bsibsi: None. **G. van Puijvelde:** None. **L. Geerts:** None. **S. Kostense:** None. **C.S. Peritore:** None. **M. Vlaming:** None. **D.F. Fischer:** None.

Poster

PSTR058: *In Vitro* Modeling of Neuroinflammation and Neurodegeneration

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR058.09/B59

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: Xu startup package
Showalter grant

Title: Alzheimer's Disease Patient Brain Extracts Induce Multiple Pathologies in Vascularized Neuroimmune Organoids for Disease Modeling and Drug Discovery

Authors: *Y. JI, R. XU;
Basic Med. Sci., Purdue Univ., West Lafayette, IN

Abstract: Alzheimer’s Disease (AD) is the most common cause of dementia afflicting 50 million individuals worldwide, with limited treatment available. Current AD models mainly focus on familial AD (fAD), which is due to genetic mutations. However, models for studying sporadic AD (sAD), which represents over 95% of AD cases without specific genetic mutations, are severely limited. Moreover, the fundamental species differences between humans and animals might significantly contribute to clinical failures for AD therapeutics that have shown success in animal models, highlighting the urgency to develop more translational human models for studying AD, particularly sAD. In this study, we developed a complex human pluripotent stem cell (hPSC)-based vascularized neuroimmune organoid model, which contains multiple cell types affected in human AD brains, including human neurons, microglia, astrocytes, and blood vessels. Importantly, we demonstrated that brain extracts from individuals with sAD can effectively induce multiple AD pathologies in organoids four weeks post-exposure, including amyloid beta (Aβ) plaques-like aggregates, tau tangles-like aggregates, neuroinflammation, elevated microglial synaptic pruning, synapse/neuronal loss, and impaired neural network. Furthermore, after treatment with Lecanemab, an FDA-approved drug targeting Aβ, AD brain extract exposed organoids showed a significant reduction of amyloid burden. Thus, the neuroimmune organoid model provides a unique opportunity to study AD, particularly sAD under a pathophysiological relevant three-dimensional (3D) human cell environment. It also holds great promise to facilitate AD drug development, particularly for immunotherapies .

Disclosures: Y. Ji: None. **R. Xu:** None.

Poster

PSTR058: *In Vitro* Modeling of Neuroinflammation and Neurodegeneration

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR058.10/B60

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH Grant RO1 AG073360

Title: Trem2-dependent immune modulation in response to alzheimer's disease pathology using human induced pluripotent stem cell-derived microglia-like cells

Authors: *C. L. CARDONA[1,2], R. PATEL[2], G. M. FINAN[2], T.-W. KIM[2], A. A. SPROUL[1,2], A. F. TEICH[1,2,3];

[1]Pathology and Cell Biol., [2]Taub Inst. for Res. on Alzheimer's Dis. and the Aging Brain, [3]Neurol., Columbia Univ., New York, NY

Abstract: Accumulation of aggregated amyloid-β (Aβ) is one of the pathological hallmarks of Alzheimer's disease (AD), a devastating progressive neurodegenerative disease. Microglia have been shown to be central players in AD pathogenesis, yet it remains unclear whether they play a protective or harmful role during disease progression. TREM2 plays critical roles in regulating microglial immune functions and has been identified as a risk gene in AD. However, the role of TREM2 in shaping microglial responses has not been fully defined, particularly in response to soluble oligomeric Aβ42 (oAβ42). To address this, we utilized a TREM2 knockout (KO) human induced pluripotent stem cell (iPSCs) line generated by CRISPR-Cas9 gene editing and its isogenic parent line. We generated iPSC-derived microglia-like cells (iMGLs) to compare the transcriptional and functional responses of TREM2 KO iMGLs against isogenic control iMGLs in response to oAβ42 after 6 hours. Preliminary time course experiments in control iMGLs treated with oAβ42 showed a rapid inflammatory response at 6 hours that was mostly resolved by 24 hours. Bulk RNA-sequencing analysis revealed largely overlapping differentially expressed genes (DEGs) in response to oAβ42 between control and TREM2 KO iMGLs. Ontology analysis of DEGs showed significant upregulation of pathways associated with cytokine signaling and inflammation. Interestingly, TREM2 KO iMGLs had an upregulation of a restricted set of immune genes in response to oAβ42, including *CCL7* and *CXCL6*. Additionally, TREM2 KO iMGLs had reduced expression of genes associated with ribosome biogenesis. We are currently comparing our data against human microglial sequencing data sets to validate our findings in iMGLs. To characterize the functional immune response, we quantified 14 cytokines and chemokines from conditioned media of iMGLs in response to oAβ42. We observed increased secretion of IL1β and reduced secretion of the IL1 antagonist IL1RA, suggesting dysregulated interleukin 1 signaling in TREM2 KO iMGLs. Interestingly, while we saw an increase in IL1β secretion, we found that TNFα, IL6, and IFNγ were reduced in TREM2 KO iMGLs. Finally, we noticed a reduction in the secretion of the chemokines IL8 and MCP1 in TREM2 KO iMGLs. We are currently studying how different concentrations and aggregation states of Aβ42 affect iMGL inflammatory responses and the contributions of toll-like receptor signaling and TREM2-mediated signaling on cytokine production in response to oAβ42. Taken together, these findings suggest that loss of TREM2 in human microglia leads to dysregulated immune signaling and may affect immune cell recruitment.

Disclosures: C.L. Cardona: None. **R. Patel:** None. **G.M. Finan:** None. **T. Kim:** None. **A.A. Sproul:** None. **A.F. Teich:** None.

Poster

PSTR058: *In Vitro* Modeling of Neuroinflammation and Neurodegeneration

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR058.11/B61

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: NIAAA R01AA02379
NIGMS T32GM8339, T32GM135141
NCATS 1TL1TR003019
U10AA008401

Title: Ethanol induces neuroimmune dysregulation and soluble TREM2 generation in a human iPSC neuron, astrocyte, microglia triculture model

Authors: *A. J. BORELAND[1], Y. ABBO[2], A. C. STILLITANO[3], S. ZHANG[4], X. LI[5], J. DUAN[6], R. P. HART[7], Z.-P. PANG[8];
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Abstract: Alcohol use disorders (AUDs) affect substantial populations worldwide and increase the risk of developing cognitive impairments and alcohol-associated dementia. While the precise mechanisms underlying alcohol-associated neuropathology remain enigmatic, inflammation likely plays an important role in alcohol-associated neurological sequalae. We hypothesize that alcohol leads to neuroimmune dysregulation among neurons, astrocytes, and microglia that is perpetuated by innate immune signaling pathways. To investigate how alcohol dysregulates neuroimmune interactions in a human context, we constructed a neural tri-culture model, derived from human induced pluripotent stem cells (hiPSCs), comprising neurons, astrocytes, and microglia. After exposure to an intermittent ethanol exposure paradigm, we observed significant differential gene expression relating to innate immune pathways, inflammation, and microglial activation. Microglial activation was confirmed with morphological analysis and protein expression of CD68, a lysosomal-associated membrane protein and marker for phagocytic microglial activation. A striking finding in our study was increased elevation of TREM2 expression and TREM2 alternative splice variants that are predicted to give rise to soluble TREM2. These data suggest that ethanol exposure in the brain may lead to increased sTREM2 species via increases in the alternatively spliced TREM2^{219} transcript variant. Ongoing investigation aims to understand how ethanol-induced neuroinflammation and microglial activation impact neuronal functionality, and the consequence of TREM2 upregulation in ethanol exposed neural tri-cultures. Deciphering the molecular and cellular mechanisms underpinning ethanol-related neuroimmune dysregulation within a human context promises to shed light on the etiology of AUD and AUD-associated dementia, potentially driving the development of effective therapeutic strategies.

Disclosures: A.J. Boreland: None. **Y. Abbo:** None. **A.C. Stillitano:** None. **S. Zhang:** None. **X. Li:** None. **J. Duan:** None. **R.P. Hart:** None. **Z. Pang:** None.

Poster

PSTR058: *In Vitro* Modeling of Neuroinflammation and Neurodegeneration

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR058.12/B62

Topic: B.09. Glial Mechanisms

Title: Differential expression of TREM2-associated adaptor protein DAP12 in TREM2-modified microglia from human induced pluripotent stem cells

Authors: *A. KARPATI[1], **S. HANSON**[2], K. XU[2], R. KUMARAN[1], G. SAHIN[2], K.-D. CHOI[2]; [1]Abcam Inc., Cambridge, United Kingdom; [2]BrainXell Inc., Madison, WI

Abstract: Triggering receptor expressed on myeloid cells 2 (TREM2) is a lipid binding protein found on the surface of microglia. It plays an essential role in mediating microglial functions such as inflammation and phagocytosis and in the context of Alzheimer's disease (AD) has been implicated in the clearance of β-amyloid (Aβ). Genetic variants of TREM2, like the loss of function variant R47H, are associated with an increased risk of developing AD through perturbations of microglial function. Upon binding of a ligand such as Aβ, TREM2 forms a complex with DNAX-activating protein of 12 kDa (DAP12), and instigates a downstream signaling cascade. Thus, the TREM2-DAP12 pathway is crucial for microglia functions including phagocytosis, migration, cytokine secretion as well as lipid metabolism, which are essential to regulate the homeostatic microenvironment of the central nervous system.
The availability of primary microglia from healthy and diseased human tissues is restricted, and therefore generation of human microglia from gene-modified human induced pluripotent stem cells (hiPSCs) is a promising tool to model AD-associated microglia models. Using CRISPR-Cas9 technology we created TREM2^{R47H} and TREM2^{KO} microglial cell lines using hiPSCs. TREM2 modification was confirmed by DNA sequencing and western blotting. TREM2-modified and TREM2-WT hiPSC lines were differentiated into hematopoietic progenitors and then further specified into a microglia fate to produce highly a homogeneous population of TREM2-modified human microglia. Cells were characterized using imaging, flow cytometry, and western blot. TREM2-modified microglia were less adherent with shorter ramified morphologies and had lower expression of homeostatic surface markers such as P2RY12, CX3CR1, and TMEM119. They also had signs of impairment in phagocytosis when exposed to a fluorochrome-conjugated Aβ peptide (1-42) compared with WT microglia. To confirm differential expression of TREM2-DAP12-SYK complexes upon TREM2 modifications, we compared expression of TREM2, DAP12, and phosphorylation of DAP12 and SYK in hiPSC-derived TREM2-modified microglia using immunocytochemistry and ELISA. As a future approach, combination of genetic risk factors including the APOE4 allele and TREM2 alteration can provide a more relevant modeling of AD-associated microglia. Our study suggests gene-modified iPSC-derived microglia provide a reliable and scalable source to study intracellular signaling pathways of TREM2 and its interaction proteins, which could be translated to other genetic-related neurodegenerative diseases.

Disclosures: A. Karpati: A. Employment/Salary (full or part-time):; Abcam Inc. **S. Hanson:** A. Employment/Salary (full or part-time):; BrainXell Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); BrainXell Inc. **K. Xu:** A. Employment/Salary (full or part-time):; BrainXell Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); BrainXell Inc. **R. Kumaran:** A. Employment/Salary (full or part-time):; Abcam Inc. **G. Sahin:** A. Employment/Salary (full or

part-time):; BrainXell Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); BrainXell Inc. **K. Choi:** A. Employment/Salary (full or part-time):; BrainXell Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); BrainXell Inc..

Poster

PSTR058: *In Vitro* Modeling of Neuroinflammation and Neurodegeneration

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR058.13/B64

Topic: B.09. Glial Mechanisms

Support: NINDS Grant R01-NS084941

Title: Cyclophilin A (Cyp A), a ligand for Triggering Receptor Expressed on Myeloid Cells 2 (TREM2), stimulates phagocytosis during oxygen glucose deprivation and reoxygenation in human microglia

Authors: *K. L. NILLES[1], J. J. LOCHHEAD[2], M. E. TEMPKIN[2], T. P. DAVIS[2], P. T. RONALDSON[2];
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Abstract: Stroke is a leading cause of death and disability in the United States. The majority of strokes are ischemic as demarcated by cerebrovascular occlusion and resultant deprivation of oxygen, glucose, and other nutrients. Microglia, the brain's innate immune cells, are activated in response to ischemic stroke and can contribute to neuronal injury post-stroke. A subset of activated microglia have potential to promote neuronal repair through phagocytosis of cellular debris (myelin) as well as substances that enter brain parenchyma due to blood-brain barrier dysfunction (albumin). TREM2 is a critical regulator of phagocytosis in microglia. Therefore, targeting TREM2 using selective ligands or antibodies has potential for development as a therapeutic intervention in stroke. Our goal was to determine whether Cyp A, a known small molecule TREM2 activating drug, could be utilized to active phagocytosis in human microglia under experimental conditions relevant to stroke pathogenesis. Primary cultures of human microglia (hMG) or an immortalized human microglial cell line (HMC3) were exposed to hypoxic conditions (1% O_2) in glucose-free media (OGD/R) for 1 h. Cells under normoxic conditions (Nx; 21% O_2) in glucose containing media were used as controls. Subsequent to OGD/R or Nx, hMGs or HMC3 cells were treated with Cyp A (100 ng/mL) or Apolipoprotein E3 (ApoE3), a known TREM2 ligand and positive control, for 24 hours. Media containing fluorescently tagged albumin (10 ug/mL), a phagocytotic substrate, was added for 24 hours after Cyp A or ApoE3 treatment. TREM2 protein expression in cultured human microglia was confirmed by western blot analysis. Immunocytochemistry was performed by labeling cell nuclei (DAPI) and microglia cell bodies (IBA1) and imaging for cellular albumin uptake using a Zeiss Axio observer 7 microscope (n = 6 independent cultures). Western blot analysis confirmed

TREM2 expression in both hMGs and the HMC3 cell line. Additionally, we showed that Cyp A significantly increased ($p < 0.05$) the number of phagocytotic cells in OGD/R conditions relative to normoxic conditions in hMGs. Comparable observations were obtained in HMC3 cells where Cyp A also enhanced albumin phagocytosis under OGD/R conditions. Taken together, our data suggest that microglial phagocytosis can be stimulated pharmacologically under pathological conditions relevant to ischemic stroke using a TREM2 agonist. Studies are ongoing in our laboratory to determine the molecular basis of phagocytosis activation via TREM2 signaling under OGD/R and Nx conditions.

Disclosures: K.L. Nilles: None. **J.J. Lochhead:** None. **M.E. Tempkin:** None. **T.P. Davis:** None. **P.T. Ronaldson:** None.

Poster

PSTR058: *In Vitro* Modeling of Neuroinflammation and Neurodegeneration

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR058.14/B65

Topic: C.02. Alzheimer's Disease and Other Dementias

Title: The role of CaMKK2 in mediating Aβ-induced alterations in transferrin-mediated Iron trafficking and microglial activation in Alzheimer’s Disease

Authors: *M. G. SABBIR[1], A. LEE[2], M. CUDIC[3];
[1]Nova Southeastern Univ., Fort Lauderdale, FL; [2]Nova Southeastern Univ., Davie, FL; [3]Dept. of Chem. and Biochem., Florida Atlantic Univ., Boca Raton, FL

Abstract: Alzheimer's disease (AD) is a progressive neurodegenerative disorder and a leading cause of dementia. Multiple hypotheses exist regarding its pathophysiology, including abnormal amyloid or tau protein aggregation, chronic brain inflammation, excessive metal ion deposition (such as iron) in the brain, and neuronal calcium ion (Ca^{2+}) dysregulation. Increasing evidence suggests that AD pathogenesis is a complex, multifactorial process wherein multiple causal factors interact and collectively influence the disease outcome.
In recent studies, we have explored how the familial AD mutation (K670M671 to N670L671) and O-glycosylation at serine 667 (S667-O-GalNAc) or threonine 663 (T663-O-GalNAc) in amyloid-β precursor protein (APP) model glycopeptides increase susceptibility to cleavage by β-secretase, potentially influencing their toxic deposition. Additionally, we have identified that calcium/calmodulin-dependent protein kinase kinase 2 (CaMKK2) regulates receptor-mediated trafficking of iron-bound transferrin (TF). CaMKK2 is highly expressed in various brain cell types, including microglia, which are involved in neuroinflammation. It has been suggested that microglial dysfunction may disrupt iron metabolism and exacerbate iron-induced neuronal degeneration in AD, while elevated brain iron levels can alter microglial phenotype and function. Building on these observations, we hypothesized that synthetic Aβ peptides, both mutated and glycosylated, activate microglia to varying degrees and alter iron metabolism by impacting CaMKK2-mediated TF-bound iron trafficking. We treated human HMC3 microglial cells with

various mutant and glycosylated Aβ peptides and studied the effects on CaMKK2-mediated TF trafficking. Our findings indicate that treatment with non-mutated and non-glycosylated Aβ peptides significantly increased CaMKK2 protein levels, correlating with a significant increase in TF secretion by activated microglial cells. However, mutated and glycosylated Aβ peptides differed in their ability to enhance CaMKK2 protein levels and TF secretion.
Overall, our research reveals a previously unrecognized connection between Aβ-mediated microglial activation and iron metabolism through CaMKK2-mediated TF trafficking. This link may provide new insights into the interconnected pathogenic factors contributing to AD progression.

Disclosures: M.G. Sabbir: None. **A. Lee:** None. **M. Cudic:** None.

Poster

PSTR058: *In Vitro* Modeling of Neuroinflammation and Neurodegeneration

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR058.15/B66

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: Cure Alzheimer’s Fund, NIA

Title: Role for amyloid beta as an antimicrobial peptide that enhances autophagy in response to HSV1 infection in a 3D-neuronal cell culture model.

Authors: *A. TIEFENBACHER[1,2], W. A. EIMER[1], A. RODRIGUEZ[1], M. DEFAO[1], R. E. TANZI[1];
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Abstract: Herpes Simplex Virus 1 (HSV1) infection has been reported to lead to a 2.5-fold increased risk for Alzheimer's Disease (AD). We have previously shown that amyloid beta protein (Aβ) exhibits antimicrobial activities against HSV1 via binding to viral glycoproteins and entrapment of virus, thereby preventing infection. These observations led to the development of the "Antimicrobial Protection Hypothesis of AD", which postulates cerebral beta-amyloid deposition is an innate immune host-defense response to an actual or perceived infection. The role of intracellular Aβ in this process has remained unclear. Colocalization of Aβ with autophagic vacuoles during HSV1 infection suggests activation of selective autophagy - a crucial cellular defense mechanism against invading pathogens. Here, we challenged RenVM neuronal cells with HSV1 in 3D cell culture models to investigate the ability of intracellular Aβ to afford host deffense via selective macroautophagy. For this purpose, 24 hours post-infection, we assessed the expression of the selective autophagy receptors (SAR), p62, NDP52 and OPTN, and ATG8 family members LC3B and LC3C via Western Blot analysis. Additionally, we measured levels of Beclin1, a component of the Autophagy-Initiation complex, which is actively

suppressed by the neurovirulent protein ICP34.5 of HSV1, to evade autophagy. At 24 hours post-HSV1 infection, selective autophagy receptors NDP52 and p62 were significantly decreased in the Aβ overexpressing cell line H10 compared to the naive cell line G10, normalized with uninfected controls (NDP52 = - 58.59%, p=0.018; p62 = -30.94%, p = 0.042). A decrease in these markers indicates activation of selective autophagy and the significant decrease observed in the H10 cell line strongly implies Aβs facilitation of autophagy during HSV1 infection. Additionally, HSV1 significantly further suppressed Beclin1 levels in the APPKO cell line compared to Beclin1 levels in the naïve cell line G10 (Beclin1 = - 86.78% p<0.0001), suggesting that Aβ counteracts autophagy suppression during HSV1 infection. In summary, we provide evidence for increased autophagy 24 hours post-HSV1 infection in both naive and Aβ overexpressing cell lines versus APP knockout cells. These findings suggest a potential antimicrobial role for Aβ in enhancing autophagy as a potent cellular defense mechanism against HSV1. Our findings also suggest novel pathways for potential therapeutic strategies that target the underlying microbial triggers of Aβ accumulation.

Disclosures: A. Tiefenbacher: None. **W.A. Eimer:** None. **A. Rodriguez:** None. **M. DeFao:** None. **R.E. Tanzi:** None.

Poster

PSTR058: *In Vitro* Modeling of Neuroinflammation and Neurodegeneration

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR058.16/B67

Topic: B.09. Glial Mechanisms

Support: Funded by employer, Axol Bioscience

Title: Establishing a robust platform for investigating the pro-and anti-inflammatory response of iPSC-derived microglia in drug discovery

Authors: *S. HUMPHREYS, **D. WALLBANK**, J. TILMAN, H. SHARPLIN, H. RAINE, S. BARRETO;
Axol Biosci., Cambridge, United Kingdom

Abstract: Microglia are the main inflammatory cell of the brain and have been implicated in the development and progression of several neuroinflammatory and neurodegenerative conditions such as Alzheimer's Disease (AD), frontotemporal dementia (FTD) and amyotrophic lateral sclerosis (ALS). iPSC-derived microglia provide a scalable, reproducible and physiologically relevant model to study this role. Axol Bioscience have developed a robust protocol to generate microglia, with over 20 lines successfully differentiated, including those derived from healthy and patient donors and gene-edited lines.
Microglia are highly plastic cells influenced by environmental cues to drive both pro- and anti-inflammatory responses. As such, any dysregulation in their activation status can drive an exaggerated and sustained state of inflammation. iPSC-derived microglia provide a reliable

platform to study phenotypes of healthy and diseased microglia and assess the ability of novel compounds to decrease inflammation. Axol used a range of assays to investigate the activation state of microglia in response to different stimuli, as well as assessing inter batch and inter assay variability of our control (ax0664) microglia.
HTRF assays for IL8, IL6 and TNFα release demonstrated consistent effects across 3 batches of microglia, when stimulated with a concentration range of lipopolysaccharide (LPS). In addition, HTRF and ELISAs were used to assess activation states of microglia induced by lipoteichoic acid (LTA) and IL4. Further characterization by flow cytometry, investigated the effect of different stimuli and incubation times on CD80, CD83 and CD206 receptor expression. Additional profiling of ax0664 investigated the release of a broad range of cytokines, using Olink technology. Furthermore, TempO-Seq analysis was used to investigate transcriptomic profiles driven by different stimuli. Overall, this supports the ability of Axol's human iPSC-derived microglia to polarise towards different activation states. These iPSC-derived microglia can be used as a relevant platform for human drug discovery where they can help predict the action of new drugs and identify mechanisms involved in neuroinflammation.

Disclosures: S. Humphreys: A. Employment/Salary (full or part-time):; Axol Bioscience. **D. Wallbank:** A. Employment/Salary (full or part-time):; Axol Bioscience. **J. Tilman:** A. Employment/Salary (full or part-time):; Axol Bioscience. **H. Sharplin:** A. Employment/Salary (full or part-time):; Axol Bioscience. **H. Raine:** A. Employment/Salary (full or part-time):; Axol Bioscience. **S. Barreto:** A. Employment/Salary (full or part-time):; Axol Bioscience.

Poster

PSTR058: *In Vitro* Modeling of Neuroinflammation and Neurodegeneration

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR058.17/B68

Topic: C.02. Alzheimer's Disease and Other Dementias

Title: Characterization of iPSC-derived human microglial activation using high-content immunofluorescence

Authors: *S. COVENEY[1], K. LEFRANCOIS[2], R. GRAY[4], V. BAIN[3], M. CURTIS[5], C. B. CARLSON[6], S. SCHACHTELE[7], **R. CHO**[2];
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Abstract: Alzheimer's disease (AD) is the most common form of dementia, affecting more than 5.5 million Americans, it is characterized by extracellular aggregates of amyloid β peptides, intraneuronal tau aggregates, and neuronal death. Activation of microglia, the native immune cells of the brain, are keen responders and critical players in numerous neurodevelopmental conditions including an increasingly recognized role in AD pathology and neurodegeneration. In particular, triggering receptor expressed on myeloid cells 2 (TREM2) is a receptor protein

localized at the membrane of microglia that has been genetically linked to AD and has become an interest as a therapeutic target. Investigating the role of microglial TREM2 and downstream signaling cascades within human-relevant in vitro human models has been historically challenging but is now accessible using human induced pluripotent stem cell (iPSC) technology and protocols for differentiating into microglia.
In this study we used commercially available iPSC-derived microglia (iCell Microglia) to investigate mechanisms of TREM2 signaling using high-throughput immunofluorescence and specific antibodies. We first validated iPSC-microglia by staining for established microglial markers (Iba-1, TREM2, CD45), showing that the cells were highly pure and absent of markers for neurons (beta-III-Tubulin) and astrocytes (GFAP). TREM2, upon ligand binding and activation, interacts with the tyrosine kinase-binding protein DNAX-activating protein 12 (DAP12, TYROBP) to form a receptor-signaling complex. To investigate TREM2 signaling in microglia in more detail, we compared TREM2 and DAP12 localization in apparently healthy normal (AHN) iPSC- derived microglia with and without stimulation with lipopolysaccharide (LPS). We then compared the effects of TREM2 on microglial activation, phagocytosis, morphology, and DAP12/TREM2 localization using AD-relevant iPSC-microglia, engineered with either a homozygous or heterozygous functional knockout of TREM2.
The identification and implementation of antibodies for neuroscience research is not a trivial task. The antibodies used and validated in this study can be leveraged to further characterize iPSC-derived human cultures. Together, these data demonstrate the utility of high-throughput immunocytochemistry and iPSC-derived microglia for investigating the TREM2-signaling cascade and can be applied to AD therapeutic research, targeting the benefits of upregulating or downregulating TREM2-dependent microglial activation to attenuate AD pathology.

Disclosures: S. Coveney: A. Employment/Salary (full or part-time):; Cell Signaling Technology. **K. LeFrancois:** A. Employment/Salary (full or part-time):; Cell Signaling Technology. **R. Gray:** A. Employment/Salary (full or part-time):; Cell Signaling Technology. **V. Bain:** A. Employment/Salary (full or part-time):; Cell Signaling Technology. **M. Curtis:** A. Employment/Salary (full or part-time):; FUJIFILM Cellular Dynamics. **C.B. Carlson:** A. Employment/Salary (full or part-time):; FUJIFILM Cellular Dynamics. **S. Schachtele:** A. Employment/Salary (full or part-time):; FUJIFILM Cellular Dynamics. **R. Cho:** A. Employment/Salary (full or part-time):; Cell Signaling Technology.

Poster

PSTR058: *In Vitro* Modeling of Neuroinflammation and Neurodegeneration

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR058.18/B69

Topic: C.02. Alzheimer's Disease and Other Dementias

Title: In vitro co-culture models to identify mechanisms underlying neuroprotective effects of an iPSC-based cell therapy in aging and Alzheimer’s disease

Authors: *L. DIMAS-HARMS[1], J. INZALACO[1], S. BELL[1], V. MOSER[1], C. N. SVENDSEN[1], E. VALENZUELA[1,2];
[1]Regenerative Med. Inst., Cedars-Sinai Med. Ctr., Los Angeles, CA; [2]Regenerative Med. Inst., Cedars Sinai Med. Ctr., Los Angeles, CA

Abstract: Several studies have demonstrated notable enhancements in cognitive function among aged animal models following treatment with young blood, plasma, or bone marrow. We have expanded on this work by evaluating the therapeutic potential of iPSC-derived mononuclear phagocytes (iMPs) in addressing the cognitive and neural decline associated with aging and neurodegenerative disorders. Thus, multiple mouse models of aging and Alzheimer's disease (AD) received intravenous administrations of iMPs over a 3-week period. Subsequent behavioral testing revealed significant improvements in hippocampus-dependent cognitive performance, particularly in spatial working memory and short-term memory. Immunohistochemical analysis demonstrated improved neural health, including elevated levels of the synaptic transporter VGLUT1, and reductions in astrogliosis and microgliosis. Additionally, proteomic profiling of plasma and single-nucleus RNA sequencing of the hippocampus were performed to uncover potential alterations to critical aging-specific pathways induced by the treatments. We found that iMP treatments in aging mice were able to reverse several changes in plasma proteins and show rejuvenating effects on multiple hippocampal cell types, including a cell type critical for spatial learning and memory. However, the precise cellular mechanisms responsible for these rejuvenating effects remain unknown. Thus, we have now focused on exploring the potential of using in vitro models to test mechanisms underlying the effects of iMP treatment. By coculturing microglia and iMPs we aim to uncover the downstream effects found in vivo. Collectively, our data present iMPs as an innovative and personalized therapeutic approach to target the neural declines found in aging.

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Poster

PSTR058: *In Vitro* Modeling of Neuroinflammation and Neurodegeneration

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR058.19/B70

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Title: Unveiling the role of glial-derived cytokines and pro-inflammatory mediators in neurodegeneration: Insights from glia-neuron coculture model

Authors: C. DUCHEMIN, L. PETER, S. WAGNER, ***E. ANDRIAMBELOSON**;
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Abstract: Neuroinflammation is increasingly recognized as a pivotal process in the pathogenesis of various neurodegenerative disorders, notably Alzheimer's disease and Parkinson's disease.

Clinical evidence underscores elevated levels of lipopolysaccharide (LPS) signals in the brains of Alzheimer's patients, implicating them as significant contributors to inflammatory cascades underlying neurodegeneration. Here, we aimed to delineate the role and temporal dynamics of glia-derived cytokines and pro-inflammatory mediators in the progression of neuronal death.Utilizing cocultures of glia and neurons derived from rat embryo brains, we investigated the impact of LPS stimulation on inflammatory responses. Upon stimulation, an early release of pro-inflammatory cytokines (first wave of inflammatory response), including IL-1β, TNF-α, IL-1α, and CXCL10, was observed within 3 hours post-LPS. Peak cytokine release was noted around 6 hours post-LPS, followed by a marked decline for IL-1β, TNF-α and IL-1α by 48 hours, time at which neuronal death remains undetectable. However, CXCL10 levels remained elevated up to 120 hours (5 days), suggesting a sustained inflammatory environment. Subsequently, a second wave of cytokines and mediators emerged around 24 hours post-LPS, peaking around 48 hours and persisting for up to 120 hours (5 days). This second wave of inflammatory response included pro-inflammatory mediators such as nitric oxide (NO) and prostaglandin E2 (PGE2), alongside the anti-inflammatory cytokine CCL5. Importantly, neuronal death became significant at 120 hours timepoint. Crucially, pretreatment with the immunosuppressive drug, dexamethasone, fully prevented LPS-induced neuronal death, most probably via glial cells dependent inflammatory pathways. Supportive of this, LPS-induced neuronal death was not observed in pure neuronal cultures. Furthermore, we found that while the individual administration of IL-1β or TNF-α alone to the coculture system did not elicit significant injury, the addition of IL-1β and TNF-α mixture induced neuronal death. In conclusion, our study elucidates the critical involvement of glial cells in orchestrating a dynamic cascade of mediators leading to that culminate in neuronal demise. We demonstrate the synergistic effect of IL-1β and TNF-α in promoting neurodegeneration within the glia-neuron coculture system, underscoring the significance of interplay between inflammatory mediators. These findings offer valuable insights into the mechanisms underlying neuroinflammation and highlight the potential for targeted therapeutic interventions in neurodegenerative diseases.

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Poster

PSTR058: *In Vitro* Modeling of Neuroinflammation and Neurodegeneration

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR058.20/B71

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: ONR Grant 24

Title: Pro-inflammatory microglia activation in an in vitro model of traumatic brain injury

Authors: *E. BLICK[1], C. FRANCK[2,3], A. HAI[1];
[1]Biomed. Engin., [2]Mechanical Engin., Univ. of Wisconsin - Madison, Madison, WI; [3]Mechanical Engin., The Univ. of Wisconsin - Madison, Madison, WI

Abstract: Neuroinflammation following traumatic brain injury (TBI) is an elusive pathological mechanism linking TBI and neurodegenerative disease. Post-mortem analysis of TBI patients have shown an activated immune response spanning the corpus callosum up to 18 years after injury. The brain's immune surveyors, microglia, are of particular interest in neuroinflammation research as their chronic activation is associated with secondary injury, cognitive decline, and cell death. Despite their suspected involvement in pathological processes following TBI, precise assays implicating microglia with the neuroinflammatory response following varying magnitudes of mechanical impact are lacking. The majority of TBI studies are conducted *in vivo* and, although they offer biological complexity, they preclude reliable application of strain with the accuracy required to determine a correlation between impact and inflammatory response at a single cell level. Existing *in vitro* studies mitigate these difficulties but rely on unreducible injury mechanisms such as a needle-scratch or are limited to one mechanical loading condition. Therefore, we utilize a customized micro-tensile testing device to apply highly controlled mechanical stress to microglia and quantify changes in viability, morphology, and cytokine expression. Microglia are isolated from primary rat glial cultures derived from P0/P1 Sprague Dawley rats and seeded onto a dogbone-shaped polydimethylsiloxane (PDMS) substrate. The dogbone shape enables the use of high strain rates without disruption the gripping points and results in the gage region, hosting the cells, to experience a uniform strain field. The PDMS dogbone is adhered between two 3D-printed grippers that are contacted by the device to apply a range of magnitudes of uniaxial stress. Strain rates of 1 s^{-1}, 25 s^{-1}, and 50 s^{-1} are evaluated at 30% strain. The device sits on the stage of a confocal microscope and enables live-cell fluorescent imaging before, during, and after impact. Twenty-four hours later, conditioned media is removed to perform an ELISA and cells are stained with live and dead cell indicators to calculate cell viability. Cultures are then fixed and stained with DAPI and Iba-1 to quantify changes in microglia morphology. This approach enables the investigation of the effects of precise and reproducible mechanical strain and strain rate on microglia to better understand their response to injury magnitudes experienced during TBI. This work offers valuable insights into the mechanosensitive response of microglia and could improve our understanding of TBI-related neuroinflammation.

Disclosures: E. Blick: None. **C. Franck:** None. **A. Hai:** None.

Poster

PSTR058: *In Vitro* Modeling of Neuroinflammation and Neurodegeneration

Location: MCP Hall A

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Program #/Poster #: PSTR058.21/B72

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: This work is supported by a grant from the Department of Defense (W81XWH-22-1-0565 to A.K.S.)

Title: Characterization of iMicroglia from Gulf War Veterans for Studies on Neuroinflammation in Gulf War Illness

Authors: *R. BABU[1], S. RAO[1], K. CASE[2], P. W. BAAS[2], K. SULLIVAN[3], A. K. SHETTY[1]; [1]Inst. for Regenerative Med., Dept. of Cell Biol. and Genet., Texas A&M Univ. Sch. of Med., Col. Station, Texas, USA., College Station, TX; [2]Dept. of Neurobio. and Anat., Drexel Univ. Col. of Med., Philadelphia, PA, USA, Philadelphia, PA; [3]Dept. of Envrn. Hlth., Boston Univ. Sch. of Publ. Hlth., Boston, MA, USA, Boston, MA

Abstract: Gulf War Illness (GWI) affects over one-third of the veterans who served in the first Gulf War. Studies on animal models have demonstrated that the central nervous impairments in GWI are strongly associated with neuroinflammation mediated by activated microglia. To understand neuroinflammation in GWI, this study investigated the properties of iMicroglia differentiated from induced pluripotent stem cells (iPSCs) of GW veterans with or without GWI. First, six iPSC lines, three from veterans with GWI (GWI-iPSCs) and three from veterans without GWI (Control-iPSCs), were differentiated into iMicroglia. iMicroglia were characterized through microglia-specific markers such as TMEM119, CX3CR1, IBA-1, and CD11b. iMicroglia from all 6 iPSC lines displayed positive staining for these markers. However, the morphology of iMicroglia varied between iPSC lines. Two Control-iPSC lines gave rise to iMicroglia with larger soma and thicker processes. However, one Control-iPSC line gave rise to iMicroglia with relatively smaller soma and thinner processes. On the other hand, two GWI-iPSC lines gave rise to iMicroglia with relatively smaller soma and thinner processes. However, one GWI-iPSC line gave rise to iMicroglia with larger soma and thicker processes. Such differential morphology within both groups may reflect different stages of maturation attained by iMicroglia. Second, we measured the expression of genes encoding TMEM119, cathepsin D (CTSD), and CD68. The overall expression of genes TMEM119, CTSD, and CD68 did not vary between iMicroglia from Control-iPSCs and GWI-iPSCs. Third, the phagocytic activity of the generated iMicroglia was evaluated by their internalization of fluorescently labeled Aβ-42 peptide (FAM-Aβ42). Only a smaller fraction of iMicroglia derived from Control-iPSC and GWI-iPSC lines could phagocytose Aβ42 particles. It appeared that iMicroglia from GWI-iPSCs displaying smaller soma and thinner processes had reduced capacity to phagocytose Aβ42 particles than iMicroglia from Control-iPSCs displaying larger soma and thicker processes. Quantification is currently underway to determine differences in iMicroglia from Control-iPSCs vis-à-vis GWI-iPSCs. Additionally, iMicroglia were stimulated with lipopolysaccharide (LPS) to study their ability to release IL-1β. Maximal levels of iMicroglia response were observed with 100ng/ml LPS in both groups. Overall, the studies show that functional iMicroglia can be generated from iPSCs of veterans with or without GWI. Such iMicroglial populations provide a tool for additional studies to comprehend neuroinflammation in veterans with GWI.

Disclosures: R. Babu: None. **S. Rao:** None. **K. Case:** None. **P.W. Baas:** None. **K. Sullivan:** None. **A.K. Shetty:** None.

Poster

PSTR058: *In Vitro* Modeling of Neuroinflammation and Neurodegeneration

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR058.22/B73

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: Community Foundation for Greater Buffalo

Title: Ipsc model of human specific α7 nachr-dependent neuroinflammation

Authors: *I. IHNATOVYCH, R. P. DORN, R. SCHWARTZ, R.-Y. HUANG, K. SZIGETI; Univ. at Buffalo, Buffalo, NY

Abstract: Alzheimer's disease (AD), a human specific neurodegenerative disorder, is characterized by loss of memory and cognitive functions caused by neuronal loss, microglia activation and neuroinflammation. The α7 nicotinic acetylcholine receptor (α7nAChR) is implicated in AD. Amyloid beta 1-42 ($A\beta_{1-42}$), a hallmark of AD, is an agonist of the α7nAChR and binds to it with high affinity. *CHRFAM7A*, a human restricted fusion gene between *CHRNA7* and *FAM7A/ULK4*, incorporates into α7nAChR leading to a hypomorphic ionotropic receptor. More than 99% of the human population expresses *CHRFAM7A;* and it can be present in different copy number and orientation. We compared the effect of $A\beta_{1-42}$ on neuronal and immune cells in an isogenic iPSC model that includes medial ganglionic eminence (MGE) progenitors and microglia like cells (MGL) differentiated from *CHRFAM7A* null, *CHRFAM7A* nascent and isogenic *CHRFAM7A*_KI cell lines; and in human AD and age matched control macrophages (26 donors). As demonstrated by flow cytometry, ELISA, and immunofluorescence, $A\beta_{1-42}$ uptake was mitigated in a dose-dependent manner in *CHRFAM7A* carriers in both MGE progenitors and MGL that is consistent with a hypomorphic receptor. Despite a decreased $A\beta_{1-42}$ uptake, innate immune cytokine expression (interleukin 1beta, interleukin 6, and tumor necrosis factor alpha) was increased in *CHRFAM7A* carriers compared to null. This finding was consistent with release of the α7nAChR-mediated anti-inflammatory effect. In MGL, $A\beta_{1-42}$ treatment resulted in higher NF-κB activation as demonstrated by a prolonged p65 translocation to the nucleus (immunofluorescence) and an increased p65 phosphorylation (immunoblot) in *CHRFAM7A* carriers compared to null. Human variance of $A\beta_{1-42}$ effect was characterized in primary human macrophages. We demonstrated a crucial role of *CHRFAM7A* in $A\beta_{1-42}$ -induced neuroinflammation: it provides a protection against toxic concentration of $A\beta_{1-42}$ in neuronal cells and increases the innate immune response by switching the α7nAChR from an anti-inflammatory to pro-inflammatory transducer. Our iPSC model presents an opportunity to elucidate the molecular mechanism of these processes and establish high throughput screens.

Disclosures: I. Ihnatovych: None. **R.P. Dorn:** None. **R. Schwartz:** None. **R. Huang:** None. **K. Szigeti:** None.

Poster

PSTR058: *In Vitro* Modeling of Neuroinflammation and Neurodegeneration

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR058.23/B74

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: Muscular Dystrophy Association 961553

Title: Understanding Microglial States in Amyotrophic Lateral Sclerosis (ALS)

Authors: *S. KHAN[1], Y. LIN[2], M. THERRIEN[3];
[1]Univ. of California Davis, Davis, CA; [2]Broad Inst., Boston, MA; [3]Mol. and Cell. Biol., Univ. of California Davis, Davis, CA

Abstract: Amyotrophic Lateral Sclerosis (ALS) is a rapidly progressive neurodegenerative disease characterized by loss of motor neurons in the spinal cord as well as the brain. There is currently no cure for ALS. Thus, it becomes imperative to investigate the cellular and molecular mechanisms involved in disease progression to develop potential therapeutics and treatments for ALS. Microglia are dynamic immune cells of the brain that play a vital role in maintaining brain homeostasis by responding to changes in the brain environment. Ongoing research has revealed that microglia exhibit and exist in various transcriptional states, including Disease-Associated Microglial states (DAMs). Furthermore, DAMs have been observed to be involved in neurodegenerative diseases such as ALS and Alzheimer's disease (AD). However, the question of whether DAMs are protective or damaging in ALS disease progression and whether DAMs differ across other neurodegenerative disorders remains elusive. Thus, the objective of this study was to 1) compare DAM signatures of microglia in different neurodegenerative diseases and 2) assess the functional and transcriptional characteristics of microglia in ALS and how neuronal health is affected. To accomplish this study, a combination of bioinformatics analyses, single-cell transcriptomics, and stem cell models were used. More specifically, iPSC cell lines from the iNDI collection harboring ALS mutation were differentiated into iPSC-derived microglia (iMGL) and subjected to transcriptomic and functional assays. Moreover, this study incorporated single-cell transcriptomic datasets from both ALS and AD patients. Our findings suggest that ALS microglia and their signatures are distinct from those of AD microglia and provide a potential avenue for using microglial signatures to develop possible therapeutic strategies for ALS.

Disclosures: S. Khan: None. **Y. Lin:** None. **M. Therrien:** None.

Poster

PSTR059: Neural Circuit Function and Dysfunction in Alzheimer's Disease

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR059.01/B75

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH R01 (1R01NS135592-01)
NIH R03 (AG062883-02)
NIH COBRE (3P20GM121310-05,-05S2, and -06)

Title: Transcriptional Profiling Reveals Circuit Alterations Associated With Sundowning-Related Circadian Dysfunction in Alzheimer's Disease Model Mice

Authors: *P. GUPTA, R. SHUKLA, W. D. TODD, III;
Zoology and Physiol. Department, Program in Neurosci., Univ. of Wyoming, Laramie, WY

Abstract: Sundowning is a poorly understood clinical phenomenon seen in many Alzheimer's disease (AD) patients that is characterized by circadian disruption and behavioral disturbances during the late afternoon and early evening. Such sundowning symptoms take a tremendous toll on the quality of life for both AD patients and their caregivers, and are a leading factor in the decision to seek institutionalization. In the TAPP mouse model of AD, we recently showed that the development of hyperphosphorylated Tau (pTau) pathology in lateral parabrachial (LPB) neurons of the brainstem that project to the central circadian system within the hypothalamus is associated with physiological and behavioral disturbances relevant to those seen in AD patients who exhibit sundowning. These included time-dependent increases in body temperature, locomotor activity, and aggression, and both this dysfunction and LPB pTau developed earlier in TAPP females compared to males. In this study, in both female and male TAPP and wild-type mice sharing the same genetic background, we collected tissue from the LPB and circadian structures of the hypothalamus, the suprachiasmatic nucleus (SCN, the master circadian pacemaker) and the adjacent subparaventricular zone (SPZ, the major axonal relay of the SCN). Subsequently, we performed comprehensive transcriptional profiling analyses using single nucleus RNA sequencing. Our preliminary results have identified cell-specific transcriptional profiles that indicate unique pTau-related modifications specific on both sides of the LPB to SCN/SPZ circuit. These results provide insight into the molecular and neural circuit mechanisms that underlie disruptions associated with sundowning. We are particularly focusing on sex-dependent differences in the molecular signatures within these regions that may underlie the sexually dimorphic timing of circadian dysfunction and pTau in TAPP mice, as women have also been shown to develop both AD and sundowning more than men. Thus, our study has the potential to reveal therapeutic targets and pathways that lay the groundwork for more tailored interventions aimed at improving circadian function and enhancing well-being for affected individuals and reducing the rate of institutionalization.

Disclosures: P. Gupta: None. **R. Shukla:** None. **W.D. Todd:** None.

Poster

PSTR059: Neural Circuit Function and Dysfunction in Alzheimer's Disease

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR059.02/B76

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH R01 (1R01NS135592-01)
NIH R03 (AG062883-02)
NIH COBRE (3P20GM121310-05, -05S2, and -06)

Title: Sexual dimorphisms in Alzheimer's disease-related disruptions of circadian entrainment and a potential role for gonadotropin receptor signaling

Authors: *M. M. RUHMANN;
Doctoral Program in Neurosci., Univ. of Wyoming, Laramie, WY

Abstract: Sexual dimorphisms in Alzheimer's disease-related disruptions of circadian entrainment and a potential role for gonadotropin receptor signaling
Madison M. Ruhmann, Amy M. Navratil, and William D. Todd
Department of Zoology and Physiology, Program in Neuroscience, University of Wyoming
Alzheimer's disease (AD) is associated with progressive disruption of entrained circadian rhythms, and sexual dimorphisms in both AD and circadian function have been well established. However, whether sex differences in AD and circadian function share a common mechanism is unknown. Gonadotropin [follicle stimulating hormone (FSH) and luteinizing hormone (LH)] levels increase with menopause and have been suggested to contribute to the fact that two thirds of AD patients are women. Yet, it is unclear whether increased gonadotropin receptor signaling also contributes to sex differences in AD-related circadian dysfunction. In the TAPP (APPSwe-Tau) mouse model of AD, we recently showed that females develop AD-related pathology and disruptions of entrained circadian rhythms much earlier than males. Markers of circadian dysfunction were strongly associated with the development of hyperphosphorylated Tau (pTau) pathology in lateral parabrachial (LPB) neurons that project to the circadian system, including the suprachiasmatic nucleus (SCN, the master circadian pacemaker) and its primary axonal relay, the adjacent subparaventricular zone (SPZ). In this current study, we examine the sexually dimorphic role of gonadotropin receptor expression and signaling on entrained rhythms of core body temperature (Tb) and locomotor activity (LMA) in wild-type (WT) and TAPP mice. Additionally, we performed gonadectomy (GDX) at ages relevant for the development of AD pathology in TAPP mice. Our preliminary findings suggest that GDX increases variability in markers of circadian entrainment in WT mice compared to shams and increases circadian disruption and LPB pTau in GDX compared to sham TAPP mice. We also collected tissue from the LPB and SCN/SPZ regions and are using quantitative PCR to determine changes in gonadotropin receptor expression and how these differences correlate to circadian disruption. We hypothesize that there will be sexually dimorphic changes in gonadotropin receptor expression in the LPB, as both FSH and LH concentrations significantly increase with GDX and have been associated with increased deposition of AD pathology.

Disclosures: M.M. Ruhmann: None.

Poster

PSTR059: Neural Circuit Function and Dysfunction in Alzheimer's Disease

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR059.03/B77

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH Grant 1R01NS135592-01 to WDT
NIH Grant AG062883-02 to WDT
NIH Grant 3P20GM1221310-05, -05S2, and -06 wherein WDT was a Project Leader

Title: Interactions between olfactory and circadian systems in Alzheimer's Disease

Authors: *Q. JEFFS[1], A. MEJÍA[1], W. D. TODD, III[2];
[2]Zoology and Physiology, Program in Neurosci., [1]Univ. of Wyoming, Laramie, WY

Abstract: Alzheimer’s disease (AD) is the leading cause of dementia, affecting over 45 million patients globally. Patients experiencing preclinical AD start to exhibit disturbances before the onset of cognitive impairment and memory loss, the most common of which include circadian and olfactory disruptions. The olfactory and circadian centers of the brain share functional similarities and influence each other. However, the mechanisms underlying such bi-directional interactions are unknown. Research has shown that there are daily time-dependent differences in cFos expression, a marker of neuronal activation, of circadian regions in response to olfactory stimuli suggesting a pathway connecting olfactory structures to the circadian system. To understand this neural circuit, and its potential role in AD-related olfactory and circadian dysfunction, we are currently assessing olfactory discrimination and rhythms of olfactory sensitivity in wild-type (WT) and AD-model mice. To assess discrimination, we are providing a series of different odors to analyze interaction times to each presentation. To assess rhythms of sensitivity, we are presenting odors at various times of day to reveal whether there is a difference in rhythms of cFos expression between the two groups. Further, we are performing retrograde tracing to reveal which activated areas project to the circadian system, and whether these regions develop AD-related pathology. A better understanding of these circadian-olfactory interactions may improve their use as biomarkers for preclinical AD and may also provide opportunities for early interventions that can slow the progression of the disease.

Disclosures: Q. Jeffs: None. **A. Mejía:** None. **W.D. Todd:** None.

Poster

PSTR059: Neural Circuit Function and Dysfunction in Alzheimer’s Disease

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR059.04/B78

Topic: C.02. Alzheimer"s Disease and Other Dementias

Support: NIH RF1 AG059405
NIH T32 HD071866

Title: Effects of Alzheimer's disease risk factor BIN1 on L-type voltage-gated calcium channel surface localization in neurons

Authors: *K. MIKHAIL[1], N. DAVIS[2], Y. VOSKOBIYNYK[1], J. ROTH[3], E. D. ROBERSON[2]; [2]Neurol., [3]Neurobio., [1]Univ. of Alabama at Birmingham, Birmingham, AL

Abstract: Alzheimer's disease (AD) is the leading cause of dementia, afflicting over 32 million individuals. Promisingly, genome-wide association studies identified bridging integrator 1 (BIN1) as the second leading AD genetic risk factor. Yet, BIN1's contribution to AD is poorly understood. In cardiac myocytes, BIN1 transports L-type voltage-gated calcium channels (LVGCCs) to the cell surface, increasing calcium influx. In neurons, increased calcium influx drives neuronal hyperexcitability - a hallmark of AD. Interestingly, BIN1 overexpression in neurons increases firing (PMID 32657270), but the mechanism is unknown. We hypothesized that BIN1 may mediate LVGCC surface localization in neurons, as in cardiac myocytes, to increase calcium influx and thus trigger neuronal hyperexcitability characteristic of AD. Here, we asked the question: does BIN1 mediate LVGCC surface localization in neurons to induce calcium influx and resultant neuronal hyperexcitability? To determine whether BIN1 mediates LVGCC surface localization, we overexpressed human neuronal isoform 1 of BIN1 via lentiviral transduction in primary hippocampal neurons. Lentivirus encoding an mCherry fluorophore was utilized as a negative control. Following transduction, cell surface biotinylation and immunoprecipitation were performed to isolate surface proteins. We subsequently ran western blots (WB) to compare surface LVGCC expression across conditions. Additionally, live-cell calcium imaging was utilized to assess whether BIN1 induces increased calcium influx and whether this increase is due to LVGCCs. Our preliminary WB results suggest a trending increase in LVGCC surface expression when BIN1 is overexpressed. Preliminary live-cell calcium imaging data revealed a trending increase in calcium influx via surface LVGCCs when BIN1 is overexpressed. Replicates of these experiments will be performed to validate these findings. Ultimately, this project will confer an enriched understanding of BIN1. Identifying how BIN1 mechanistically contributes to neuronal hyperexcitability will enable novel therapeutic strategies targeting a leading genetic risk factor for AD.

Disclosures: K. Mikhail: None. **N. Davis:** None. **Y. Voskobiynyk:** None. **J. Roth:** None. **E.D. Roberson:** A. Employment/Salary (full or part-time):; UAB. 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.; Grants from NIH, Bluefield Project to Cure FTD, Alzheimer's Drug Discovery Foundation, site PI for clinical trials with Eisai and Lilly. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Owner of IP related to tau, royalties on mouse model licensed to Genentech. F. Consulting Fees (e.g., advisory boards); Member of SAB for AGTC, Member of DMC for Lilly, Member of Editorial Board for SfN.

Poster

PSTR059: Neural Circuit Function and Dysfunction in Alzheimer's Disease

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR059.05/B79

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH RF1 AG059405
NIH T32 NS061788
NIH T32 HD071866

Title: Loss of Alzheimer's disease risk factor BIN1 in inhibitory neurons induces network hyperexcitability and behavioral abnormalities

Authors: *N. DAVIS[1], Y. VOSKOBIYNYK[1], J. COCHRAN[1], K. MIKHAIL[1], M.-M. B. COOPER[2], E. D. ROBERSON[3];
[2]Psychology, [3]Neurol., [1]Univ. of Alabama, Birmingham, Birmingham, AL

Abstract: Alzheimer's disease (AD) is the most common neurodegenerative disease, affecting more than 6 million Americans. Despite its prevalence, much is still not understood about the disease. To better understand AD, genome-wide association studies have been conducted to identify genetic risk factors. One risk factor, a single nucleotide polymorphism in the *bridging integrator 1 (BIN1)* gene, is present in approximately 40% of the population and has the largest effect size of the common AD genetic risk factors. While the association between *BIN1* and AD has been established, the function of the protein and its contribution to AD remains understudied. Given evidence of a reduction of the neuronal isoform of *BIN1* in AD patients, we generated cell-type specific conditional knockout mice to study the effects of loss of Bin1 from various neuronal cell types. We found that a loss of Bin1 from all neurons (*Nestin*-Cre-driven) increased pentylenetetrazol (PTZ)-induced seizure susceptibility in a gene-dose dependent manner. Examining cell-type specificity, we found that a loss of Bin1 from excitatory neurons (*CaMKIIα*-Cre-driven) decreased seizure susceptibility, while a loss of Bin1 from inhibitory neurons (*Viaat*-Cre-driven) increased seizure susceptibility much like the pan-neuronal loss of Bin1. These data suggest that it is a loss of Bin1 from inhibitory neurons that drives network hyperexcitability, but does not address what type of interneurons. Parvalbumin (PV) expressing interneurons are altered in AD, contributing to inhibitory dysfunction, oscillatory network activity, and cognitive functioning. Therefore, we hypothesized that loss of Bin1 from PV interneurons contributes to network hyperexcitability and cognitive dysfunction. While Bin1 loss from PV interneurons (Bin1-pvKO) had no effect in the PTZ-induced seizure susceptibility assay, electroencephalogram (EEG) recordings showed differences in sub-epileptiform activity in the Bin1-pvKO mice compared to controls. Additionally, Bin1-pvKO mice showed very few differences from controls in traditional behavioral assays, but utilizing machine-learning based behavioral analysis, we found differences in kinematics and pose dynamics between groups. Overall, our findings show that Bin1 alters network hyperexcitability and cognitive functioning in a cell type-specific manner, but complete inhibitory loss is needed to induce widespread changes.

Disclosures: N. Davis: None. **Y. Voskobiynyk:** None. **J. Cochran:** None. **K. Mikhail:** None. **M.B. Cooper:** None. **E.D. Roberson:** A. Employment/Salary (full or part-time):;

University of Alabama, Birmingham. 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.; Grants from NIH, Bluefield Project to Cure FTD, Alzheimer's Drug Discovery Foundation, site PI for clinical trials with Eisai and Lilly.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Owner of IP related to tau, royalties on mouse model licensed to Genentech. F. Consulting Fees (e.g., advisory boards); Member of SAB for AGTC, Member of DMC for Lilly, Member of Editorial Board for SfN.

Poster

PSTR059: Neural Circuit Function and Dysfunction in Alzheimer's Disease

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR059.06/B80

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: R21AG075807
R01AG066171
Japan Agency for Medical Research and Development
Japan Society for the Promotion of Science

Title: Transplantation of Interneuron Progenitors Restores Cortical Circuit Function in an Alzheimer's Disease Mouse Model

Authors: *S. YOKOMIZO[1], M. MACI[1], A. M. STAFFORD[2], M. R. MILLER[3], S. J. PERLE[1], S. TAKAHASHI[1], H. BROWN-HARDING[4], A. LOVELY[4], M. ALGAMAL[1], T. J. ZWANG[1], D. S. RICHARDSON[4], J. R. NAEGELE[5], D. VOGT[2], K. V. KASTANENKA[1];
[1]Neurol., Massachusetts Gen. Hosp., Boston, MA; [2]Pediatrics and Human Develop., Michigan State Univ., Grand Rapids, MI; [3]Univ. of Michigan, Ann Arbor, MI; [4]Mol. and Cell. Biol., Harvard Univ., Cambridge, MA; [5]Biol., Wesleyan Univ., Middletown, CT

Abstract: Alzheimer's patient numbers are rising globally. While patients are now gaining access to disease modifying therapies, these drugs pose serious health risks. Therefore, development of innovative therapeutic strategies is a priority. Alzheimer's patients and those with mild cognitive impairment have sleep disturbances. Altered slow oscillations during deep NREM sleep facilitate disease progression. We identified disruptions in slow oscillations due to dysfunction in endogenous GABAergic interneurons in young APP/PS1 mice. We thus hypothesized that stem cell therapy using transplantation of healthy donor interneuron progenitors would rescue slow wave activity in APP/PS1 mice. We harvested medial ganglionic eminence (MGE) progenitors from mouse embryos expressing VGAT-Venus, VGAT-ChR2-EYFP, or Thy1-GCaMP6f. We transplanted progenitors via a single injection of 500,000 cells into cortex of each APP/PS1 mouse. We assessed the survival and migration of donor cells within the hosts using 3D light-sheet microscopy after tissue clearing. The cell fate and maturity

of the transplanted cells was evaluated for known interneuron markers, including NKX2.1, LHX6, SST, PV and PROX1. Furthermore, we confirmed the functionality of donor interneurons in host circuits by monitoring calcium transients with GCaMP6f using multiphoton microscopy in vivo. Finally, the effect of cell transplants on slow wave activity was measured using voltage-sensitive dye imaging in presence or absence of optogenetic stimulation. Transplanted progenitors survived, migrated within the APP/PS1 host cortex, and matured into healthy interneurons, expressing LHX6, maturity markers SST and PV and not the CGE marker PROX1. Matured donor interneurons had calcium transients, suggesting incorporation into host circuitry. Finally, cell transplantation restored slow oscillations in host APP/PS1 mice. Our work indicates that stem cell therapy may serve as a viable strategy to rescue functional impairments in cortical circuits of APP/PS1 mice. Thus, stem cell therapy holds promise for Alzheimer's patients to manage sleep impairments and slow disease progression.

Disclosures: S. Yokomizo: None. **M. Maci:** None. **A.M. Stafford:** None. **M.R. Miller:** None. **S.J. Perle:** None. **S. Takahashi:** None. **H. Brown-Harding:** None. **A. Lovely:** None. **M. Algamal:** None. **T.J. Zwang:** None. **D.S. Richardson:** None. **J.R. Naegele:** None. **D. Vogt:** None. **K.V. Kastanenka:** None.

Poster

PSTR059: Neural Circuit Function and Dysfunction in Alzheimer's Disease

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR059.07/B81

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH Grant R01AA027768
NIH Grant R01AA030293

Title: Chronic Alcohol Consumption Exacerbates Pathology and Disrupts Neurotransmission in a humanized APP knock-in Mouse Model of Alzheimer's Disease

Authors: *Y. HUANG[1,2], R. CHEN[3,4], X. WANG[3], J. WANG[3,5,4];
[1]Texas A&M Inst. for Neurosci., College Station, TX; [2]Department of Neuroscience and Experimental Therapeutics, College of Medicine, Texas A&M University Health Science Center, Bryan, TX; [3]Dept. of Neurosci. and Exptl. Therapeut., Col. of Med., Texas A&M Univ. Hlth. Sci. Ctr., Bryan, TX; [4]Interdisciplinary Faculty of Toxicology, College of Veterinary Medicine and Biomedical Sciences, Texas A&M University, College Station, TX; [5]Texas A&M Institute for Neuroscience, College Station, TX

Abstract: Excessive alcohol consumption is associated with the development of chronic diseases and neurological impairments. Although numerous epidemiology studies have suggested a link between alcohol use history and Alzheimer's disease (AD), the direct evidence to support this connection and the underlying mechanisms of this association are not well understood. In our study, we utilized a humanized APP knock-in (hAPP-KI) mouse model of AD to investigate the

impact of chronic alcohol consumption on AD progression. Starting from 2 months old, hAPP-KI mice experienced 4 -months of alcohol exposure using the intermittent access 2-bottle choice drinking procedure. We then conducted electrophysiology recording, live confocal imaging, histology study, and behavior tests. Our findings showed that alcohol-consuming hAPP-KI mice exhibited higher levels of amyloid-beta (Aβ) accumulation and enhanced glutamatergic transmission in the cortex, as compared to water controls. Additionally, we found that microglia-depleted WT mice displayed similar enhancements in glutamatergic transmission in the cortical neurons. Furthermore, immunohistochemical analyses demonstrated an increase in the number of increased activation microglia within Aβ plaques in alcohol-consuming mice. Importantly, live-tissue confocal imaging revealed a reduction in striatal acetylcholine (ACh) levels in alcohol-consuming mice relative to water controls. In summary, our findings provide direct evidence that chronic alcohol consumption exacerbates AD pathology and disruption of neurotransmission in the cortex. Furthermore, our results suggest that alcohol-induced microglial activation may represent a key mechanistic link between alcohol consumption and AD progression. These insights highlight the importance of further elucidating the neurobiological effects of alcohol on AD pathogenesis.

Disclosures: Y. Huang: None. **R. Chen:** None. **X. Wang:** None. **J. Wang:** None.

Poster

PSTR059: Neural Circuit Function and Dysfunction in Alzheimer's Disease

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR059.08/B82

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: Marie Skłodowska-Curie Fellowship ANCoDy
ONO Rising Star Fellowship

Title: Assessment of gradual perceptual learning by behaviour and neuron-glia imaging in AD model mice

Authors: P. KNAK[1], T. YOKOYAMA[2], M. SAKAMOTO[3], M. NEDERGAARD[4], H. HIRASE[5], ***A. ASIMINAS**[6];
[1]CTN - Ctr. for Translational Neuromedicine, Univ. of Copenhagen, Copenhagen, Denmark; [2]Neurochemistry, The Univ. of Tokyo, Kyoto, Japan; [3]Kyoto Univ. Inst. For Virus Res., Kyoto, Japan; [4]Ctr. for Translational Neuromedicine, Univ. of Copenhagen, Rochester, NY; [5]Ctr. for Translational Neuromedicine, Univ. of Copenhagen, Copenhagen, Denmark; [6]Centtre for translational Neuromedicine, Univ. of Copenhagen, Copenhagen, Denmark

Abstract: Understanding the cellular mechanisms underlying learning and their alteration in Alzheimer's disease (AD) is crucial for developing targeted therapies. We aimed to elucidate coordinated astrocytic and neuronal activities in learning, with a specific focus on their dynamics influenced by experience and alterations in AD. Using calcium imaging of neurons and

astrocytes in the APP/PS1 double transgenic Alzheimer's disease mouse model, we investigated behavioural and cellular responses to repetitive, in comparison with littermate wild type (WT) mice.
We collected from 32 female and male mice. Our findings revealed that while WT mice exhibited progressively decreased arousal to repetitive visual stimuli over seven days, consistent with prior studies, mice exposed to random stimuli showed no significant behavioural changes. Intriguingly, APP/PS1 mice did not show habituation to repetitive visual stimuli. This was mirrored in a distinct pattern of astrocytic activity, particularly a reduction in calcium activity in APP/PS1 mice astrocytes, notable only on the final day of the visual habituation protocol. These results highlight a unique, experience-dependent astrocytic activity phenotype in the APP/PS1 mouse model of AD, suggesting altered cellular mechanisms. We are currently expanding upon these initial findings through in-depth imaging data analysis. Future research directions include investigating molecular changes that may underlie the abnormal cellular response to novelty habituation in APP/PS1 mice.

Disclosures: P. Knak: A. Employment/Salary (full or part-time):; ONO Pharmaceuticals. **T. Yokoyama:** None. **M. Sakamoto:** None. **M. Nedergaard:** None. **H. Hirase:** None. **A. Asiminas:** A. Employment/Salary (full or part-time):; ONO Pharmaceuticals. 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 Pharmaceuticals.

Poster

PSTR059: Neural Circuit Function and Dysfunction in Alzheimer's Disease

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR059.09/B83

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH grant number AG081931

Title: Increasing cerebral blood flow increases visual cortex orientation selectivity in mouse models of Alzheimer's disease

Authors: R. T. ZIRKEL[1], M. ISAACSON[1], M. LAMONT[1], *N. NISHIMURA[1], **C. B. SCHAFFER**[2];
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Abstract: Alzheimer's disease (AD) is characterized by progressive, irreversible neurodegeneration, leading to memory loss and cognitive decline. In mouse models of AD, global decreases in cerebral blood flow (CBF) are brought on by the plugging of capillaries by arrested neutrophils, and the administration of antibodies against the neutrophil-specific surface protein Ly6G (anti-Ly6G) reduces these capillary stalls in minutes and improves cognitive function within hours. This suggests that at least some aspects of neural activity impairment are

reversible, but the mechanism of this recovery - and what specific neural activity is normalized - is not yet known. Previous studies found orientation tuning selectivity to drifting gratings in primary visual cortex neurons to be decreased in mouse models of AD. Here, we hypothesized that the impaired neural response can be improved by CBF increase with anti-Ly6G treatment in the APP/PS1 mouse model of AD. We transduced neurons in layer 2/3 of the primary visual cortex (V1) of mice with a fluorescent calcium indicator using AAV9 vectors (pAAV.Syn.GCaMP6s.WPRE.SV40, 10^{12} vg/mL). We injected fluorescent labels methoxy-X04 to detect amyloid plaques and Texas-red-dextran into the vasculature to detect blocked capillaries. Drifting grating visual stimuli were presented to isoflurane-anesthetized mice using MouseGoggles during recording with two-photon microscopy before and one day after anti-Ly6G or isotype control antibody administration (4mg/kg). At baseline and consistent with prior results, APP/PS1 mice exhibited both decreased spontaneous neural activity and decreased orientation selective tuning of neurons to drifting gratings, as compared to wild-type mice. One day after anti-Ly6G administration to reduce stalls and increase CBF in APP/PS1 mice, we observed a significant increase in orientation tuning relative to baseline in the same animals, and an increase in spontaneous activity in the V1 neuron population. Isotype control treatments had no effect on spontaneous or stimulus-triggered neural activity. Our data suggests some aspects of the neural and behavioral deficits in AD are acutely recoverable by increasing CBF. Such recovery demonstrates a promising avenue for future therapeutic targets to combat the symptoms of AD in humans.

Disclosures: R.T. Zirkel: None. **M. Isaacson:** None. **M. Lamont:** None. **N. Nishimura:** None. **C.B. Schaffer:** None.

Poster

PSTR059: Neural Circuit Function and Dysfunction in Alzheimer’s Disease

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR059.10/B84

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: Ministry of Science, Technology and Space - 0601166781

Title: Analyzing EEG Signatures in a Mouse Model of Alzheimer's Disease: Implications for Early Detection

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Abstract: The development of predictive tools for Alzheimer's disease (AD) is crucial for timely intervention to slow down or prevent disease progression, as well as for monitoring new treatment and prevention strategies, which often rely on animal models. In this study, we propose

a novel analytical approach to identify electroencephalographic (EEG) features potentially associated with AD development, using a transgenic 5xFAD mouse model. The 5xFAD model is characterized by early onset amyloid plaque accumulation, leading to progressive cognitive impairment. Our aim was to chronologically characterize alterations in brain electrical activity accompanying the pathological process, in order to identify specific electrical patterns indicative of the disease's latent period. We conducted 3-hour EEG recordings from the prefrontal (PFC) and parietal cortices, as well as the hippocampal region, in freely moving 4-, 6-, and 9-month-old 5xFAD mice compared to C57BL/6 wild type (WT) mice. Employing several methodological approaches, including power spectrum density, Hilbert spectrum, principal and independent component analysis, bispectrum analysis, phase-amplitude coupling (PAC), and a computational model based on the Ensemble classifier - Boosted Trees algorithm implemented in MATLAB, we made several key observations: A) 5xFAD mice exhibited lower signal energy over the hippocampus; B) In theta, alpha, beta, and gamma bands, there was alternating phase shift over time in 5xFAD mice across the 1-100 Hz range compared to their WT counterparts; C) PAC patterns differed between 5xFAD and WT mice over the hippocampal and PFC regions. Combining these findings, we developed a classifier capable of differentiating the brain electrical behavior of 5xFAD and WT mice with an accuracy of 96% as early as 4 months of age. Interestingly, alterations in brain electrical activity in 5xFAD mice were accompanied by an age-dependent change in the glutamate/GABA ratio It indicates a shift in excitatory/inhibitory (E/I) balance, as detected by chromatographic analysis (UHPLC) of the extracted neurotransmitters from the 1, 2, 4, 6 and 9 months mice (PFC, hippocampus regions). Our findings suggest that the deterioration of E/I balance observed during AD-like pathology in 5xFAD mice coincides with alterations in EEG patterns. These results support the use of EEG methodology as a robust approach for predicting the development of AD.

Disclosures: P. Buzaeva: None. **M. Kabirova:** None. **Y. Zuntz:** None. **I. Michaelevski:** None.

Poster

PSTR059: Neural Circuit Function and Dysfunction in Alzheimer’s Disease

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR059.11/B85

Topic: E.09. Motor Neurons and Muscle

Support: NIA/NIH 1R01AG067758
NIA/NIH R01AG067758-02S2

Title: Motor dysfunction, an early pathophysiological feature preceding cognitive decline in Alzheimer's Disease

Authors: *A. ROSHANI DASHTMIAN[1], F. B. DARVISHI[2], S. AYYAGARI[3], P. MOORE[2], N. KERR[4], W. ARNOLD[5];
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Abstract: Alzheimer's disease (AD) is primarily associated with cognitive decline but is increasingly recognized for early signs of motor dysfunction. The link between motor dysfunction and cognitive impairment in AD, as well as the underlying mechanisms, remain unclear. Importantly, mobility loss and frequent falls are major contributors to morbidity and mortality in patients with AD. Accordingly, our study explores the temporal relationship of motor and cognitive function in the 5XFAD mouse model (n=18, 50% males), compared to age-matched wildtype controls (C57BL/6J, n=20, 50% males). Starting at 2 months of age, cognitively presymptomatic mice underwent a longitudinal battery of electrophysiological, motor function and cognitive tests including muscle excitability (compound muscle action potential, CMAP), corticospinal excitability (Motor Evoked Potential, MEP, following cervical spinal stimulation), in vivo plantarflexion muscle contractility following tibial nerve stimulation, strength (grip testing), motor power (max weight pulling), and cognition (Novel Object Recognition test, NOR). These assessments were performed every 2 months with repeat testing planned through 12 months of age. At 6 months, 5XFAD mice exhibited a 14% decrease in hindlimb grip strength (p=0.0952) and a 12% reduction in muscle power, as shown by the max weight pulling test (p=0.039), compared to control mice. The NOR test revealed no changes through 6 months. There was a 57% increase in MEP amplitude measures from the gastrocnemius muscle following cervical spinal cord stimulation in 5XFAD mice compared with wildtype controls (p=0.0018) at 2 months. However, the MEP amplitude was no longer significantly increased at 4 and 6 months. CMAP amplitude remained unchanged recorded from the gastrocnemius but showed a 36% reduction recorded from the intrinsic foot muscle (p=0.0257) at 6 months indicating a length dependent loss of muscle excitability. Nerve stimulated plantarflexion muscle contractility remained unchanged through 6 months. Our data indicate an early decline in motor function and neuromuscular excitability prior to overt cognitive dysfunction. Furthermore, neuromuscular dysfunction was preceded by alterations in corticospinal excitability. These results underscore that motor dysfunction is an early feature of AD and highlight the need for further exploration of the underlying mechanisms. By elucidating the temporal relationship between motor and cognitive decline in AD, our ongoing longitudinal study will provide an understanding for how motor
dysfunction affects disease progression and may inform the development of novel therapeutic strategies.

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Poster

PSTR059: Neural Circuit Function and Dysfunction in Alzheimer’s Disease

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR059.12/B86

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: P01AG073082

Title: Cognitive deficits and network dysfunction in mice modelling the pathogenic interaction of amyloid-beta and apoe4

Authors: *E. S. BRADY[1], J. SHIN[2], J. HERBERT[1], P. NAMBIAR[3], J. J. PALOP[4]; [1]Gladstone Inst., San Francisco, CA; [2]Gladstone Inst. of Neurodegenerative Dis., Gladstone Inst., San Francisco, CA; [3]Gladstone Inst. of Neurolog. Dis., San Francisco, CA; [4]Gladstone Inst. & UCSF, South San Francisco, CA

Abstract: The etiology of Alzheimer's disease (AD) is multifaceted, involving multiple complex interactions between pathologies such as amyloid-beta, ApoE4 and microtubule associated protein tau. In particular, evidence points towards amyloid-beta and ApoE4 as being crucial in the development of both sporadic and familial forms of AD, but how these two pathologies interact to affect cellular and network function is unknown. To model this interaction, we bred together mice that express humanized APOE4 with the App^{NL-F} mouse model which contains a humanized amyloid-beta coding sequence flanked by the familial Swedish and Iberian mutations. We chose to use humanized knock-in mouse lines as opposed to transgenic, over-expression models as it allows us to study these proteins under more physiological levels of expression. The genotypes studied were $APOE^{E4/E4}$ x $App^{NL-F/NL-F}$ (E4NLF), $APOE^{E4/E4}$ (E4), $App^{NL-F/NL-F}$ (NLF) and wild-type (WT) littermates. Using only female mice, we observed slight cognitive deficits at 12-13-months of age in E4NLF and NLF animals when mice were tested in the Morris water maze. These same mice also exhibited changes to their spontaneous behavior in an open-field, measured using deep learning methods. In a separate cohort at 15-months old, implantable wireless devices continuously recorded EEG and EMG signals for 2 weeks while mice were in their home cage. Offline analysis of the signals revealed that relative to WT controls, E4NLF and NLF mice had a reduction in the power of both gamma and theta oscillations during the dark cycle. Additionally, these genotypes exhibited locomotive hyperactivity, circadian disruptions, epileptiform activity as well as changes to the sleep cycle. Taken together, these results point towards amyloid-beta as being the driving factor affecting network activity and cognition between 12-15 months of age. Behavioral testing and EEG analysis at later time points is currently being carried out to asses if the effects of ApoE4 appear at later pathological stages.

Disclosures: E.S. Brady: None. **J. Shin:** None. **J. Herbert:** None. **P. Nambiar:** None. **J.J. Palop:** None.

Poster

PSTR059: Neural Circuit Function and Dysfunction in Alzheimer's Disease

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Program #/Poster #: PSTR059.13/B87

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: CIHR Grant (to LAMG PJT 148662)
Alzheimer's Association (to PDG AARF-17-529705)
Brain Canada (to PDG)
NSERC CGS-M (to BHL)
UBC Marshall's Scholar Program (to BHL)
womenmind (to BHL)

Title: The influences of previous parity and APOEε4 genotype on functional connectivity in middle-aged rats

Authors: *B. H. LEE[1,2], M. CEVIZCI[3], S. LIEBLICH[3], Y. WEN[3], P. DUARTE-GUTERMAN[4], L. A. GALEA[1,5];
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Abstract: Females have a higher lifetime risk of Alzheimer's disease (AD) and show greater neuropathology and cognitive decline than males. Furthermore, possession of APOEε4 alleles confers greater risk and burden of AD in females than males. To better understand how AD affects females, female-specific factors like parity (pregnancy and motherhood) are important to consider. Indeed, parity impacts brain aging trajectories in both humans and rodents, and has been associated with increased risk, greater neuropathology, and earlier age of onset for AD. Neurogenesis, the production of new neurons, declines with AD severity as well as APOEε4 genotype. Furthermore, functional connectivity between the hippocampus and frontal lobes has been shown to be disputed in individuals with AD. However, there is limited research on how previous parity and APOEε4 genotype together influence AD endophenotypes. As such, this research explores the long-term influences of parity on cognition, neurogenesis, and functional connectivity in middle-aged rats depending on APOEε4 genotype.
We used a rat model of sporadic AD risk that expresses humanized (h) APOEε4. Wildtype and hAPOEε4 rats were either nulliparous (never mothered) or primiparous (one-time mothers). At middle age, rats were tested on the delayed win-shift version of the spatial working memory task, in which performance relies on the integrity of the hippocampus and frontal cortex. Rats were then euthanized to examine markers of neurogenesis and functional connectivity between the hippocampus and frontal cortex. We found that primiparous hAPOEe4 rats increased use of a non-spatial strategy in the cognitive task and had fewer and less active new-born neurons in the dentate gyrus of the hippocampus than all other groups. Together, these findings suggest that primiparous hAPOEε4 rats are less likely to recruit the hippocampus during spatial working memory. Analyses are ongoing to examine functional connectivity. This work underscores the importance of considering genotype and female-specific factors in aging and AD research.

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Poster

PSTR059: Neural Circuit Function and Dysfunction in Alzheimer's Disease

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR059.14/B88

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIA AG062581

Title: Consequences of locus coeruleus degeneration in a rat model of Alzheimer's disease

Authors: *A. E. MARRIOTT[1], M. A. KELBERMAN[2], J. P. SCHROEDER[1], A. KORUKONDA[1], B. S. PATE[1], K. E. MCCANN[1], D. WEINSHENKER[1];
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Abstract: Background: The noradrenergic locus coeruleus (LC) is exceptionally susceptible to insult in Alzheimer's disease (AD), beginning with the early accumulation of hyperphosphorylated tau and culminating in frank neuronal loss. Inducing LC damage with the selective neurotoxin N-(2-chloroethyl)-N-ethyl-2-bromobenzylamine hydrochloride (DSP-4) exacerbates AD-like neuropathology and cognitive impairment in amyloid- and tau-based murine models of AD, indicating a causal relationship between LC degeneration and disease progression. Unlike other rodent models, TgF344-AD rats display both amyloid and tau pathology, and moreover develop endogenous hyperphosphorylated tau in the LC prior to other brain regions as observed in human AD. By inducing LC-specific damage in TgF344-AD rats using DSP-4, this study will explore the impact of LC degeneration on AD- and noradrenergic-relevant behaviors.
Methods: At ~1 month of age, male and female TgF344-AD rats and wild-type littermates received 2 injections of DSP-4 (50 mg/kg, i.p.) or saline spaced 1 week apart, followed by single monthly injections until ~5 months of age. Behavioral testing began ~1 week following the final injection to assess social behavior, stress-induced repetitive behaviors, arousal, anxiety-like behavior, and learning and memory.
Results: In general, the effects of DSP-4 were more pronounced than those of genotype. DSP-4 treated animals showed blunted stress-induced repetitive behaviors and circadian locomotor activity. DSP-4 animals also displayed augmented contextual freezing in a fear conditioning paradigm. There was a significant effect of genotype on social behavior, where TgF344-AD rats failed to display the normal preference for the novel conspecific in the social discrimination paradigm.
Conclusions: DSP-4-induced damage of the LC-noradrenergic system did not exacerbate or uncover behavioral deficits in TgF344-AD rats. However, regardless of genotype, DSP-4 had profound effects on stress-induced repetitive behaviors, locomotor activity, and contextual fear memory. The reduction in repetitive behaviors as well as diminished locomotor activity in NE-depleted rats is consistent with the important role of LC-NE transmission in arousal. We also revealed a novel effect of genotype on social behavior. While WT animals spent more time exploring the side of the arena with the novel animal, Tg animals did not display a preference, indicative of a social memory deficit. We are currently assessing the effects of the DSP-4 on AD-like pathology and noradrenergic dysfunction using immunohistochemistry and high-performance liquid chromatography.

Disclosures: A.E. Marriott: None. **M.A. Kelberman:** None. **J.P. Schroeder:** None. **A. Korukonda:** None. **B.S. Pate:** None. **K.E. McCann:** None. **D. Weinshenker:** None.

Poster

PSTR059: Neural Circuit Function and Dysfunction in Alzheimer's Disease

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR059.15/B89

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: RISE Fellowship Grant
HBGI - Title III Grant
K01 Career Development Grant

Title: Aging effects of central acetylcholine release on cholinergic-linked behavior

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Abstract: Acetylcholine (ACh) is a ubiquitous neurotransmitter found in both the central nervous system (CNS) and peripheral nervous system (PNS). Following its synthesis in the cytoplasm of cholinergic neurons, acetylcholine is transported and stored in synaptic vesicles for exocytotic release by the vesicular acetylcholine transporter (VAChT). Vesicular Acetylcholine Transporter (VAChT) is a protein that transports ACh from the cytoplasm to the synaptic vesicles. Despite the wealth of knowledge regarding the regulation of ACh synaptic transmission, including the fact that cholinergic decline is an important feature of aging, behavior related to changes in ACh release during aging, remains an important area of study. Our lab has previously identified that mutations in VAChT disrupt movement, learning, memory, and survival. We are interested in using Drosophila as a model system to understand how age-related alterations in ACh synapses, change the expression and function of VAChT, and the role of an overexpression of VAChT, in that process. We are using immunohistochemistry to measure the effect of aging on the cholinergic synapse in both wildtype and VAChT overexpressors. We are also measuring the effects that changes in VAChT levels have on ACh-linked behaviors, like locomotion and sleep. Both behavioral circuits are known to contain strong cholinergic inputs, although the mechanism through which the neurotransmitter regulates both behaviors during the lifespan, is not fully understood. We report that the overexpression of VAChT causes an increase in sleep in young female flies but has no effect on males. We now investigate the sleep states in old VAChT-overexpressing flies. Moreover, building on our published work, that VAChT overexpressors have elevated VAChT expression in synaptic vesicles and at/around the plasma membrane of cholinergic neurons, we present results of our preliminary investigations of the expression and distribution of the neurotransmitter in aged brains. We build on our prior data about increased vesicular expression of VAChT in the overexpressors; taken together, these findings support the idea of a central role for ACh release in mediating conserved neurological

functions and future studies will elucidate the synaptic physiological changes that accompany these neuronal effects of acetylcholine.

Disclosures: D. Osborne: None. **H.O. Lawal:** None. **P. Meera:** None.

Poster

PSTR059: Neural Circuit Function and Dysfunction in Alzheimer's Disease

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR059.16/B90

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: BX004693
BX004646

Title: Novel Therapeutic Approach for Comorbid Psychosis in Alzheimer's Disease

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Abstract: An often-overlooked symptom of Alzheimer's Disease (AD) is psychosis (hallucinations and/or delusions), which occurs in up to 50% of cases. The main risk factor for AD is age and the standard treatment for comorbid psychosis is antipsychotics; however, the FDA has issued a black box warning due to the risk of increased death in elderly dementia patients. Thus, there are few options available to treat comorbid psychosis in AD. Recently, the genetic contribution to psychosis within AD patients has been studied and an association of single nucleotide polymorphisms (SNPs) within ENPP6 and SUMF1 genes was reported. ENPP6 is highly expressed in the brain and ENPP6 knockout mice show hippocampal alterations that are consistent with AD patients with psychosis. SUMF1 is also highly expressed in the brain and can lead to deficits in myelination, consistent with what is seen in AD patients with comorbid psychosis. The symptoms of psychosis are thought to be driven by aberrant dopamine transmission in mesolimbic brain regions, known as the dopamine hypothesis of psychosis, which is driven by hyperactivity in the hippocampus. Here, we show that knockdown of ENPP6 or SUMF1 in the hippocampus of Sprague Dawley rats is sufficient to produce psychosis-like alterations in dopamine neuron activity. ENPP6 knockdown likely alters the production of sphingosine-1-phosphate (S1P) which acts at S1P receptors (S1PR). These receptors function in multiple systems but particularly relevant in the nervous system to regulate myelination and oligodendrocyte/glial cell survival which has been shown to be affected in AD. Thus, restoring S1P signaling may be an effective treatment for comorbid psychosis in AD. Fingolimod is an FDA approved non-specific agonist of S1P receptors. Here we demonstrate that administration of fingolimod, directly into the vHipp, was able to restore the altered dopamine activity to control levels in a transgenic model of AD pathology (TgWKY-AD rats). Furthermore, chronic systemic administration was also able to reverse aberrant dopamine system function in the

TgWKY-AD model. Taken together, targeting S1P receptors may be a promising novel target for the treatment of comorbid psychosis in Alzheimer's Disease.

Disclosures: S. Perez: None. **N. Eassa:** None. **A.M. Boley:** None. **D.J. Lodge:** None.

Poster

PSTR059: Neural Circuit Function and Dysfunction in Alzheimer's Disease

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR059.17/B91

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH MH113257 (to AD)
NIDA-DA023999 (to PR)

Title: Age related changes in cholinergic cells of the NHP striatum

Authors: L. GREENE[1], P. RAKIC[2], *A. DUQUE[3];
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Abstract: The cholinergic system is important in arousal and attention. Deterioration and death of cholinergic cells is a main pathological signature of Alzheimer's disease (AD). The current investigation focuses on understanding changes in cholinergic cell populations across ages, brain regions, and gender in the non-human primate (NHP) rhesus macaque as a model for human. Because neurons and glia cells are the basic building blocks of neural networks and quantification of cell numbers is a fundamental aspect of biological research, understanding how cholinergic cell numbers vary is essential to our understanding of their involvement in normal and pathological brain physiology. However, proper quantification requires unbiased methods. Traditional stereology for cell counts is extremely laborious and time-consuming, and the need for several human individual observers can introduce biases over time. To overcome this limitation, we used artificial intelligence (AI) to expedite the counting process in an accurate, reproducible, and unbiased manner. Here we used the cloud based Aiforia^{TM} platform to create an in-house algorithm to measure striatal area and to identify and count cholinergic cells. Materials were drawn from Collection 6 (https://macbraingallery.yale.edu/collection6/) of the MacBrain Resource Center (MBRC). In n=6 naïve female macaques, the first 18 sections (coronal, one hemisphere) rostral to caudal (with the first section being where the caudate nucleus first appears) were analyzed for cholinergic cells identified immunohistochemically by the presence of the enzyme acetylcholine transferase (ChAT+). The animals were divided in two groups: 3 infants ages 74, 75 and 78 days postnatal and 3 adults ages 9.80, 10.08 and 10.22 years old. Analysis of these 108 sections indicates that, on average, 1) the density of ChAT+ cells increases steadily from rostral to caudal ($y=14.8x+143$ $R^2=0.96$ vs. $y=10.5x+123$ $R^2=0.94$), 2) the rate of increase is similar in both age groups, and 3) there is a lower ChAT+ cell density in

the adult specimens than in the infants (mean+/- SD 284+/80 vs. 223+/-58; p=0.01). Our preliminary results strongly indicate age related changes in the striatal ChAT+ population in normal female animals. This encourages further research to establish if the same trends are present in the basal forebrain, in expanded age groups, and in males. Because the investigation is in the basal ganglia, besides the obvious relationship to our understanding of motor deficits, these details may help us understand why the incidence of AD is different in human males and females and why ChAT+ cells in the basal forebrain seem more heavily affected than in other regions.

Disclosures: L. Greene: None. **P. Rakic:** None. **A. Duque:** None.

Poster

PSTR059: Neural Circuit Function and Dysfunction in Alzheimer's Disease

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Topic: C.02. Alzheimer's Disease and Other Dementias

Support: PA Department of Health grant SAP# 4100083102
National Institute on Aging grant U19 AG074866
National Institute on Aging grant R24 AG073190

Title: Resting state functional connectivity assessment of healthy aging trajectories in the marmoset brain

Authors: *R. BHIK-GHANIE[1], D. SZCZUPAK[2], B. ZHANG[1], D. PAPOTI[5], V. P. CAMPOS[6], M. BISHOP[2], I. ZIMMERMANN ROLLIN[1], L. DUBBERLEY[1], K. T. HITCHENS[1], F.-C. YEH[1], S. J. SUKOFF RIZZO[7], D. J. SCHAEFFER[3], A. C. SILVA[4];
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Abstract: The common marmoset (Callithrix jacchus) is an important animal model in neuroscience and neurological diseases (e.g., Alzheimer's disease - AD), as they present primate-specific evolutionary features such as an expanded frontal cortex. Here, we aim to characterize healthy aging trajectories by investigating their resting state functional connectivity for a population of marmosets. We imaged a cohort of 24 marmosets (17 males, 7 females) across the lifespan (22 to 115 months) using a dedicated 9.4T 30cm bore MRI scanner (Bruker BioSpin Corp, Billerica). The animals were acclimated to restrainers and helmets that provided head fixation during fully awake scans. BOLD EPI images (500 µm isotropic) were acquired for a duration of 2 hours and 16 minutes, yielding 4,096 volumes total. The brain images were pre-processed for fMRI using Analysis of Functional NeuroImages (AFNI) and FMRIB Software Library (FSL). For each run, the first ten time points were removed for magnetization to reach a

steady state. The images were then despiked (AFNI's 3dDespike), and volume registered to the middle volume of each time series (AFNI's 3dvolreg). Slice timing was corrected (AFNI's 3dTshift), phase encoding distortion was corrected using the FSL top-up. Subsequently, brain images were registered to the Marmoset Brain Mapping V3 template and brain-wide connectomics were calculated using the GRETNA toolbox. We have found that several cortical regions network-based-statistics are affected by age (e.g., entorhinal cortex, area 10, area 8, area 47, and somatosensory cortex, among others). We have also found that the brain is directly affected by age, reflected by an increase in weighted assortativity. Our work is the first to thoroughly describe the resting state brain networks of the marmoset during normal aging, a valuable model for age-related neuropathologies (e.g., AD). This research will set the normal parameters for marmoset aging and will be vital for generating transgenic marmoset models for AD, which is the goal of the MARMO-AD consortium.

Disclosures: R. Bhik-Ghanie: None. **D. Szczupak:** None. **B. Zhang:** None. **D. Papoti:** None. **V.P. Campos:** None. **M. Bishop:** None. **I. Zimmermann Rollin:** None. **L. Dubberley:** None. **K.T. Hitchens:** None. **F. Yeh:** None. **S.J. Sukoff Rizzo:** None. **D.J. Schaeffer:** None. **A.C. Silva:** None.

Poster

PSTR059: Neural Circuit Function and Dysfunction in Alzheimer's Disease

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR059.19/B93

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH Grant R01AG076227
NIH Grant RF1MH130415

Title: Exploring Beta Oscillatory Events in Alzheimer's Disease Conversion: A Translational PerspectiveExploring Beta Oscillatory Events in Alzheimer's Disease Conversion: A Translational PerspectiveExploring Beta Oscillatory Events in Alzheimer's Disease Conversion: A Translational Perspective

Authors: D. SHPAKIVSKA BILAN[1], G. SUSI[2], D. W. ZHOU[3], M. LÓPEZ[4], J. CABRERA-ÁLVAREZ[1], E. PEREDA DE PABLO[1], R. BRUÑA[5], F. MAESTÚ[5], *S. JONES[6];
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Abstract: Despite numerous studies in animal models of Alzheimer's disease (AD) suggesting that hyperexcitability, stemming from an imbalance between excitation and inhibition, is a key mechanism underlying this disease, the precise explanatory mechanisms linking its pathophysiology to cerebral oscillatory slowing and cognitive decline remain elusive. In the

early stages of AD progression, mild cognitive impairment (MCI) patients who later convert (CONV, N=41, Age= 74.1 + 0.50) present a magnetoencephalography (MEG) oscillatory slowing and a reduced beta band power compared to those who do not convert (NOCONV, N=44, Age=74.7 + 0.49) to AD . To better understand how these phenomena could be related to local neural dynamics, we studied how beta oscillations emerge as transient high-power events. We compared characteristic features of these transient events, namely the event rate (in 4 second time windows), average event duration, frequency span and maximum power across CONV and NOCONV groups. Results revealed a higher number of beta [12-30Hz] events in precuneus (PC) ($p = .001$) in NOCONV compared to CONV . Further, events of NOCONV presented a higher duration in the anterior cingulate cortex (ACC) ($p = .002$), along with the same tendency in PC. Finally, the greatest differences were found in the power of the beta events of PC ($p < .001$). This reduced expression of beta events predicted lower values of mean relative beta power spectral density as well as poorer cognitive performance within the CONV group. In conclusion, our findings suggest a potential relationship between the hyperexcitability observed in animal models and the observed oscillatory slowing in the CONV group, which in the beta-band emerges from a decrease in event number, along with shorter durations and reduced power. Prior associations between beta band activity and inhibition indicate that the preservation of these beta features in NOCONV individuals may serve as a protective mechanism against the progression of AD.

Disclosures: D. shpakivska bilan: None. **G. Susi:** None. **D.W. Zhou:** None. **M. López:** None. **J. Cabrera-Álvarez:** None. **E. Pereda De Pablo:** None. **R. Bruña:** None. **F. Maestú:** None. **S. Jones:** None.

Poster

PSTR059: Neural Circuit Function and Dysfunction in Alzheimer’s Disease

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR059.20/B94

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: Boll-Foundation
Brandau-Laibach-Foundation

Title: Effects of non-invasive brain stimulation on EEG measures in patients suffering Alzheimer´s Disease

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Abstract: As pharmacological interventions to treat Alzheimer's disease (AD) show only limited effects on mnestic deficits, non-invasive brain stimulation (NIBS) has revealed promising findings for modulating cognitive functioning in the recent years. The aim of this study was to evaluate repetitive Transcranial Magnetic Stimulation (rTMS) as a therapeutic tool in AD. 17

MCI patients due to AD confirmed by biomarkers and 19 age-matched healthy controls were recruited at the University Hospital Cologne. Two sessions applying rTMS were performed simultaneously with EEG measurements (rTMS-EEG) in a sham-controlled manner and in a randomized order. Four circular coils with low-intensity and high-frequency stimulation were placed in a cushion (CERTIS, ABNeurotech). The head was positioned in a way that the coils targeted parietal and occipital areas on both hemispheres. Stimulation or sham stimulation occurred throughout an item-memory object-location task, which encompassed encoding, immediate recall, consolidation, and delayed recall. Behavioral measures, relative Power Spectral Density (PSD) and individual alpha peak level (iAPL) were analyzed using SPSS and EEGlab. In addition, lagged coherence was chosen to measure electrophysiological functional connectivity. Parietal, occipital, and global alpha coherence were analyzed by mixed variance analyses. The stimulation was well tolerated, subjects could not determine whether stimulation took place or not. PSD analysis in the resting state before the stimulation revealed a decrease of alpha power and an increase in theta power in the group of AD patients as described before. Relative PSD yielded no stimulation effect. However, during stimulation, in contrast to sham stimulation, increased iAPL was detected at the occipital electrodes in the group of AD patients. Concerning the connectivity analyses, no main or interactions effects were found. Post-hoc analyses showed a higher global alpha coherence under stimulation in the AD group. Although no effect of stimulation on memory performance during the paradigm was found, iAPL and alpha coherence were related to memory functioning. In this study, we were able to demonstrate that a single session of low-intensity and high-frequency rTMS leads to an increase of iAPL and increase the alpha coherence in AD patients. It remains to be determined in which stage of the learning process stimulation could have the most beneficial behavioral effect. This rTMS-system is a promising approach as it could be easily applied also in out-of-hospital settings due to the small coils and the low-intensity of the magnetic field.

Disclosures: R.V. Faßbender: None. **C. Kehm:** None. **O. Onur:** None.

Poster

PSTR059: Neural Circuit Function and Dysfunction in Alzheimer's Disease

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR059.21/B95

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIA Grant AG063909
Siemens Skyra 3T scanner, S10 RR29577
KU Alzheimer's Disease Center, P30 AG072973

Title: Understanding functional and structural brain connectivity in adults with downs syndrome

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Abstract: Introduction: Most adults with Down syndrome (DS) show pathology related to Alzheimer's disease starting in their 30s. In adults without DS resting-state (RS) functional connectivity within the default mode network (DMN) and fractional anisotropy (FA) as a measure of structural connectivity are shown to decrease in general as individuals age. The goal of this analysis is to understand functional and structural connectivity in adults with DS as a function of age.**Methods:** A cross-sectional analysis was conducted using baseline multi-modal imaging data from 40 adults with DS (58% female, 0.05% hispanic, 82% white, 13% black, 5% mixed race), ages 18-45 enrolled in a longitudinal physical activity trial. RS functional magnetic resonance imaging was collected to measure regional brain connectivity. The posterior cingulate cortex was extracted to measure average connectivity within the DMN. Diffusion tensor imaging was collected to measure FA within all white matter tracts in the brain. Pearson correlations were run to establish the relationship between the DMN, FA, and age.
Results: Baseline DMN connectivity (M=0.25, SD=0.09) was positively correlated with FA (M=0.38, SD=0.03). The association between DMN connectivity and FA was not significant (r=0.209, p=.195). When adding age (M=25.43, SD=7.76) to the regression, there was a negative relationship between DMN connectivity and age (r=-0.471, p=.002) and between FA and age (r=-0.208, p=.198).**Conclusion:** Adults with DS show associations between functional and structural connectivity that seem to decrease with age. This analysis may inform future research looking to strengthen both functional and structural connectivity in adults with DS and to help understand the association between functional and structural connectivity and development of dementia.

Disclosures: M. Brucks: None. **R.J. Lepping:** None. **L. Martin:** None. **J. Danon:** None. **B.C. Helsel:** None. **L. Ptomey:** None.

Poster

PSTR059: Neural Circuit Function and Dysfunction in Alzheimer's Disease

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR059.22/B96

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: 1R43AG076088

Title: Exclusive antagonists of extrasynaptic NMDA receptors for the treatment of Alzheimer's disease

Authors: R. GULIA[1], T. QUACH[2], A. GROMOVA[1], T. ZHOU[4], V. PRAGNA[5], A. SALEM[5], A. MADAN[2], A. SAVTCHENKO[6], A. R. LA SPADA[3], ***E. MOLOKANOVA, PHD**[5]; [1]Pathology, Univ. of California Irvine, Irvine, CA; [2]Pathology, Univ. of California Irvine, Irivine, CA; [3]Pathology & Lab. Med. and Neurol., Univ. of California Irvine, Irvine, CA;

[4]Bioengineering, Univ. of California - San Diego, La Jolla, CA; [5]NeurANO Biosci., La Jolla, CA; [6]Nanotools Biosci., La Jolla, CA

Abstract: NMDA receptors (NMDARs) are a clinically validated drug target for Alzheimer's disease (AD). Although NMDAR antagonists are excellent for combating glutamatergic excitoxicity, they also may inhibit normal brain functions, triggering side effects and limiting their therapeutic value. The solution to this conundrum may lie in exclusive targeting of extrasynaptic NMDARs (eNMDARs), as compelling evidence suggests that eNMDARs mediate neurodegeneration and make a major contribution to AD-relevant pathology. Our team was the first to successfully develop functionally active exclusive eNMDAR antagonists by exploiting spatial differences in extracellular localization of sNMDARs and eNMDARs. Our exclusive eNMDAR antagonists (AuM) comprise PEGylated gold (Au) nanoparticles functionalized with multiple memantine (M) molecules. Due to its size, AuM is excluded from the synaptic cleft, assuring that eNMDARs are exclusively targeted.
Published studies demonstrated that soluble Aβ oligomers can trigger signaling pathways, overactivating eNMDARs followed by a decrease in dendritic spine density. To test if AuM can protect dendritic spines from Aβ oligomer neurotoxicity**,** we treated organotypic hippocampal slices from Thy1-YFP-H mice with 250 nM $A\beta_{1-42}$ oligomers in the presence or absence of 10 μM memantine or 50 nM AuM, each for 10 days. We determined that AuM was significantly more effective than free memantine in protecting synaptic dendritic spines from Aβ oligomers. We performed a preclinical trial of AuM, where animals received a ICV single administration of AuM at 4 months of age. The protocol was based on our previous pilot study in wild-type mice demonstrating that AuM is well-tolerated, and can be retained in the brain for at least 3 months after ICV infusion. We found that AuM reduce microglial activation, and provided strong neuroprotection as evident from the analysis of NeuN immunostaining of the brain slices from treated animals. Most impressively, AuM was able to reverse several other AD-related phenotypes triggered by glutamatergic excitoxicity: *e.g.*, AuM restored the levels of GluR1 (a subunit of glutamatergic AMPA receptors), GluN2B (a NMDAR subunit predominantly found at extrasynaptic locations), and BDNF. Finally, we discovered that the AuM may act as a disease-modifying drug, because the AuM treatment led to a decrease in Aβ aggregates in the brain.
Conclusion: Our findings suggest that nanotherapeutics exclusively targeting eNMDARs represent a promising therapeutic strategy for AD.

Disclosures: R. Gulia: None. **T. Quach:** None. **A. Gromova:** None. **T. Zhou:** A. Employment/Salary (full or part-time):; NeurANO Bioscience. **V. Pragna:** A. Employment/Salary (full or part-time):; NeurANO Bioscience. **A. Salem:** A. Employment/Salary (full or part-time):; NeurANO Bioscience. **A. Madan:** None. **A. Savtchenko:** A. Employment/Salary (full or part-time):; Nanotools Biosciece. **A.R. La Spada:** None. **E. Molokanova, PhD:** A. Employment/Salary (full or part-time):; NeurANO Bioscience.

Poster

PSTR060: Abeta Structure, Function, and Interactions in Physiological and Disease States

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR060.01/B97

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: JST Grant JPMJPF2213

Title: Effect of the astaxanthin against amyloid β aggregation on SH-SY5Y cells

Authors: *S. HULIMANE ANANDA, M. KURAGANO, K. TOKURAKU;
Div. of sustainable and Envrn. Engin., Muroran Inst. of Technol., Muroran, Japan

Abstract: Alzheimer's Disease (AD) is a chronic neurogenerative disorder characterized by neurofibrillary tangles, intercellular senile plaques, and substantial decline of cognitive progress which is associated with aggregation of amyloid β (Aβ) peptide and tau protein. Aβ is a toxic polypeptide of 39-34 amino acids that can form accumulations of amyloid fibrils and oligomers. Thus Aβ aggregation might be the primary cause for dementia. Astaxanthin (AxN), a xanthophyll carotenoid and potent antioxidant found in microalgae *Haematococcus pluvialis*. Various studies have shown that AxN enables its antioxidant property to protect cells from oxidative damage and cell death. In this study, we analysed the neuroprotective effect of AxN against Aβ aggregation in human neuroblastoma SH-SY5Y cells. First, we performed fluorescence imaging of Aβ aggregation in the presence of cells using quantum dot nanoprobes. We found that depositions of Aβ aggregates on SH-SY5Y cells could be attenuated by the treatment of from 0.032μM to 20μM AxN. Next, we confirmed -the inhibition effects of AxN on apoptotic cell death caused by Aβ aggregation were analysed using pSIVA-IANBD and propidium iodide, early and late apoptotic markers, respectively. We also found that AxN could prevent early apoptotic cell death but not late necrosis. Further, we tried to assess the effects of AxN on cell motility using a wound-healing assay. The cell migratory rate was evaluated using Hoechst-stained cells. The results illustrated that AxN could rescue the cell motility inhibition in SH-SY5Y cells caused by Aβ aggregation. In general, the inducing neuroprotective effect of the AxN against Aβ aggregation on human neuroblastoma SH-SY5Y cell lines was observed.

Disclosures: S. Hulimane Ananda: None. **M. Kuragano:** None. **K. Tokuraku:** None.

Poster

PSTR060: Abeta Structure, Function, and Interactions in Physiological and Disease States

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR060.02/B98

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: King's/Stavanger Award

Title: Alpha-synuclein and beta-amyloid drive synapse loss via the same pathway

Authors: *A. GHOSH, E. M. RIBE, R. KILLICK;
King's Col. London, London, United Kingdom

Abstract: It has repeatedly been suggested that alpha-synuclein (αSyn), the major component of Lewy bodies which characterise Parkinson's Disease (PD) and dementia with Lewy bodies (DLB), may play a role in Alzheimer's disease (AD), but this remains elusive. Across all these diseases, initially synaptic communication breaks down which then leads to neuronal loss and clinical symptoms. Therefore, dissecting the pathways leading to synapse loss is key to development of timely treatments for these diseases.
The loss of synapses is driven by soluble oligomeric forms of beta-amyloid (Aβ) in AD and fibrillar forms of αSyn in DLB and PD. Several reports indicate a functional relationship exists between Aβ and αSyn; not only does each promote the propensity of the other to aggregate, but the synaptotoxic effects of αSyn and Aβ appear synergistic. However, the nature of this relationship is obscure.
We have previously investigated the mechanism of Aβ-driven synapse loss, demonstrating that it involves activation of the RhoA/ROCK arm of the Wnt/PCP pathway. We have now examined αSyn-driven synapse loss in rat primary cortical neurons by super resolution microscopy of fluorescently labelled dendritic spines. Using preformed fibrils (PFFs) of a recombinant αSyn protein carrying the familial PD A53T mutation (A53T-PFFs) (3 μM), we find substantial dendritic spine loss after 24 hours' exposure. Inhibition of Wnt signalling using the small molecule inhibitor IWP2 (1 μM) blocks A53T-PFF-driven spine loss, suggesting it is a Wnt-dependent phenomenon. We also find that silencing *Daam1*, an element unique to the Wnt/PCP pathway, blocks A53T-PFF-driven spine loss. Inhibiting the downstream RhoA/ROCK pathway using the pan-ROCK inhibitor fasudil (10 μM) also blocks A53T-PFF-driven spine loss.
Based on these observations, we now propose that αSyn and Aβ act to drive synapse loss via a common pathway, the Wnt/PCP-RhoA/ROCK pathway.

Disclosures: A. Ghosh: None. **E.M. Ribe:** None. **R. Killick:** None.

Poster

PSTR060: Abeta Structure, Function, and Interactions in Physiological and Disease States

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR060.03/B99

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: Karolinska Institutet
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Olle Engkvist Foundation
Swedish Research Council (2020–02014)
Swedish Brain Foundation
Erling Persson Foundation

Title: Humanized APP-knock-in Alzheimer's disease mice model displays age-dependent cholinergic alterations

Authors: *S. MITRA[1], R. GERA[2], S. TAMBARO[3], P. NILSSON[3], B. LINDEROTH[4], H. BEHBAHANI[2], T. DARREH-SHORI[2], M. ERIKSDOTTER[2,5];
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Abstract: Alzheimer's disease (AD) is often associated with altered cholinergic pathways and memory dysfunction, linked to the early loss of basal forebrain cholinergic neurons (BFCNs). BFCNs innervate wide regions of the brain, including hippocampus which is a crucial site of neurotrophic factor production like nerve growth factor (NGF) and brain derived neurotrophic factor (BDNF). Hippocampus coordinates memory and cognition and is affected early with amyloid-beta (Aβ) pathology in AD. Till date, a clear connection between Aβ pathology in modulating cholinergic alteration has not been proven. Recently, the anti-amyloid antibodies Aducanumab and Lecanemab were approved for AD therapy by the United States of America Food and Drug Administration but whether Aβ deposition or clearance modulates cholinergic activity is not yet established. To evaluate and compare cholinergic status during Aβ pathology, hippocampus tissue was isolated from a humanized APP-knock-in mouse model of AD ($App^{NL\text{-}G\text{-}F}$, female) at different stages of Aβ pathology - 2-month age (pre-plaque stage), 7-month age (plaques present +initiation of cognitive deficits), and 12-month age (advanced Aβ pathology), along with age and gender matched wildtype controls (C57BL/6JRj). Tissues were processed to isolate total protein achieved by extraction in various buffers (soluble, ionic, and detergent soluble fractions) and pooled together. Enzyme assays for cholinergic markers including acetylcholinesterase (AChE), butyrylcholinesterase (BuChE) and choline acetyltransferase (ChAT) were performed, along with ELISA for the estimation of total NGF and BDNF levels, respectively. We observed different trajectories during age-dependent Aβ pathology development wherein AChE and BDNF were increased while BChE was reduced in $App^{NL\text{-}G\text{-}F}$ mice relative to wild-type controls. ChAT activity showed similar age-dependent trends in both genotypes, but significantly reduced at 7 months compared to other age groups. Cross sectional analysis presented considerable changes at different time-points. In $App^{NL\text{-}G\text{-}F}$ mice brains, AChE activity was significantly higher at 7 months, BuChE activity was reduced while BDNF protein levels were elevated from 7 month onwards, compared to wildtype control mice of similar ages. Age-dependent changes were not evident in NGF protein levels among the genotypes. Taken together, we report significant alterations in cholinergic activity and neurotrophic factors in hippocampus tissue of $App^{NL\text{-}G\text{-}F}$ mice, when compared to wild-type counterparts highlighting vulnerability of cholinergic pathways in relation to amyloid pathology.

Disclosures: S. Mitra: None. **R. Gera:** None. **S. Tambaro:** None. **P. Nilsson:** None. **B. Linderoth:** None. **H. Behbahani:** None. **T. Darreh-Shori:** None. **M. Eriksdotter:** None.

Poster

PSTR060: Abeta Structure, Function, and Interactions in Physiological and Disease States

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR060.04/B100

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH Grant DP2GM146322

Title: Super-resolution live microscopy reveals a mechanistic pathway linking APP processing to Tau dynamics in Alzheimer’s disease

Authors: *K. SHEN, G. SHUM, A. WOODS, T. BELTON, E. LEISTEN, Y. C. WONG; Neurol., Northwestern Univ., Chicago, IL

Abstract: Alzheimer’s disease (AD) is characterized by the pathological accumulation of amyloid plaques and neurofibrillary tau tangles in patient brains, suggesting a critical role for both amyloid-beta (Aβ) and tau proteins in AD etiology. Past studies have implicated heightened amyloidogenic processing of Aβ precursor protein (APP) as a key factor in AD pathogenesis, leading to increased Aβ and tau deposition, neurodegeneration, and clinical symptoms of AD in patients. However, the underlying mechanistic pathway relating APP processing and resulting tau pathology in Alzheimer’s disease remains unknown. Here, we present a mechanistic model that may bridge the gap between APP processing and tau accumulation. Using super-resolution live cell microscopy, we demonstrate that inhibition of APP processing and accumulation of intracellular cholesterol converge on a novel pathway of organelle dynamics, further highlighting a role of APP in regulating cholesterol metabolism. Disruption of this pathway in AD may induce a cascade of subcellular events that ultimately leads to the accumulation of tau aggregates. To test this, we conducted imaging experiments and immunoassays to analyze tau dissociation from microtubules and subsequent oligomerization. Together, our findings highlight a dynamic pathway connecting APP processing and tau localization on microtubules. We demonstrate that disruption of this novel molecular mechanism may contribute to elucidating Alzheimer’s disease etiology.

Disclosures: K. Shen: None. **G. Shum:** None. **A. Woods:** None. **T. Belton:** None. **E. Leisten:** None. **Y.C. Wong:** None.

Poster

PSTR060: Abeta Structure, Function, and Interactions in Physiological and Disease States

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR060.05/B101

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH Grant KS0JHNIA22

Title: The role of Serine 1928 phosphorylation of $Ca_V1.2$ during impaired synaptic plasticity in Alzheimer's disease.

Authors: *S. ROUGE, Z. ZENG, J. W. HELL;
Dept. of Pharmacol., UC Davis, Davis, CA

Abstract: The early stage of Alzheimer's Disease (AD) is indicated by a high concentration of soluble β-Amyloid (Aβ) peptide. In the hippocampus, our recent studies show that Aβ increases $Ca_V1.2$ activity through phosphorylation of S1928. Aβ is also responsible for the increase of the ratio Calcium Permeable (CP)-AMPAR/Calcium Impermeable (CI)-AMPAR at the post-synaptic site and for decreasing Long-Term Potentiation (LTP) that could be linked to memory decay. We hypothesize that the decrease in LTP mediated by Aβ, is driven by the increase of CP-AMPAR at the Post Synaptic Density (PSD) caused by the increase of $Ca_V1.2$ activity through the phosphorylation of S1928. To verify this hypothesis, after 1 hour incubation of hippocampus slices from WT or S1928A KI mice with only Aβ or Aβ with $Ca_V1.2$ blocker nimodipine, we have measured 1) the ratio of surface GluA1/total GluA1 after BS3 crosslinking 2) the field Excitatory Post Synaptic Potential (fEPSP) after LTP induction in CA1 region. We found that Aβ causes an increase of surface GluA1 at the neuronal surface. Accordingly, GluA1 homomers, which are the prevalent CP-AMPAR, have been inserted at the plasma membrane. In the hippocampus of WT mice, blocking $Ca_V1.2$ can restore LTP (160.9% of baseline, n=13) altered by Aβ (115% of the baseline, n=16). Moreover, LTP is unaffected in S1928A KI mice with Aβo (158% of the baseline, n=5) compare to vehicle (163% of baseline, n=9), confirming that the S1928 phosphorylation site plays a key role in Aβ toxicity.

Disclosures: S. Rouge: None. **Z. Zeng:** None. **J.W. Hell:** None.

Poster

PSTR060: Abeta Structure, Function, and Interactions in Physiological and Disease States

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR060.06/B102

Topic: C.02. Alzheimer's Disease and Other Dementias

Title: Calcium- and PTK-Dependent Suppression of Macroscopic Homomeric Kv1.1, 1.2, and Heteromeric Kv1.1/1.2 currents by AB (1-42) Peptide: Implications for Alzheimer's Disease

Authors: *D. JAMSHIDI[1], L. YAKLIN[2], S. BURCH[3], D. A. DRAVES[1], K. DEBOEUF[4], J. FARLEY[5];
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Abstract: The roles of Aβ in Alzheimer ’s disease (AD) pathogenesis include disruption of synaptic communication/function and synaptic plasticity mechanisms thought to underlie learning and memory. Exactly how these abnormal processes arise is incompletely understood, but evidence suggests that dysregulation of intracellular Ca^{2+} levels is involved in alterations of neuronal excitability, synaptic remodeling, and neurodegeneration in AD. Our lab has focused on the potential involvement of voltage-gated potassium channels (VGKCs) in these processes, particularly Kv1.x family members. VGKCs contribute to resting membrane potential, regulate Ca^{2+} influx, and their inhibition may lead to synapto- and neuro-toxicity through hyperexcitability and excess glutamate release. Kv1.x family members are expressed as homotetramers, or as select heterotetramers (e.x Kv1.1/1.2) contributing to the diversity of electrical signaling. We have previously observed rapid and robust suppression (50% in 30 minutes) of macroscopic current by Aβ(1-42) in homomeric Kv1.1 expressing *Xenopus laevis* oocytes. We therefore sought to understand 1) if suppression by Aβ(1-42) is exclusive to Kv1.1, affects other Kv1.x members such as homomeric Kv1.2 and heteromeric Kv1.1/1.2 channels 2) The extent to which the suppression is Ca^{2+} dependent, and 3) whether the suppression is additionally dependent on endogenous tyrosine kinase activity. To explore this, stage V/VI *Xenopus laevis* oocytes were injected with Kv1.1, Kv1.2, or both Kv1.1 and 1.2 cRNA for homomeric and heteromeric expression respectively. Oocytes were exposed to a bath application of 1 μM of Aβ(1-42), with currents evaluated using two-electrode voltage clamp electrophysiology (TEVC) for a total recoding period of 30 minutes. Experiments testing for Ca^{2+} dependency were evaluated using BAPTA-AM (a Ca^{2+} chelator) and Cyclosporin A (CsA; a PP2B inhibitor), with oocytes being incubated prior to recordings. For both homo-and heteromeric channel expressing oocytes, incubation in BAPTA-AM reduced suppression by ~45%, while incubation with CsA blocked any suppressive effects of Aβ(1-42). Incubation in genistein, a non-specific tyrosine kinase inhibitor, resulted in the greatest resistance to Aβ-suppression (>98%). Our results suggest that suppression of current is dependent on Ca^{2+} and endogenous PTK activity. Suppression of homo and heteromeric Kv1.x channels may lead to larger and longer action potentials, resulting in greater Ca^{2+} influx into presynaptic terminals, resulting in enhanced glutamate release and increased depolarization of spines. These effects may contribute to synapto- and neuro-toxicity in AD.

Disclosures: D. Jamshidi: None. **L. Yaklin:** None. **S. Burch:** None. **D.A. Draves:** None. **K. Deboeuf:** None. **J. Farley:** None.

Poster

PSTR060: Abeta Structure, Function, and Interactions in Physiological and Disease States

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR060.07/B103

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH R01DA038635-S1

Title: Development of Novel Delta Opioid Receptor (DOR) Antagonist for the Treatment of Alzheimer's Disease

Authors: *P. TANGUTURI[1], S. MITCHELL[1], S. ANANTHAN[2], O. MOUKHA-CHAFIQ[3], C. AUGELLI-SZAFRAN[4], J. M. STREICHER[5];
[1]The Univ. of Arizona, Tucson, AZ; [2]Div. of Neurosci., NIDA, NIH, ROCKVILLE, MD; [3]Chem., Southeren Res. Inst., Birmingham, AL; [4]Southeren Res. Inst., Birmingham, AL; [5]Pharmacol., Univ. of Arizona, Tucson, AZ

Abstract: Alzheimer's disease (AD) is the most common form of dementia, which affects 47 million people worldwide. There are over five million AD patients over the age of 65 in the U.S. which is predicted to increase to 16 million by 2050. There are currently no approved disease-modifying therapies for AD and attempts to prevent or slow the progression of the formation of beta-amyloid plaques by targeting both the beta-secretase 1 (BACE1) and gamma-secretase enzymes have not yet achieved clinical success. Studies suggest that indirect modulation of the function of these enzymes via G-protein coupled receptors (GPCRs) may provide a novel strategy to reduce A-beta peptide production with potentially fewer side effects. Among GPCRs that influence amyloidogenesis, the delta opioid receptor (DOR), in particular, has been shown to play an important role in the trafficking and function of BACE1 and gamma-secretase and in the production of A-beta peptide. DOR activation increases BACE1 and gamma-secretase activity *in vitro* and in a mouse model of AD, and antagonism of DOR specifically blocks the amyloidogenic pathway and efficaciously prevents AD progression in mice. These effects were demonstrated using a known DOR antagonist, naltrindole. However, the potential of DOR antagonists as therapeutic agents for AD has yet to be explored. The aim of this project is to create novel DOR antagonists via medicinal chemistry and identify the most promising lead compound based on binding, selectivity, and functional profile *in vitro*. Further, select a small set of the most promising compounds and evaluate the compound's ability to mitigate AD-like pathology *in vivo* using APP/PS double-transgenic mice. We report here the identification of several selective DOR antagonists with low nanomolar affinity/potency that have been shown to block BACE1 activity *in vitro*. DOR antagonist Lead compound SRI-22136 with low nanomolar affinity/potency that have been shown to block BACE1 activity *in vitro and* further showed greater brain penetration and pharmacokinetic profile following single dose of Oral and Subcutaneous at 5mg/kg in male C57BL/6 mouse.SRI-22136 also showed efficacy in Novel Object Recognition (NOR) behavioral studies at a dose of 1mg/kg twice daily for 90 days continuous treatment *in vivo* using the APP/PS AD model double-transgenic mice. Also, in our brain histological analysis the compound exhibited greater efficacy in reduction of the AD pathology markers such as Aβ and inflammatory markers GFAP (astrocytes) and CD11b (microglia) in AD transgenic mice. These results suggest that SRI-22136 and similar DOR antagonists could be novel therapies for the treatment of AD.

Disclosures: P. Tanguturi: None. **S. Mitchell:** None. **S. Ananthan:** None. **O. Moukha-Chafiq:** None. **C. Augelli-Szafran:** None. **J.M. Streicher:** None.

Poster

PSTR060: Abeta Structure, Function, and Interactions in Physiological and Disease States

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR060.08/B104

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: Krembil Foundation
Swedish Research Council
Swedish Alzheimer Foundation
Swedish Brain Foundation

Title: Unraveling the contributions of single amino acids on the increased aggregation of the Aβ(19Δ22) Uppsala mutant

Authors: *G. GRIMMER[1,2], L. WU[1], S. DI GREGORIO[1,2], D. SEHLIN[3], P. E. FRASER[1,4], M. INGELSSON[1,2], S. ZAMPAR[1,2];
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Abstract: The Uppsala mutation of the amyloid precursor protein gene (APPΔ690-695) was recently described as the first autosomal dominant deletion related to Alzheimer's disease (AD), causing early onset of symptoms and rapid disease progression. The lack of six amino acids was found to affect the processing of APP both at the β-secretase and α-secretase cleavage sites, leading to increased production of amyloid-β (Aβ) peptides. Moreover, AβUpp1-42$_{\Delta 19\text{-}24}$ displayed increased aggregation propensities. Several mutations causing AD or hereditary cerebral amyloid angiopathy (CAA) have been described within the amino acid sequence deleted in the Uppsala mutation, generally influencing APP processing or displaying enhanced Aβ fibrillization. As alterations in this region seem critical for Aβ aggregation, we aim to understand how each absent amino acid within the Uppsala mutation influences Aβ aggregation kinetics. For this purpose, five Aβ1-42 peptide variants, each containing a single amino acid deletion (F19Δ, A21Δ, E22Δ, D23Δ, V24Δ) within the Uppsala mutation frame, have been synthesized and their aggregation profiles will be analyzed *in vitro*. Size exclusion chromatography will be performed on synthetic Aβ1-42 peptides to isolate monomers. Serial dilutions of Aβ monomers of each mono-deletion will be incubated in triplicates at 37°C for 24 h in the presence of ThT to monitor their aggregation in a time-dependent manner. Preliminary results have shown that synthetic AβUpp1-42$_{\Delta 19\text{-}24}$ aggregates faster than Aβ1-42 WT, confirming previous findings. The half-times of aggregation curves will be compared to Aβ1-42 WT and AβUpp1-42$_{\Delta 19\text{-}24}$ to understand how the single amino acid deletions influence the aggregation kinetics.

Disclosures: G. Grimmer: None. **L. Wu:** None. **S. Di Gregorio:** None. **D. Sehlin:** None. **P.E. Fraser:** None. **M. Ingelsson:** F. Consulting Fees (e.g., advisory boards); Paid consultant for BioArctic AB. **S. Zampar:** None.

Poster

PSTR060: Abeta Structure, Function, and Interactions in Physiological and Disease States

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR060.09/B105

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH RF1 AG063903 - Klein, Kelleher, Patrie
Gift from Acumen Pharmaceuticals

Title: Structure of immuno-targeted amyloid beta oligomers of the human Alzheimer's disease brain.

Authors: *O. O. DE LEÓN VÉLEZ, J. JERISHA, W. L. KLEIN;
Dept. of Neurobio., Northwestern Univ., Evanston, IL

Abstract: Over two decades of research place soluble oligomers (ABOs) of the amyloid beta (Aß) peptide, rather than amyloid plaques, as key pathological drivers of Alzheimer's disease. ABOs have been shown to cause synaptic loss, inhibition of long-term potentiation, and promote tau hyperphosphorylation and neuroinflammation. Therapeutic targeting of ABOs is impeded by poor understanding of oligomeric structure and how it dictates pathological activity. This gap is sustained by the high heterogeneity of oligomers and the lack of tools that examine specific assemblies, which has led to the notion of oligomers as disordered and transient aggregates without a clear structure-to-function role in AD pathology.Research by our laboratory shows that ABOs bind neurons in a saturable and cell type-dependent manner and target specific dendritic receptors. This ligand-like binding is in harmony with a functional oligomeric structure, which is further supported by work with monoclonal antibodies developed by our laboratory. An example is the NU1 antibody, which can immunolabel dendrite-bound oligomers and has been shown to inhibit ABO-induced neurotoxicity in primary rat hippocampal cell cultures.We have used NU1 to selectively detect ABOs in extracts of the human AD brain, with little recognition of non-demented aging brains, which suggests that NU1 targets an oligomeric structure characteristic of AD pathology. NU1 - affinity chromatography has allowed us to isolate human AD brain oligomers and characterize their structure with atomic force (AFM) and transmission electron microscopy (TEM). AFM shows $NU1^+$ ABOs as uniform spherical particles with Z-height in the range of 3 to 4.5 nm, which resembles well-studied synthetic oligomers. Negative-stain TEM is consonant with AFM results by consistently detecting particles of similar size that are comparable to control synthetic oligomer preparations and are non-fibrillar as compared to synthetic Aß fibrils.Experiments are in process to probe purified oligomers with gold nanoparticle - NU1 conjugates for AFM validation and higher resolution Cryogenic EM, which is expected to provide insight into the quaternary structure of $NU1^+$ ABOs. Additionally, size exclusion chromatography is being used to determine the molecular weight of $NU1^+$ ABOs.These findings and experiments in process provide an approach to study oligomer structure by isolating and characterizing an oligomeric subpopulation of the AD brain as targeted by NU1.

Disclosures: O.O. De León Vélez: None. **J. Jerisha:** None. **W.L. Klein:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Acumen Pharmaceuticals.

Poster

PSTR060: Abeta Structure, Function, and Interactions in Physiological and Disease States

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR060.10/B106

Topic: C.02. Alzheimer's Disease and Other Dementias

Title: Mechanisms of Interaction of alpha-synuclein and amyloid-beta co-pathology

Authors: *S. WYCOFF[1], J. R. CIRRITO[2];
[1]Washington Univ. in St. Louis, St Louis, MO; [2]Neurol., Washington Univ., St. Louis, Saint Louis, MO

Abstract: Normal 0 false false false EN-US JA X-NONE /* Style Definitions */ table.MsoNormalTable {mso-style-name:"Table Normal"; mso-tstyle-rowband-size:0; mso-tstyle-colband-size:0; mso-style-noshow:yes; mso-style-priority:99; mso-style-parent:""; mso-padding-alt:0in 5.4pt 0in 5.4pt; mso-para-margin-top:0in; mso-para-margin-right:0in; mso-para-margin-bottom:8.0pt; mso-para-margin-left:0in; line-height:107%; mso-pagination:widow-orphan; font-size:11.0pt; font-family:"Calibri",sans-serif; mso-ascii-font-family:Calibri; mso-ascii-theme-font:minor-latin; mso-hansi-font-family:Calibri; mso-hansi-theme-font:minor-latin; mso-bidi-font-family:"Times New Roman"; mso-bidi-theme-font:minor-bidi; mso-font-kerning:1.0pt; mso-ligatures:standardcontextual;} There remains a large gap in knowledge about the pathological overlap of Alzheimer Disease (AD) and Parkinson’s Disease (PD). Approximately half of all AD patients exhibit formation of Lewy Bodies containing α-syn, and in the roughly 30% of PD patients with dementia (PDD), amyloid plaque burden is strongly correlated to severity of dementia. The two principal proteins involved in these diseases, α-syn and Aβ, promote each other’s aggregation and have synergistic toxicity in cells, while not affecting each other’s protein expression. Therefore we hypothesized that common clearance mechanisms of both proteins are involved in the increased toxicity. Intracellular clearance of both Aβ and α-syn is mediated through cellular autophagy (ALP), which is found to be dysregulated in both AD and PD patients. Here we show that α-syn and Aβ both inhibit ALP, with co-pathology having a multiplicative effect. Additionally, membrane interaction has been suggested to be key to Aβ/α-syn interaction, and key to the co-promotion of aggregation. A-syn is a naturally disordered protein, but can interact with membranes, leading to a higher rate of aggregation and interaction with Aβ. We propose that disengaging α-syn from the membrane reduces aggregation of both Aβ and α-syn and mitigates cellular toxicity.

Disclosures: S. Wycoff: None. **J.R. Cirrito:** None.

Poster

PSTR060: Abeta Structure, Function, and Interactions in Physiological and Disease States

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR060.11/B107

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: APP2009991 Javed
APP1197373 Davis

Title: Gut-bacteria can control the ultra-structure, pathogenicity and self-replication of amyloid-plaques in Alzheimer's disease

Authors: *K. CHUNG;
Australian Inst. for Bioengineering and Nanotechnology, Brisbane, Australia

Abstract: Gut-bacteria can control the ultra-structure, pathogenicity and self-replication of amyloid-plaques in Alzheimer’s diseaseKa Hang Karen Chung[1], Thomas Paul Davis[1], Ibrahim Javed[11]Australian Institute for Bioengineering and Nanotechnology, The University of Queensland, Brisbane Qld, 4072 Australia
Alzheimer disease (AD) is a multifactorial disease with a rising number of approximately 10 million new cases annually, while current treatments are targeting amyloid-plaques with limited success in early stages of the disease. Amyloid hypothesis involves Amyloid-β (Aβ) and this peptide can undergo cross-seeding with other biomimicry. Previous studies have shown cross-seeded Aβ can adopt the biomimicry morphology with alternated biochemical properties. The gut-brain axis has gained increasing attention as the gut is found to be associated with numerous extraintestinal diseases, including AD. Although the proximal effect of gut microbiome has been widely discussed, the distal effect is still unfolding.We have performed Thioflavin T assay, transmission electron microscopy (TEM), surface plasmon resonance, cellular experiments with neuroblastoma cells (SHSY-5Y cells and tau producing SHSY-5Y cells) including interaction studies and cytotoxicity studies to study the cross-seeding between microbial amyloids, specifically FapC amyloids from *Pseudomonas aeruginosa* and Aβ.Through biophysical and cellular characterisations, we found that microbial amyloids can induce the production of metastable short fibrils of Aβ. Figure 1. TEM micrograph illustrating different morphologies and sizes of Aβ species resulted from self-seeding (Aβ fibrils), cross-seeding (short fibrils) and probe sonication (Aβ seeds).These short fibrils have relatively high binding affinity with Aβ monomers due to electrostatic attraction and they can self-replicate through repeated seeding.
By combining immunostaining and TEM, we deduced these short fibrils are fibrillar oligomers. In cellular environment, short fibrils are highly colocalized with Aβ monomers and have higher deposition in the presence of short fibrils. These short fibrils are also found to be highly toxic to neuronal cells.In this study, we have revealed the pathogenic implications of gut microbial amyloids. This will provide a wider understanding of the potential distal effect of pathogenic gut microbial for future drug development for AD patients.

Disclosures: K. Chung: None.

Poster

PSTR060: Abeta Structure, Function, and Interactions in Physiological and Disease States

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR060.12/B108

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH Grant R00EY024653

Title: Amyloid precursor protein is required for circadian rhythm of the sleep-wake cycle

Authors: D. T. HUANG[1], B. MILLER[2], ***J.-E. K. MILLER**[1];
[1]Columbia Univ., NEW YORK, NY; [2]Psychiatry, Columbia Univ., new york, NY

Abstract: We discovered a diurnal rhythm of interstitial fluid amyloid-beta level in the hippocampus using Tg2576 mouse model of Alzheimer's disease in 2009. We also found diurnal rhythms of CSF amyloid-beta level in healthy young subjects and interstitial fluid endogenous murine amyloid-beta level in C57BL6 wild-type mice. This diurnal rhythm in amyloid-beta level was tightly linked to the sleep-wake cycle. Finally, disturbing sleep by giving 6 hours of sleep deprivation during the normal sleep cycle disturbed amyloid-beta fluctuation. Amyloid-beta stayed high during sleep deprivation, and this was followed by sleep rebound and decreased amyloid-beta level during sleep recovery. Based on these discoveries, we hypothesized that amyloid precursor protein (APP) and/or its cleavage products including amyloid-beta may play an important physiological function in regulating the sleep-wake cycle. We also hypothesized that APP may be required for sleep rebound after sleep deprivation. We tested this hypothesis using APP knockout mice where amyloid-pressor protein and its cleavage products are deficient. We measured sleep using a sleep piezo box under the constant dark condition and discovered that the circadian sleep rhythm is impaired in APP knockout mice. They slept more during the normal active cycle and slept less during the normal sleep cycle compared to the control C57BL6 mice. However, the total sleep amount per day was same as the control. Both C57BL6 and APP knockout mice had a significant circadian period in sleep behavior (around 23.75 hours) estimated by a chi-square periodogram. However, the circadian amplitude measured as the amplitude above the Qp value at the dominant period was significantly lower in APP knockout mice compared to control, suggesting that circadian rhythm was significantly less reliable in APP knockout mice. Finally, we measured sleep rebound after giving 9 hours sleep deprivation (ZT3-ZT12) and found that sleep rebound was significantly diminished in APP knockout mice. These findings indicate that APP is required for normal circadian sleep and homeostatic sleep rebound after sleep deprivation. In future study, we will determine the molecular/cellular mechanism of how APP regulates circadian sleep and sleep rebound after sleep deprivation.

Disclosures: D.T. Huang: None. **B. Miller:** None. **J.K. Miller:** None.

Poster

PSTR060: Abeta Structure, Function, and Interactions in Physiological and Disease States

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR060.13/B109

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH Grant R01 AG060203
Gift from Acumen Pharmaceuticals, Inc.
NIH Grant RF1 AG063903

Title: Amyloid beta oligomers' role in neurodevelopment may be mediated via extracellular vesicles

Authors: *B. HOOD[1], O. DE LEÓN VÉLEZ[2], I. SHEPOTINOVSKAYA[2], W. L. KLEIN[2]; [1]Dept. of Neurobio., Northwestern Univ., Evanston, IL; [2]Neurobio., Northwestern Univ., Evanston, IL

Abstract: Amyloid Beta Oligomers (AβOs), germane to the onset and progression of Alzheimer's Disease (AD), have recently been discovered to be transiently expressed through neurodevelopment in embryonic chick retina. Despite AD research shifting to the role of AβOs as one of the main neurotoxic molecules in Alzheimer's Disease, little attention has been paid to the potential of these neurodegenerative molecules during neurodevelopment. Discovering the mechanisms involved in their production, trafficking, and down-regulation throughout neurodevelopment could shed light on similar mechanisms in Alzheimer's Disease progression. In these studies, chicken embryos were euthanized and dissected at various ages (between E8 and E20) and subsequently the eyes were collected for use in immunofluorescent microscopy. Primary antibodies included ACU193 (specific for AβOs), markers for vesicles (anti-LAMP-1, anti-CD81), and markers for retinal cell types (anti-ChAT, anti-Lim-1, anti-TH). Here we report findings that indicate ACU193 associates with both specific cell types throughout retinal development and certain subpopulations of vesicles. As early as E8 in the retina, AβOs are detectable through immunofluorescent microscopy by ACU193 manifesting as puncta in the cytoplasmic area of cells. From E8 to E15, ACU193 was shown to directly associate with cholinergic and dopaminergic amacrine cells and horizontal cells. In addition to association with varying cell types, ACU193 was shown to selectively associate with vesicles at E8, E14, and E20. ACU193+ AβOs were found to not associate with LAMP-1+ lysosomes in these ages. An alternative possibility is that these AβOs are contained within extracellular vesicles and actively participate in some developmental role (i.e., synaptic pruning, programmed cell death, cell signaling, etc.). Enrichment of exosomes from chick retina tissue was confirmed using electron microscopy. Initial blotting results indicate the presence of AβOs in exosomes within these exosome-enriched samples. In addition, preliminary double-labeling immunofluorescence using ACU193 and anti-CD81 (a marker for exosomes) suggests co-localization between ACU193+ AβOs and CD81+ exosomes. Further identification of the relationship between AβOs and cellular components during neurodevelopment would reveal specific mechanisms involved in AβO production, trafficking, and eventual down-regulation. These findings in turn would assist in identifying parallel mechanisms involved in the onset and progression of Alzheimer's Disease and potentially provide new targets for early diagnostics and therapeutics.

Disclosures: B. Hood: C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Acumen Pharmaceuticals, Inc. **O. De León Vélez:** C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Acumen

Pharmaceuticals, Inc. **I. Shepotinovskaya:** C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Acumen Pharmaceuticals, Inc. **W.L. Klein:** C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Acumen Pharmaceuticals, Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Acumen Pharmaceuticals, Inc..

Poster

PSTR060: Abeta Structure, Function, and Interactions in Physiological and Disease States

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR060.14/B110

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: AA028710
P50 AA017823
T32 AA025606
U01 AA028710-04S1

Title: Adolescent intermittent ethanol exacerbates amyloid-βlevels in the entorhinal cortex and medial prefrontal cortex of female TgF344-AD rats

Authors: *S. M. DAY[1], N. REITZ[2], P. T. NUNES[1], L. M. SAVAGE[3];
[1]Psychology, Binghamton Univ., Binghamton, NY; [2]Psychology, SUNY Binghamton, Binghamton, NY; [3]Psychology-Behavioral Neurosci., SUNY - Binghamton Univ. Behavioral Neurosci., Binghamton, NY

Abstract: Alcohol use disorder is a risk factor for Alzheimer’s disease (AD), and preclinical studies have shown that chronic ethanol exposure increases Aβ in rodent models. However, little is known about how alcohol misuse drives the progression of AD-related pathology. Adolescence is an especially vulnerable period of cortical neurodevelopment, and binge-like ethanol drinking during this period can have long-lasting neurophysiological consequences. Adolescent intermittent ethanol (AIE) leads to age-dependent increases in amyloid-β (Aβ) levels in rodent models of AD-related pathology. In this study, we explored the long-term consequences of AIE on soluble Aβ (sAβ) levels in the orbitofrontal cortex (OFC), entorhinal cortex (EC), and medial prefrontal cortex (mPFC) of male and female TgF344-AD rats. Rats were given 5.0 g/kg ethanol or water on an intermittent exposure schedule (2 days on/2 days off) from postnatal day 28-P58, and then aged to 11 months of age. Rats were euthanized by rapid decapitation and brains were flash frozen in -20ºC methyl butane. The OFC, EC, and mPFC were bilaterally micropunched. sAβ40 and sAβ42 levels were measured using ELISA, and differences between groups were analyzed via two-way (Sex [Female/Male], Ethanol [AIE/Water) ANOVA. There were no effects of Sex or AIE-treatment in sAβ40 or Aβ42 levels in the OFC. In the EC, there was an effect of Sex on sAβ40 levels that was driven by higher levels in females, with no Ethanol effects on Aβ42 levels. In the mPFC, there was a Sex X Ethanol interaction on both

sAβ40 and sAβ42 levels. Post-hoc tests showed that AIE-treated females had higher mPFC sAβ40 levels than water-treated females and AIE-treated males, and higher mPFC sAβ42 levels than water-treated females and males. Collectively, these data indicate that alcohol misuse during adolescence has cortical region-specific effects on Aβ levels in the aged brain with AD transgenes, with the greatest impact on females in the mPFC.

Disclosures: S.M. Day: None. **N. Reitz:** None. **P.T. Nunes:** None. **L.M. Savage:** None.

Poster

PSTR060: Abeta Structure, Function, and Interactions in Physiological and Disease States

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR060.15/B111

Topic: C.02. Alzheimer's Disease and Other Dementias

Title: Effect of sex hormones on the kinetics of amyloid-beta in an awake and behaving mouse

Authors: *H. EDWARDS[1], C. M. YUEDE[2], J. R. CIRRITO[3];
[1]Washington Univ. Sch. of Med., St Charles, MO; [2]Psychiatry, Washington Univ. Sch. of Med., Saint Louis, MO; [3]Neurol., Washington Univ., St. Louis, Saint Louis, MO

Abstract: Effect of sex hormones on the kinetics of amyloid-β in an awake behaving mouse
Hannah M. Edwards, Carla Yuede, John R Cirrito
Washington University, Department of NeurologyKnight Alzheimer's Disease Research CenterHope Center for Neurological DisordersSt. Louis, MO 63110
Alzheimer's disease (AD) is a neurodegenerative disease that is hallmarked by the accumulation of amyloid-beta (Aβ) and tau, followed by a progressive decline in cognitive acuity. Interestingly, AD affects women at a higher rate than men, even when controlling for differences in lifespan. Clinical trials utilizing hormone replacement therapy in older women have yielded conflicting results. To explain this difference, we looked at the direct effect of sex hormones on the temporal kinetics of brain interstitial fluid (ISF) Aβ using in vivo microdialysis. With probes implanted in the hippocampus of awake, behaving mice, we measured Aβ levels over a three-day period. Female animals were injected intraperitoneally with beta-estradiol. An increase in Aβ was seen after 12 hours. Hippocampus tissue sections from female animals dosed with beta-estradiol were then processed for qPCR, and differences in MMP9 were seen between control and dosed animals, suggesting a decrease in clearance is responsible for the increase in (Aβ) seen during microdialysis experiments. Animals were then dosed with LY 411575, a gamma secretase inhibitor that blocks the production of Aβ, in addition to beta-estradiol. A difference in clearance rate was seen between the groups. Animals were also dosed with norethindrone, a progesterone receptor agonist, using reverse microdialysis to focally target the hippocampus. Interestingly, a decrease in Aβ was seen almost immediately with Aβ levels returning to baseline after administration of the drug was ceased. Animals injected intraperitoneally with progesterone show similar results, suggesting that peripheral progesterone signaling is sufficient to cause the

decrease seen in Aβ. These novel results suggest a differential effect of the two most prevalent sex steroids in females, and work is ongoing to uncover the cause of this effect.

Disclosures: H. Edwards: None. **C.M. Yuede:** None. **J.R. Cirrito:** None.

Poster

PSTR060: Abeta Structure, Function, and Interactions in Physiological and Disease States

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR060.16/B112

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: Shanghai Municipal Science and Technology Major Project
National Natural Science Foundation of China
2020CXB049

Title: Beta-amyloid regulates the microglial response to lipopolysaccharide via increasing APOE

Authors: *W. CAI;
Fudan Univ., Shanghai, China

Abstract: Background Although the neurotoxicity of β-amyloid has been researched well, the role of Aβ in inflammation is not clear. APOE has the most enriched gene expression in neurodegenerative glia, while the implication of APOE expression induced by Aβ is unknown. **Methods** Wildtype and APPswe/PS1ΔE9 (APP/PS1) mice were given 1μg lipopolysaccharide (LPS) by lateral ventricles injection to give rise to inflammatory stress. Intragastric administration (100 mg/kg) with bexarotene, the agonist of APOE, and intraperitoneally injection with anti-APOE mouse monoclonal antibody HJ6.3 (10 mg/kg) were performed respectively, to explore the role of APOE in regulation of microglial response to LPS. **Results** APP/PS1 mice had less proinflammatory cytokine and activated microglia compared to wildtype mice after LPS stimulation, which is mimicked by administration with APOE agonist while is reversed by blocking APOE with monoclonal antibody. APOE was high expressed in APP/PS1 mice especially in microglia as well as astrocytes, which is detected to interplay with complement C1qa. **Conclusion** We found Aβ restricted inflammation by regulating microglial activation, and we identified endogenic APOE as a negative regulator of microglial response to LPS. It was demonstrated that Aβ regulated the microglial response to LPS by APOE-C1qa pathway. It was suggested that Aβ was protective in unresolvable inflammation and APOE was a target to modulate inflammation during anti-Aβ therapy.

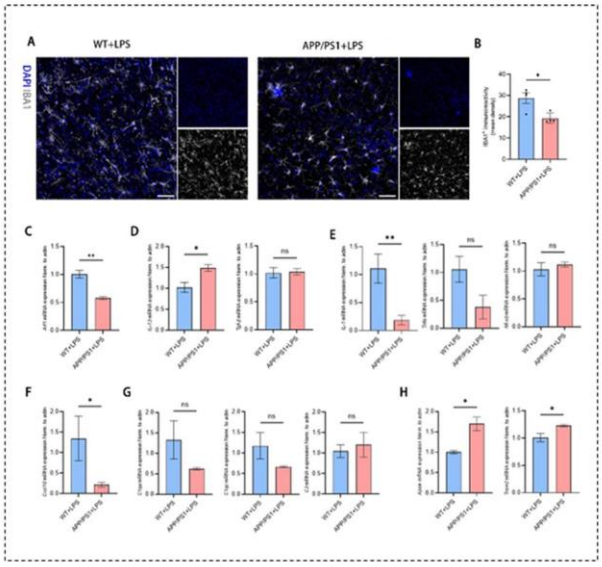


Figure 1. Restricted inflammation in APP/PS1 mice after LPS i.c.v.

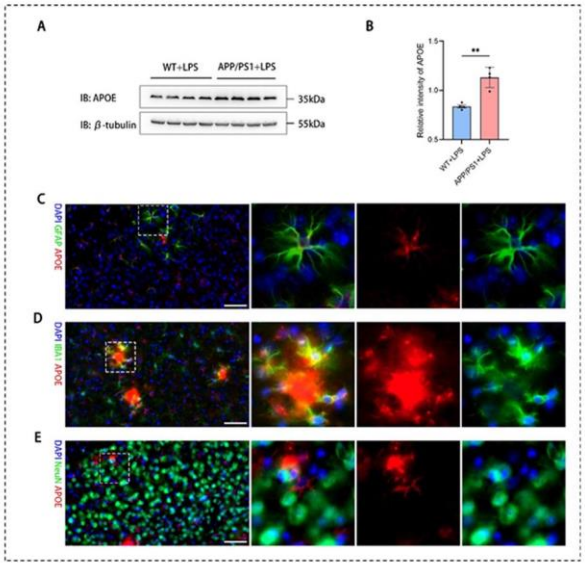


Figure 2. Increased expression of APOE especially in glia in APP/PS1.

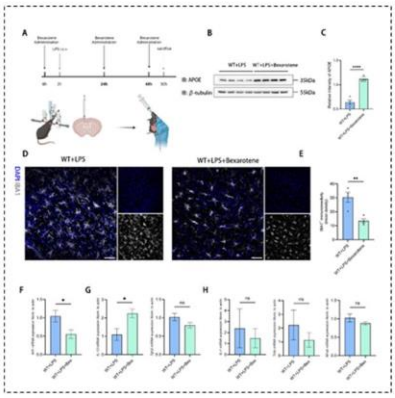


Figure 3. Increased expression of APOE attenuated inflammation induced by LPS i.c.v.

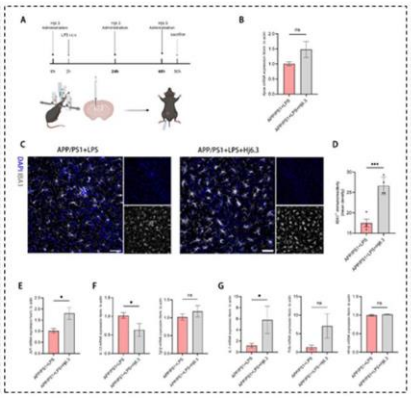


Figure 4. Enhanced microglial response to LPS by APOE blockage in APP/PS1 mice.

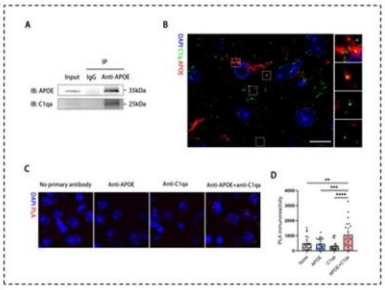


Figure 5. APOE mediated microglial response by interplaying with C1qa.

Disclosures: W. Cai: None.

Poster

PSTR060: Abeta Structure, Function, and Interactions in Physiological and Disease States

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR060.17/B113

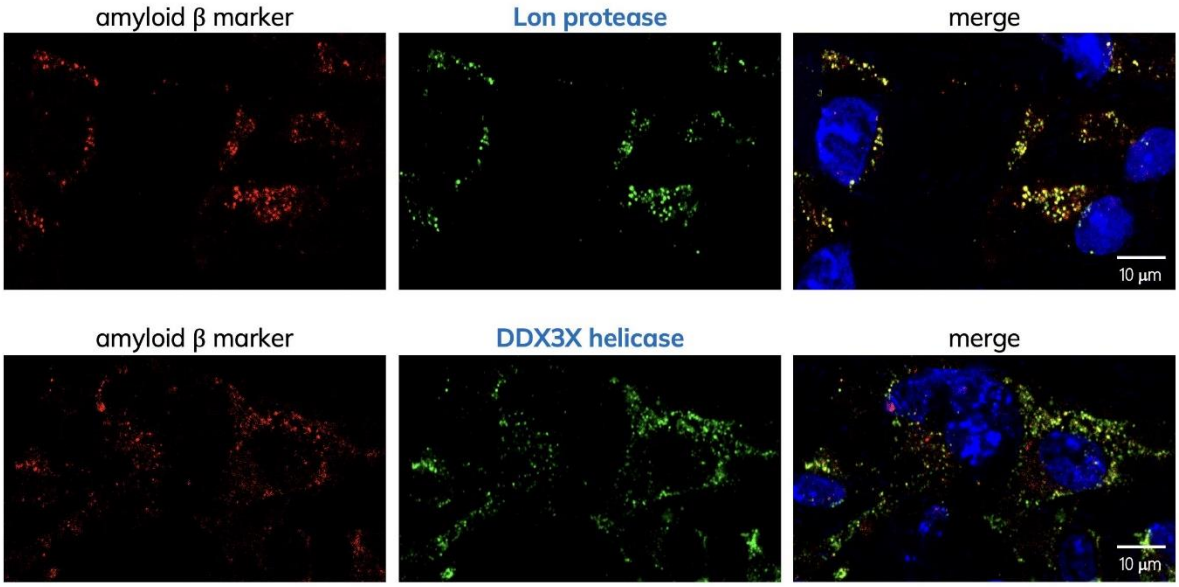
Topic: C.02. Alzheimer's Disease and Other Dementias

Title: Microscopy-guided spatial protein purification identifies novel amyloid-β aggregate-associated proteins Lon protease and DDX3X helicase

Authors: C.-C. HUANG[1], T. CHONG[2], H.-J. CHANG[2], H. HUANG[2], Y.-D. CHEN[2], E. CHUNG[2], ***J.-C. LIAO**[2];
[1]Syncell, Inc., Taipei, Taiwan; [2]Syncell Inc., Taipei, Taiwan

Abstract: Aggregation of amyloid-β peptides (Aβ) is a prominent feature of Alzheimer’s disease (AD). However, our understanding of the proteome of Aβ aggregates and their interactions with associated proteins remain incomplete. Existing spatial proteomics methods often rely on

antibody panels/arrays, limiting *de novo* proteomic discovery with high sensitivity and subcellular precision. To address this gap, here we employ Microscoop, a novel microscopy-based proteomics platform, for ultra-content microscope-guided photo-biotinylation and subsequent pulldown of subcellular Aβ-associated proteins. This platform enables subcellular spatial protein purification from thousands of fields of view for subsequent LC-MS/MS-based proteome identification. Using Aβ1-42 overexpression in human neuroblastoma SH-SY5Y differentiated cells as an AD model, we perform photo-biotinylation on millions of Aβ1-42 aggregates with locations of aggregates calculated on the fly fully automatically with Microscoop. The proteomic results show that we not only find known Aβ-associated proteins, but also identify proteins not previously reported in the literature. Two of the newly identified proteins, Lon protease and DDX3X helicase, are colocalized with Aβ1-42 shown in antibody staining. Colocalization with the animal amyloid plaques is further positively validated using brain sections of the 5XFAD mouse, a familial Alzheimer's disease mouse model. Our study unveils that at least Lon protease and DDX3X, two proteins that are rarely regarded as Aβ-associated proteins, are localized with Aβ, suggesting further hypothesis testing needed for their roles in Aβ.



Disclosures: C. Huang: A. Employment/Salary (full or part-time):; Syncell Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Syncell Inc. **T. Chong:** A. Employment/Salary (full or part-time):; Syncell Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Syncell Inc. **H. Chang:** A. Employment/Salary (full or part-time):; Syncell Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Syncell Inc. **H. Huang:** A. Employment/Salary (full or part-time):; Syncell Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Syncell Inc. **Y. Chen:** A. Employment/Salary (full or part-time):; Syncell Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Syncell Inc. **E. Chung:** A. Employment/Salary (full or part-time):; Syncell Inc.. E. Ownership Interest (stock, stock options,

royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Syncell Inc. **J. Liao:** A. Employment/Salary (full or part-time):; Syncell Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Syncell Inc..

Poster

PSTR060: Abeta Structure, Function, and Interactions in Physiological and Disease States

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR060.18/B114

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH Grant 2RF1NS110437-06
Swedish Research Council 2016-00748
Swedish Research Council 2021-01083
Swedish Research Council 2021-03524
Swedish Research Council 2023-03275
Swedish Research Council 2023-03931
Swedish Brain Foundation FO2022-0072
Swedish Brain Foundation FO2020-0207
Swedish Brain Foundation ALZ2019-0004
Swedish Brain Foundation ALZ2022-0004
Gustav V and Drottning Viktorias Foundation

Title: Multiple-ligand fluorescence microscopy enables chronological and spatial histological assignment of distinct amyloid-beta deposits

Authors: *T. KLINGSTEDT[1], L. BJÖRK[1], H. SHIRANI[1], X. WU[1], F. PARVIN[1], S. NYSTRÖM[1], P. HAMMARSTROM[1], M. INGELSSON[2,3,4], D. SEHLIN[5], S. SYVÄNEN[5], R. VIDAL[6], B. F. GHETTI[6], P. NILSSON[1];
[1]Dept. of Physics, Chem. and Biol., Linköping Univ., Linköping, Sweden; [2]Krembil Brain Inst., Univ. Hlth. Network, Toronto, ON, Canada; [3]Department of Public Health and Caring Sciences, Uppsala University, Uppsala, Sweden; [4]Tanz Centre for Research in Neurodegenerative Diseases, University of Toronto, Toronto, ON, Canada; [5]Dept. of Publ. Hlth. and Caring Sci., Uppsala Univ., Uppsala, Sweden; [6]Dept. of Pathology and Lab. Med., Indiana Univ. Sch. of Med., Indianapolis, IN

Abstract: In the brain of Alzheimer’s disease (AD) patients, extracellular plaques formed by filaments of the amyloid-β (Aβ) peptide are found. The development of ligands that detect these pathological lesions in living subjects would allow for an earlier diagnosis as well as aid in the studies of the pathogenesis of the disease. However, ligand development is challenging since Aβ filaments exhibit a conformational heterogeneity. In our laboratory, we are developing thiophene-based ligands that bind to protein aggregates. The aim with this study was to investigate binding of these ligands to Aβ deposits in genetically modified mice and in AD

patients. The included mouse models were APP ArcSwe, APP23 and APP NL-G-F. The human brain samples were obtained from patients diagnosed with sporadic AD (sAD) or dominantly inherited AD (diAD) caused by a mutation in the presenilin 1 (*PSEN1 A431E*) or the amyloid precursor protein (*APP E693G*) gene. Samples from the frontal and visual cortices were included. The murine or human cerebral tissue sections were stained with combinations of ligands having distinct binding and fluorescence properties. In mice, the ligand staining patterns were mutation and age dependent. For example, with combination HS-84/HS-259, both ligands were binding to Aβ plaques in young APP ArcSwe and APP23 mice, whereas in old mice, deposits that were only stained with either HS-84 or HS-259 could be seen. For the human cases, Aβ deposits in sAD versus diAD showed different binding properties when stained with ligand combination HS-276/HS-169. In sAD, HS-276 was the most prominent ligand, whereas HS-169 was dominating in *APP E693G* cases. In *PSEN1 A431E* tissue samples, HS-276 was binding to diffuse plaques and HS-169 to cotton wool plaques (CWPs). When comparing Aβ deposits in different brain regions in sAD, ligand combination HS-276/HS-259 showed distinct staining patterns. In frontal cortex, HS-276 was the most prominent ligand, whereas in visual cortex, the dominating ligand was HS-259. Furthermore, HS-259 did not stain CWPs in the *PSEN1 A431E* cases but showed excellent labelling of cotton wool like plaques (CWLPs) in *APP E693G* tissue. By performing structural modifications of HS-259, it was possible to pinpoint the chemical determinants for achieving detection of CWLPs. Overall, the results in this study show that our dual-staining protocols allow a more precise detection and differentiation of the entire spectrum of disease-associated Aβ pathologies. Hence, a variety of aggregate-specific ligands is probably essential for an early diagnosis of different types of AD, as well as for monitoring disease progression and evaluating potential treatment strategies.

Disclosures: T. Klingstedt: None. **L. Björk:** None. **H. Shirani:** None. **X. Wu:** None. **F. Parvin:** None. **S. Nyström:** None. **P. Hammarstrom:** None. **M. Ingelsson:** F. Consulting Fees (e.g., advisory boards); BioArctic AB. **D. Sehlin:** None. **S. Syvänen:** None. **R. Vidal:** None. **B.F. Ghetti:** None. **P. NIlsson:** None.

Poster

PSTR061: Alzheimer's Disease: Abeta Pathway

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR061.01/B115

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: APP2009991/NHMRC
APP1197373/NHMRC
8021-00208B/Independent Danish Research Council | Natural Sciences
Sino-Danish Center

Title: Alzheimer's Progenitor Amyloid-β Targets and Dissolves Microbial Amyloids and Impairs Biofilm Function

Authors: *S. ALI;
The Univ. of Queensland, Brisbane, Australia

Abstract: Alzheimer's disease (AD) is a leading form of dementia where the presence of extra-neuronal plaques of Amyloid-β (Aβ) is a pathological hallmark. However, Aβ peptide is also observed in the intestinal tissues of AD patients and animal models. In this study, it is reported that Aβ monomers can target and disintegrate microbial amyloids of FapC and CsgA formed by opportunistic gut pathogens, Pseudomonas aeruginosa and Escherichia coli, explaining a potential role of Aβ in the gut-brain axis. Employing a zebrafish-based transparent in vivo system and whole-mount live-imaging, Aβ is observed to diffuse into the vasculature and subsequently localize with FapC or CsgA fibrils that were injected into the tail muscles of the fish. FapC aggregates, produced after Aβ treatment (Faβ), present selective toxicity to SH-SY5Y neuronal cells while the intestinal Caco-2 cells are shown to phagocytose Faβ in a non-toxic cellular process. After remodeling by Aβ, microbial fibrils lose their native function of cell adhesion with intestinal Caco-2 cells and Aβ dissolves and detaches the microbial fibrils already attached to the cell membrane. Taken together, this study strongly indicates an anti-biofilm role for Aβ monomers that can help aid in the future development of selective anti-Alzheimer's and anti-infective medicine.

Disclosures: S. Ali: None.

Poster

PSTR061: Alzheimer’s Disease: Abeta Pathway

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR061.02/B116

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH Grant NS085171
NIH Grant NS086965
NIH Grant F30 AG085919

Title: Activity-dependent regulators of paraventricular oxytocin expression in amyloid precursor protein transgenic mice

Authors: *C. ST. ROMAIN[1], C.-H. FU[1], T. PUNNEN[2], J. CHIN[1];
[1]Baylor Col. of Med., Houston, TX; [2]Rice Univ., Houston, TX

Abstract: Alzheimer’s Disease (AD) is a heterogeneous disease diagnosed clinically by memory impairment and cognitive decline. The presence of amyloid plaques and neurofibrillary tangles on autopsy provides a definitive diagnosis. However, a subset of cognitively intact individuals also has significant AD neuropathology on autopsy, suggesting that these individuals were resilient to AD-related cognitive impairments. To begin to identify mechanisms that may underlie such resilience, we studied a transgenic mouse model of AD neuropathology that expresses mutant human amyloid precursor protein (APP mice, Line J20). Approximately 30%

of APP mice exhibit cognitive resilience, whereas their susceptible littermates exhibit progressively worsening memory despite similar time courses of Aβ accumulation and plaque deposition. In addition, APP mice exhibit spontaneous seizure activity beginning early in disease progression, similar to AD patients; such activity is also reduced in resilient APP mice. We previously identified an increase in the number of oxytocin-expressing cells of the paraventricular nucleus (PVN) of the hypothalamus in resilient APP mice, suggesting a potential mechanism of resilience. To determine what upstream pathways might drive this increase in oxytocin expression, we investigated activity-dependent genes. We focused on the activity-induced transcription factors cFos and ΔFosB given the spontaneous recurrent seizures exhibited by APP mice, our previously published work describing ΔFosB-induced epigenetic regulation of gene expression in the hippocampus in conditions of hyperexcitability, and literature demonstrating seizure-induced cFos expression in oxytocin-expressing cells of the PVN. We found that whereas few oxytocin-positive PVN cells co-expressed ΔFosB, the expression of cFos and oxytocin were highly colocalized in the PVN of APP mice. Resilient APP mice exhibited higher levels of cFos expression in oxytocin-positive cells of the PVN compared to those in susceptible APP mice. Moreover, increases in cFos fluorescence intensity predicted increased oxytocin fluorescence intensity on a per cell basis across mouse phenotypes (resilient and susceptible APP mice and nontransgenic littermates), suggesting cFos could play a role in regulating oxytocin expression. Given oxytocin's role in social behavior and evidence that social interaction can delay AD onset and help mitigate cognitive decline, identifying and manipulating genetic regulators of oxytocin expression could prove therapeutically beneficial in conferring resilience to AD progression.

Disclosures: C. St. Romain: None. **C. Fu:** None. **T. Punnen:** None. **J. Chin:** None.

Poster

PSTR061: Alzheimer's Disease: Abeta Pathway

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR061.03/B117

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: James Fickel Alzheimer's Disease Research Fund
NIH Grant R01EY028158
NIH Grant R01EY032488

Title: A new mice model to evaluate relationship of glutathione dysregulation in Alzheimer's Disease.

Authors: *K. RADEEN[1,2], C. HAO[1], Z. WEI[1], K. LI[1], K. SHANAZZ[3], D. T. BLAKE[3], F. DEAK[4], X. FAN[1];
[1]Cell. Biol. and Anat., Med. Col. of Georgia at Augusta Univ., Augusta, GA; [2]National Institute of Biotechnology, Dhaka, Bangladesh; [3]Neurosci. and Regenerative Med., Med. Col. of Georgia

at Augusta Univ., Augusta, GA; [4]Neurosci. & Regenerative Med., Med. Col. of Georgia at Augusta Univ., Augusta, GA

Abstract: Alzheimer's Disease (AD) is a progressive neurodegenerative disorder characterized by Aβ plaques and neurofibrillary tangles, with aging being the primary risk factor. Age-related accumulation of oxidative stress is considered a major causative factor in AD and other neurodegenerative disorders. Glutathione (GSH), the most abundant antioxidant in the body, declines in the brain with age and is further depleted in patients with AD and dementia. Despite this, the molecular mechanisms of GSH in brain aging and AD are not fully understood. To simulate aging brain conditions, we established a mouse model characterized by increased Aβ production and depleted glutathione levels. This was achieved through a combination of well-established APP/PS1 transgenic mice and glutathione biosynthesis enzyme modifier subunit, Gclm, knockout mice. We evaluated Aβ plaque deposition, mechanisms of neuronal cell death, electrophysiological changes, and cognitive function in this model. Significant Aβ plaque formation was observed in both APP/PS1 and APP/PS1/Gclm$^{-/-}$ mice brains starting at 5 months of age, while no detectable Aβ plaque was found in Gclm knockout mice brains. By 8 months of age, no significant difference in Aβ plaque deposition was observed between APP/PS1 and APP/PS1/GCLM$^{-/-}$ mice. Electrophysiological changes were assessed using video EEG at awake state, while cognitive function was evaluated using the light/dark box and radial arm water maze tests. Furthermore, we are currently investigating the molecular mechanisms underlying neuronal cell loss. In summary, we established an animal model that mimics the aged brain condition with reduced GSH level and increased Aβ production.

Disclosures: K. Radeen: None. **C. Hao:** None. **Z. Wei:** None. **K. Li:** None. **K. Shanazz:** None. **D.T. Blake:** None. **F. Deak:** None. **X. Fan:** None.

Poster

PSTR061: Alzheimer's Disease: Abeta Pathway

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR061.04/B118

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH R01 AG068215
NIH R01 AG068215-03S1
NIH T32 AG078110

Title: Breeding History Affects Alzheimer's Pathology, Cognition, Sleep and Circadian Rhythm

Authors: *C. E. JOHNSON[1], M. P. MURPHY[2], K. KOHLER[1], S. BARTH[1], S. PADGETT[1], S. TURTON[1], V. BUZINOVA[1], T. MACHEDA[3], A. D. BACHSTETTER[4], M. T. MAISEL[1], L. Z. GUO[1], M. J. DUNCAN[5];
[1]Univ. of Kentucky, Lexington, KY; [2]Mol. and Cell. Biochem., Univ. of Kentucky, Lexington,

KY; [3]Neurosci., Univ. of Minnesota, Dept. Neurosci., Lexington, KY; [4]Adam Bachstetter, Lexington, KY; [5]Neurosci., Univ. of Kentucky Med. Sch., Lexington, KY

Abstract: Hormone fluctuations are known to affect sleep/circadian rhythm, cognition, and Alzheimer's Disease (AD) pathology. How sleep fragmentation (SF) during periods of dramatic hormonal shifts (e.g. pregnancy and menopause) influence AD risk/progression is unknown. Sleep disruptions, which increase AD risk, rise in frequency during periods of major hormone fluctuations, and while menopause has been linked to AD, less is known about long-term effects of pregnancy. Some evidence shows that pregnancy increases AD risk and amyloid-beta (Aβ) levels, and decreases cognition. To our knowledge, no studies examine pregnancy history on sleep and AD. Our work on SF and AD uses female mice with varying breeding histories. Prior data in APPxPS1 knock-in (KI), and wild type (WT) mice was analyzed for sleep and circadian patterns of retired female breeders vs non-breeders (n=63; 7-12 mo) after SF. For 3-4 weeks, mice experienced undisturbed sleep (US) or SF - 4xdaily 1hr sessions of enforced wakefulness evenly timed throughout the day. Sleep was recorded weeks 1+3 with PiezoSleep cages. Additional mice (n=72; aged 9-13 mo) were used for cognitive testing. Brain tissue was tested for Aβ and amyloid precursor protein (APP) via ELISA. All SF mice lost sleep in the light phase ($p<0.001$) and gained sleep in the dark phase ($p<0.001$); breeders of both genotypes had more rebound sleep in the dark phase ($p<0.05$) after SF; and SF breeders had a higher circadian amplitude ($p=0.012$). Breeders had increased levels of Aβ in the hippocampus ($p=<0.001$), and higher levels of APP in a cortex+hippocampus composite ($p=0.026$). Cognitive radial arm water maze testing showed APPxPS1 (KI) breeders had no significant improvement in error rate between test days. Increased Aβ, impaired learning, and more sensitivity to SF in retired female breeders indicates a relationship between pregnancy history, sleep, and AD pathology and behavior. Pregnancy may have long-term effects on AD pathology, cognition, sleep and circadian rhythm. As 2/3 of those with AD are women, and the majority of women will have at least 1 child by age 49, determining the underlying mechanisms linking hormonal changes, disrupted sleep, and AD in women is critical in mitigating and treating AD.

Disclosures: C.E. Johnson: None. **M.P. Murphy:** None. **K. Kohler:** None. **S. Barth:** None. **S. Padgett:** None. **S. Turton:** None. **V. Buzinova:** None. **T. Macheda:** None. **A.D. Bachstetter:** None. **M.T. Maisel:** None. **L.Z. Guo:** None. **M.J. Duncan:** None.

Poster

PSTR061: Alzheimer's Disease: Abeta Pathway

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR061.05/B119

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH Grant RF1AG083029

Title: Detection of β-amyloid in App^{NL-G-F} mouse lungs and secretion from human lung epithelial cells

Authors: *C. CHENG, B. SAHU, A. M. FLODEN, C. K. COMBS;
Univ. of North Dakota, Grand Forks, ND

Abstract: Alzheimer's disease (AD) is a neurodegenerative disorder affecting around 6.9 million in the U.S. in 2024 with numbers expected to be greater than 80 million by 2050. A characteristic of AD brains is the accumulation of amyloid beta (Aβ) peptide-containing plaques in the brain. The Aβ peptide is proteolytically derived from the transmembrane amyloid precursor protein (APP). Although APP is robustly expressed by neurons and other cells in the brain, it is also made by numerous cell types outside of the central nervous system. Our previous work demonstrated APP expression in intestinal epithelial cells as well as their ability to secrete Aβ peptide. To further explore the biology of epithelial APP we cultured human bronchial epithelial cells, 16HBE14o-, on collagen coated transwell inserts. Transepithelial electrical resistance (TEER) was measured as an indicator of the tight junction integrity of the cultures, which showed a time-dependent change. Soluble Aβ1-40 and Aβ1-42 secretion into the apical and basal culture supernatants were quantified by ELISA. Secreted levels of both Aβ1-40 and Aβ1-42 were significantly higher in the basal compared to the apical compartment suggesting polarity of secretion from these cells. To assess Aβ secretion by lung epithelium *in vivo*, 12-month-old C57BL/6 wild-type and App^{NL-G-F} mice were sacrificed, and broncho-alveolar lavage fluid (BALF) and lungs were collected. We observed Aβ1-42 in BALF supernatant from male but not female App^{NL-G-F} mice with no significant detection of Aβ 1-40. These findings demonstrate a polarized secretion for both Aβ1-40 and Aβ1-42 in human lung epithelial cells and disease and sex-associated Aβ1-42 secretion changes in App^{NL-G-F} mice lungs. Further exploration of the function of lung epithelial APP and secreted Aβ may improve our understanding of unique changes related to AD or roles for these proteins in lung diseases such as asthma.

Disclosures: C. Cheng: None. **B. Sahu:** None. **A.M. Floden:** None. **C.K. Combs:** None.

Poster

PSTR061: Alzheimer's Disease: Abeta Pathway

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR061.06/B120

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH R01 NS086965
NIH R01 NS085171

Title: Sfrp3 restoration normalizes adult-born neuron maturation and neurogenesis-dependent cognition in an Alzheimer's disease transgenic mouse model

Authors: *C.-H. FU[1], J. PARK[1], F. A. BLANCO[2], Y. ZHENG[1], K. R. TOLIAS[1,2], J. CHIN[1];
[1]Neurosci. Dept., [2]Biochem. and Mol. Biol. Dept., Baylor Col. of Med., Houston, TX

Abstract: Adult hippocampal neurogenesis is important for cognition, and impairments may contribute to symptoms of various neurological disorders including Alzheimer's disease (AD)

and epilepsy. Previous research demonstrated in an amyloid precursor protein (APP) transgenic mouse model for studying AD that, compared with non-transgenic (NTG) littermates, the development of adult-born granule cells is aberrantly accelerated at early stages of cell maturation, with newborn cells from APP mice initially showing increased spine density and dendritic length. However, development was deficient at later cell maturation stages in APP mice, resulting in newborn neurons that had decreased spine density and dendritic length. We hypothesized that the abnormal development of these adult-born granule cells may contribute to impaired performance in neurogenesis-dependent tasks in APP mice. Indeed, we previously reported that APP mice were impaired in a spatial discrimination task, which relies on adult-born granule cells. Using RNA-sequencing, we looked for differentially expressed genes in the dentate gyrus of APP mice and NTG controls that may regulate adult-born granule cell maturation. We found that APP mice had decreased expression of secreted Frizzled-related protein 3 (sFRP3), a Wnt signaling inhibitor that was previously found to slow down spine and dendritic development of adult-born granule cells. To test whether the reduction in sFRP3 expression contributes to aberrant newborn neuron maturation in APP mice, we overexpressed sFRP3 in the hippocampi of APP and NTG mice via an adeno-associated virus (AAV). We found that AAV-sFRP3 normalized spine density of newborn granule cells at both early and later neuronal developmental stages in APP mice. AAV-sFRP3 also improved the performance of APP mice in a spatial discrimination task. Our results suggest that sFRP3 may be a critical dysregulated factor that drives neurogenesis-related impairments in cognition in our AD model mice, and perhaps also in AD.

Disclosures: C. Fu: None. **J. Park:** None. **F.A. Blanco:** None. **Y. Zheng:** None. **K.R. Tolias:** None. **J. Chin:** None.

Poster

PSTR061: Alzheimer's Disease: Abeta Pathway

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR061.07/B121

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIA R44 AG084491

Title: Quantification of progression of amyloid deposition and cerebral amyloid angiopathy in novel mouse models of familial Alzheimer's disease

Authors: *D. T. GARCEAU[1], K. P. KOTREDES[2], R. CHIDAMBARAM[3], P. KAMELIN[3], N. RYAN[4], T. RAGAN[3], M. SASNER[1];
[2]Res., [1]The Jackson Lab., Bar Harbor, ME; [3]TissueVision, Inc, Newton, MA; [4]Sasner Lab. - MODEL AD, Sasner Lab. / The Jackson Lab., Bar Harbor, ME

Abstract: While the amyloid hypothesis of Alzheimer's disease (AD) has been studied for decades, we do not yet fully understand the cellular and mechanisms driving the spatial and

temporal progression of amyloid pathology, the initial neuroinflammatory responses to amyloid deposition and how they change over time, and the factors that drive vascular versus parenchymal amyloid deposition. Vascular amyloid (cerebral amyloid angiopathy or CAA) is seen in most AD patients in later stages of disease and has become an urgent area of research since anti-amyloid therapies have been found to lead to increased risk of amyloid-related imaging abnormalities (ARIA), which is associated with CAA. Given the lack of access to clinical samples from early stages of AD or anti-amyloid treatment, animal models are essential to study these issues. Traditional transgenic APP models have numerous limitations for these studies (e.g. over- and mis-expression of mutant APP). Here we describe the creation and characterization of parenchymal vs vascular amyloid deposition and progression in novel knock-in mouse models. We engineered the APP^{SDI} model with Swedish, Dutch, and Iowa mutations; the latter two are associated with CAA. We engineered the APP^{SFL} model with Swedish, Florida, and London mutations. We then quantified amyloid deposition by brain region relative to vascular imaging in these novel models as well as in the APP^{SAA} model (Xia et al, 2022) using the TissueVision Marinus MP Serial Two-Photon Plus imaging platform. At 8 months of age, APP^{SDI} homozygotes exhibited minimal amyloid deposition that is exclusively in vasculature. The APP^{SFL} had no detectable amyloid deposition. As previously published, the APP^{SAA} model displayed significant parenchymal amyloid after 4 months of age. At 12 months, there was significant amyloid in both new models, mainly in parenchyma for the APP^{SFL} model and mostly as CAA in the APP^{SDI} model. Ongoing work will use the IBEX technique (Radtke, 2022) of multiplex immunohistochemistry to analyze neuroinflammation on sections produced in the TissueCyte process for each model at multiple ages/stage of pathology; these results will then be mapped back to the original amyloid and vasculature images. We expect that this comparative study will produce a better understanding of: the initiation of amyloid pathology, including specificity by brain regions; the temporal pattern of amyloid deposition and neuroinflammation; and whether the neuroinflammatory response is a cause or consequence of whether deposition is in the parenchymal or vasculature. This set of mouse models should be useful for both basic and preclinical research, including the study of CAA and ARIA.

Disclosures: D.T. Garceau: A. Employment/Salary (full or part-time):; The Jackson Laboratory. **K.P. Kotredes:** A. Employment/Salary (full or part-time):; The Jackson Laboratory. **R. Chidambaram:** A. Employment/Salary (full or part-time):; TissueVision. **P. Kamelin:** A. Employment/Salary (full or part-time):; TissueVision, Inc. **N. Ryan:** A. Employment/Salary (full or part-time):; The Jackson Laboratory. **T. Ragan:** A. Employment/Salary (full or part-time):; TissueVision, Inc. **M. Sasner:** A. Employment/Salary (full or part-time):; The Jackson Laboratory.

Poster

PSTR061: Alzheimer’s Disease: Abeta Pathway

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR061.08/B122

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: JPB grant MR-2023-4260

Title: Genetic screens identify QSOX1 as a novel regulator of APP levels

Authors: *X. DENG[1], J. KIM[1], I. AL-RAMAHI[2], D.-E. C. CHUNG[1], J.-P. REVELLI[1], H. LEE[3], Y. LI[2], J. BOTAS[1], H. Y. ZOGHBI[1,4];
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Abstract: Alzheimer's disease (AD), the most common type of dementia, is associated with the aberrant deposits of the β-amyloid peptide (Aβ) in the brain. Duplications of the gene coding for Amyloid precursor protein (APP) can cause autosomal dominant early-onset AD. Hence, lowering APP levels could be a promising approach to treat familial AD. We conducted a cross-species genetic screens to identify modifiers of APP levels in human cells and *Drosophila* by targeting 6,581 genes encoding potential druggable proteins. From this screen, we validated 33 candidates using western blot analysis in human cells. Using shRNAs targeting four of these genes, we further validated the effect on APP levels in mouse brain. Among them, we discovered Quiescin Sulfhydryl Oxidase 1 (QSOX1) regulates APP levels in the mouse brain. Downregulation or inhibition of QSOX1 reduced APP protein levels. To explore the mechanism by which QSOX1 regulates APP levels, we assessed whether it mediates APP clearance via proteosome or autophagy pathway. We found that knockdown of QSOX1 lowered APP levels via autophagic flux. Taken together, our findings highlight the new role of QSOX1 in regulating APP levels and suggest that targeting QSOX1 to modulate autophagy can be a potential therapeutic strategy of AD.

Disclosures: X. Deng: None. **J. Kim:** None. **I. Al-Ramahi:** None. **D.C. Chung:** None. **J. Revelli:** None. **H. Lee:** None. **Y. Li:** None. **J. Botas:** None. **H.Y. Zoghbi:** None.

Poster

PSTR061: Alzheimer’s Disease: Abeta Pathway

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR061.09/B123

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: 1R21AG079292-01

Title: Characterization of the PSEN1WT/Δexon9 pig model for Alzheimer’s disease research

Authors: *D. MURPHY[1], T. A. ALLEN[2], L. M. ALLEN[3], T. J. JAROME[4], J. VARGAS[5], K. LEE[6], K. MONARCH[7], J. YOON[6];
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Abstract: Alzheimer's Disease (AD) is the predominant cause of dementia in the United States. While great strides have been made using rodent AD models, there is a growing need to validate large animal models of AD to benefit translational development. Pigs have emerged as a preferred preclinical model in biomedical research due to their physiological resemblance to humans across several major organ systems, including the brain. The size and structural similarity of the pig brain, including the hippocampal formation, humans make it a particularly attractive model for studying the pathology of AD. Additionally, we recently developed an automated T-maze for rigorous assessments of memory in pigs (Allen et al., 2023). Here, we validated genetically modified pig models of AD that manipulated the Presenilin-1 gene (PSEN1 on chromosome 14), which is strongly associated with early-onset familial AD (FAD). Specifically, pigs lacking functional exon 9 of PSEN1 we developed using the CRISPR/Cas9 in developing embryos followed by a breeding protocol to produce heterozygous pigs (PSEN1WT/Δexon9) to better mimic genotypes observed in FAD. We targeted PSEN1 as it encodes the catalytic subunit of the gamma-secretase enzyme, known for breaking down amyloid-beta precursor protein (APP) into smaller subunits, including beta-amyloid (Aβ) peptides, particularly the more toxic Aβ42 variant. It also plays a critical role in development, notably endothelial cell migration and also in blood-brain barrier construction. We first tested PSEN1WT/Δexon9 for deficits in spatial working memory using our automated T-maze apparatus. We did not observe significant differences between PSEN1WT/Δexon9 and WT control pigs at shorter delays (<5sec). This suggests comparable motivation and other cognitive functions in PSEN1WT/Δexon9 relative to WT controls. However, at longer delays (>60s), PSEN1WT/Δexon9 exhibited significant performance deficits indicative of spatial working memory deficits. These deficits are closely associated with dysfunction in the hippocampal formation in other species and are similar to those observed in mild to moderate AD human patients. Next, we looked at the whole brain and cellular characteristics of PSEN1 brains using MRI and histological approaches, respectively. Initial results show reduced cerebral blood flow, cerebral microbleeds, and increased microglia activation. While additional validations are required, these results help advance the PSEN1WT/Δexon9 as large animal model preclinical model for AD research.

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Poster

PSTR061: Alzheimer’s Disease: Abeta Pathway

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR061.10/B124

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: RF1AG076653
R01AG074248
UG3MH126864
DP2MH136390

Title: Axonal organelle buildup from loss of AP-4 complex function causes exacerbation of amyloid plaque pathology and gliosis in Alzheimer's disease mouse model

Authors: A. ORLOWSKI[1], J. KARIPPAPARAMBIL[2], J.-M. PAUMIER[1], S. GHANTA[3], E. PALLARES[1], J. TANDUKAR[3], R. GAO[4], *S. GOWRISHANKAR[3];
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Abstract: Lysosomes and related precursor organelles robustly build up in swollen axons that surround amyloid plaques and disrupted axonal lysosome transport has been implicated in worsening Alzheimer's pathology. Our prior studies have revealed that loss of Adaptor protein-4 (AP-4) complex function, linked primarily to Spastic Paraplegia (HSP), leads to a similar build of lysosomes in structures we term "AP-4 dystrophies". Surprisingly, these AP-4 dystrophies were also characterized by enrichment of components of APP processing machinery, Beta- site cleaving enzyme 1 (BACE1) and Presenilin 2. Our studies examining whether the abnormal axonal lysosome build up resulting from AP-4 loss could lead to amyloidogenesis revealed that the loss of AP-4 complex function in an Alzheimer's disease model resulted in a strong increase in size and abundance of amyloid plaques in the hippocampus and corpus callosum as well as increased microglial association with the plaques. Interestingly, we found a further increase in enrichment of the secretase, BACE1, in the axonal swellings of the plaques of Alzheimer model mice lacking AP-4 complex compared to those having normal AP-4 complex function, suggestive of increased amyloidogenic processing under this condition. Additionally, the exacerbation of plaque pathology was region-specific as it did not increase in the cortex. The burden of the AP-4 linked axonal dystrophies/AP-4 dystrophies was higher in the corpus callosum and hippocampus compared to the cortex, establishing the critical role of AP-4 - dependent axonal lysosome transport and maturation in regulating amyloidogenic amyloid precursor protein processing.

Disclosures: A. Orlowski: None. **J. Karippaparambil:** None. **J. Paumier:** None. **S. Ghanta:** None. **E. Pallares:** None. **J. Tandukar:** None. **R. Gao:** None. **S. Gowrishankar:** None.

Poster

PSTR061: Alzheimer's Disease: Abeta Pathway

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR061.11/B125

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH Grant

Title: Membrane-tethered APP Intracellular Domain Signaling in the Suprachiasmatic Nucleus Influences Contextual Memory and Circadian Rhythm in a Tauopathy Mouse Model

Authors: *E. SANDEFUR[1], N. COLEMAN[2], R. WANG[2], M. WEINRICH[2], A. SADANAND[2], J. J. GAMSBY[2], D. GULICK[2], A. PARENT[2];
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Abstract: Alzheimer's Disease (AD) patients commonly experience circadian dysfunction, including sundowning (agitation and aggravation of cognitive symptoms at the end of the day), and signs of circadian disruption are often reported before the decline in cognitive function develops. During wakefulness, levels of phosphorylated tau (p-tau) and amyloid beta peptides (Aβ) increase in the brain, two pathological hallmarks of AD. Aβ is produced from amyloid precursor protein (APP) cleavage. APP processing also produces APP C-terminal fragments (APP-CTF) or membrane-tethered APP intracellular domain (mAICD). We previously reported that mAICD could engage in heterotrimeric Gαs coupled signaling through a direct interaction site within mAICD and downstream cAMP/PKA activation and GSK3β inhibition, a major contributor to tau phosphorylation. To examine if mAICD signaling impacts circadian function in AD pathology, we used the PS19 tauopathy mouse model and overexpressed mAICD in the suprachiasmatic nucleus of the hypothalamus (SCN). This brain area controls and synchronizes the circadian rhythm. PS19 mice were injected in 3-4 months-old mice into the SCN with the adeno-associated virus that translated the following constructs: mAICD, mAICDmutAAA (which lack the Gαs interaction site), or mCtl (a control membrane-tethered random protein of the same length). An equal number of male and female mice were used. Circadian running wheel activity and contextual fear conditioning behaviors were performed at the peak of viral expression (2-3 months post-injection). Mice were placed in circadian cabinets, allowing controlled light conditions and recording running wheel activity. The fear conditioning behavior test was performed a week before brain harvest. Our results indicated that PS19 mice (n=14) show less freezing time than non-transgenic littermates (NTg, n=13, p=0.0034), supporting an impairment of cognitive function in PS19 mice. PS19 mice (n=8) also exhibit greater levels of running wheel activity during the active/dark period, indicating more wakefulness than the NTg mice (n=7, p=0.0308). In addition, we evaluated the contextual fear conditioning memory in mice expressing mAICD and other variants. PS19 mice expressing mAICDmutAAA (n=13) in the SCN display a lesser extent of freezing behavior than PS19-mCtl (n=12, p=0.0058), an effect that was not seen in PS19 mice expressing mAICD compared to PS19-mCtl (n=11, p>0.9999). Our findings support that reduced sleep in PS19 mice might enhance cognitive impairment. Our results also indicate that APP-mediated signaling in the SCN might preserve memory function in a tauopathy mouse model. Supported by an NIH grant.

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Poster

PSTR061: Alzheimer's Disease: Abeta Pathway

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR061.12/B126

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: P01AG073082

Title: Understanding the genetic interplay between human APOE4 and App^{NL-F} knock-in Alzheimer's disease mouse models

Authors: *J. SHIN[1], E. BRADY[1], P. NAMBIAR[1], S. BANGERA[1], S. R. MILLER[1], J. J. PALOP[1,2];
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Abstract: Novel humanized knock-in mouse models, integrating precise genetic modifications of disease-associated mutations, offer a more functional and biologically relevant experimental framework. In our study, we focused on the generation of mice carrying two prominent Alzheimer's disease (AD) risk factors, APOE4 and amyloid-**β**; (A**β**;), by crossing APOE4 and humanized AppNL-F knock-in mice endogenously expressing the Swedish (NL) and the Iberian (F) familial AD mutations. Our objective was to employ a multifaceted approach to characterize the disease progression caused by the genetic interaction between these two factors. This approach included immunohistochemistry to evaluate A**β**; plaque deposition and microglial immunoreactivity, with preliminary data revealing prominent AD-related pathology in APOE4/AppNL-F mice. Additionally, using the machine learning behavioral phenotyping tool VAME, we observed unique signatures of behavioral alterations in APOE4, AppNL-F, and APOE4/AppNL-F mouse models, suggesting complex interactions of these risk factors on behavior. These findings underscore the potential of novel knock-in models to elucidate the complex genetic interplay underlying AD pathogenesis, thus facilitating more precise disease modeling and therapeutic development.

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Poster

PSTR061: Alzheimer's Disease: Abeta Pathway

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR061.13/B127

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: P20AG068053
R01AG062762
NIH 1R56AG062762-01

Title: Streptozotocin induced chronic hyperglycemia exacerbates amyloid beta levels in the APP/PS1 mouse model of Alzheimer's disease

Authors: *A. A. ORTIZ[1], A. S. MURTISHAW[2], A. M. OSSE[1], B. BALSAMO[3], K. SUK[1], R. RIVERA SANCHEZ[1], S. SHARMA[1], L. PASIA[4], J. W. KINNEY[5];

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Abstract: Alzheimer's disease (AD) is a neurodegenerative disease that is characterized by progressive synaptic and neuronal loss, learning and memory deficits, and cognitive decline. AD affects over 6.7 million Americans and is the 6th leading cause of death in the US. Furthermore, by 2050, the US is projected to spend over $1.1 trillion on AD-related treatments. Pathological hallmarks of AD include senile beta-amyloid (Aβ) plaques, intracellular neurofibrillary tangles (NFTs), and chronic neuroinflammation, which can promote and exacerbate both Aβ and NFTs levels and lead to synaptic and neuronal loss. AD is classified as early onset (EOAD) or late onset (LOAD). EOAD is associated with genetic mutations and accounts for 3-5% of all AD cases. In contrast, LOAD accounts for 95-97% of all AD cases with no genetic etiology; however, several genetic and/or other comorbidities confer increased risk for LOAD. Diabetes mellitus (DM) is a major risk factor for AD. DM confers up to a 4-fold increased risk for developing AD, and approximately 81% of individuals with AD have type II diabetes or are glucose intolerant. Hyperglycemia - abnormal elevated blood glucose levels - is the primary characteristic of DM. We have previously shown that chronic hyperglycemia can initiate and promote neuroinflammation, resulting in significant increases in hyperphosphorylated tau protein (pTau), learning and memory impairments, and other AD-related targets that are consistent with other AD models. However, the mechanisms by which chronic hyperglycemia increases Aβ levels are still being elucidated. We administered low and staggered dosages of streptozotocin (STZ) over a period of 6 months to induce hyperglycemia; glucose levels were taken weekly. The aim was to investigate the underlying mechanisms by which chronic hyperglycemia increases Aβ levels in the well-establish APP/PS1 mouse model of AD. Briefly, our data indicate altered fasting blood glucose levels, Aβ load, and other AD-DM-related targets in the hippocampus (a region that is first affected by AD). This data will provide useful insights on understanding the molecular pathways by which DM increases AD-pathogenesis to ameliorate and/or create better therapeutics for both DM and AD patients.

Disclosures: A.A. Ortiz: None. **A.S. Murtishaw:** None. **A.M. Osse:** None. **B. Balsamo:** None. **K. Suk:** None. **R. Rivera Sanchez:** None. **S. Sharma:** None. **L. Pasia:** None. **J.W. Kinney:** None.

Poster

PSTR061: Alzheimer's Disease: Abeta Pathway

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR061.14/B128

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: Krembil Foundation
Swedish Research Council

Swedish Alzheimer Foundation
Swedish Brain Foundation

Title: Assessments of pathogenic features associated with the novel de novo APP Y681H Aros mutation

Authors: *S. ZAMPAR[1], S. LIBARD[2], W. MICHNO[3], T. KLINGSTEDT[4], L. KILANDER[5], L. WU[6], G. GRIMMER[1], S. DI GREGORIO[1], H. WANG[7], S. F. LICHTENTHALER[8], G. F. SCHRÖDER[9], J. WATTS[10], G. SCHMITT-ULMS[11], P. NILSSON[12], D. SEHLIN[13], P. E. FRASER[14], N. DAHL[15], V. GIEDRAITIS[16], M. INGELSSON[1];
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Abstract: Mutations in the amyloid precursor protein (APP) gene can cause early onset familial Alzheimer's disease (FAD) and/or cerebral amyloid angiopathy (CAA). A novel *de novo* APP Y681H *Aros* mutation was identified in a Swedish subject who presented with a large cerebral hemorrhage at the age of 55 and died at the age of 66. Analysis of the brain revealed prominent amyloid-β (Aβ) plaque deposition in the cortex and abundant CAA. When subjecting brain tissue sections to different fluorescent thiophene-based ligands, a unique staining pattern could be seen in vascular Aβ deposits, suggesting a particular mutation-induced conformation of the *Aros* Aβ. Because the *Aros* mutation is located next to the BACE1 β'-cleavage site on APP and in proximity of neprilysin (NEP) and insulin degrading enzyme (IDE) Aβ cleavage sites, we analyzed how it affects APP processing, Aβ degradation and Aβ aggregation propensities *in vitro*, next to wild type (WT) APP and Aβ. We have also included in the analyses the *Leuven* (*APP* E682K) and *Dutch* (*APP* E693Q) FAD mutants for comparison, as they are located at the BACE1 β'-cleavage site or cause hereditary CAA, respectively. HEK293 cells were transfected with vectors containing WT or *Aros APP* sequences, and levels of Aβ1-40 and Aβx-40 were measured in the supernatants with Aβ-specific ELISAs. Monomeric synthetic Aβ peptides were isolated via size exclusion chromatography (SEC). Serial dilutions of Aβ1-42 and Aβ1-40 WT, *Aros, Leuven* and *Dutch* monomers were incubated at 37°C for 18-80 h in the presence of ThT to monitor their time-dependent aggregation. *In vitro* digestion of Aβ monomers was performed by incubation with recombinant NEP and IDE for 2 h at 37°C. Quantification of the digested products was performed with Image Lab software comparing band intensities in western blots. A significant increase of both Aβ1-40 levels and the ratio of Aβ1-40/Aβx-40 was measured in the supernatant of *APP Aros* transfected cells compared to *APP* WT. ThT aggregation assay data showed no changes in Aβ1-40 or Aβ1-42 *Aros* aggregation kinetics compared to WT, while Aβ

peptides with the *Leuven* or *Dutch* mutation aggregated faster. Aβ *Aros* monomers were digested to a lesser extent by NEP and IDE compared to WT, *Leuven* and *Dutch*, although with no statistical significance. The *APP Aros* mutation, causing AD with CAA, appears to influence APP processing and increase Aβ production. An increase in Aβ levels could be enhanced by the decreased degradation of Aβ *Aros* peptides. Toxicity of this novel mutation, however, does not seem to be related to changes in aggregation propensities. The deposit composition, structural features, and toxic properties of the *Aros* Aβ mutant are currently being assessed.

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Poster

PSTR061: Alzheimer's Disease: Abeta Pathway

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR061.15/B129

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: Alzheimer's Research Foundation Grant; AARG-NTF-22-924957
NIA R01; 1R01AG082135

Title: Estrogen Receptor Beta (ERβ): A Transcriptional Repressor of APP and ITPKB in Alzheimer Disease

Authors: *Y. YILDIZ[1], A. FAN[1], S. FLURY[1], A. HARTOUN[1,2], Y. NGAI[1], T. R. PAK[1]; [1]Cell. & Mol. Physiol., Loyola Univ. Chicago, Chicago, IL; [2]Cell. & Mol. Physiol., Loyola Univ. Chicago Stritch Sch. of Med., Chicago, IL

Abstract: Women account for approximately 2/3 of all Alzheimer Disease (AD) patients, face worse cognitive impairment and faster disease progression. Furthermore, early onset menopause has been linked as a risk factor for AD, suggesting a lack of hormone signalling could be a mechanistic explanation for this sex bias. Estrogen Receptor Beta (ERβ) is a nuclear receptor expressed in regions of the brain that regulate mood, learning, memory and cognition, processes which are impaired in patients with AD. Our lab has previously demonstrated that ERβ:protein interactions were altered with advanced age in a rat model of menopause. One of these proteins was gelsolin (GSN), an actin binding protein that can sever actin fibrils and amyloid plaques, which are key neuropathological hallmarks of AD. ERβ regulates gene transcription by binding to estrogen response elements (ERE) on promoters, or tethered by other transcription factors to specific motifs, such as AP-1. We previously showed that GSN facilitated ERβ-mediated gene repression at AP-1 sites. Some AD associated genes contain AP-1 sites in their promoters, such

as amyloid precursor protein (APP) and inositol-trisphosphate 3-kinase B (ITPKB). We hypothesized that 1) ERβ represses transcription of APP and ITPKB, and 2) GSN facilitates that repression. To test this, we transiently transfected APP and ITPKB promoter-luciferase constructs into SK-N-SH cells, a human neuroblastoma cell line. Our results showed that GSN activated transcription of APP and ITPKB, which was repressed by ERβ. We also used an endogenously produced ERβ splice variant, ERβ1Δ3, which is unable to directly bind DNA, to test if ERβ-mediated repression was mediated by an ERE or AP-1 site on the promoter. Our results showed that ERβ1Δ3 repressed activity at both promoters, indicating that a majority of ERβ repression was the result of indirect ERβ:promoter interactions. These results suggest that a decrease in ERβ:GSN interactions in advanced age leads to reduced gene repression and potentially increased production of APP and ITPKB, which is consistent with AD pathology. We also observed that GSN facilitated ERβ nuclear transport using immunofluorescent microscopy. Taken together, our data suggest that the loss of ERβ:GSN interactions with age leads to ERβ sequestered in the cytoplasm, thus reducing the repressive effects of ERβ on genes implicated in contributing to AD pathology.

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Poster

PSTR061: Alzheimer’s Disease: Abeta Pathway

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR061.16/B130

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH Grant AG067832

Title: Cognition in intrathecal amyloid-beta-oligomer model of Alzheimer's disease in African green monkeys

Authors: I. CASTRO COLMENARES[1], S. BUTLER[1], J. D. ELSWORTH[2], M. LAWRENCE[1], *M. WEED[2];
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Abstract: Alzheimer’s disease (AD) is the most common form of dementia and a major health burden across the world. Amyloid beta oligomers (AβOs) play a major role in initiating an AD pathological cascade that includes induction of phosphorylated tau (p-tau) in the brain and cerebrospinal fluid (CSF), neurofibrillary tangles, amyloid plaques, loss of synapses and neurons, neuroinflammation, and the clinical manifestation of cognitive decline. The current study utilized repeated administration of AβOs to adult African green monkeys through a subcutaneous access port into the lumbar intrathecal CSF. We have previously demonstrated this regimen to induce AD-like pathology in green monkeys, including increasing brain p-tau. In the current study, 11 males and 10 females were trained to perform a delayed match to sample

(DMS) test for recognition memory on Cambridge Neuropsychological Test Automated Battery (CANTAB) touch screen cognitive testing devices. After baseline DMS performance was established, awake monkeys in a primate chair were placed in a prone position and dosed with 200 ug of AβOs or vehicle on Monday, Wednesday, and Friday for four weeks. Twice weekly DMS testing continued for 8 months (N=11) or 12 months (N=10) after dosing. There were no significant differences before and after AβO dosing on DMS accuracy out to 8 and 12 months. DMS accuracy tended to improve over time in both AβO and vehicle treated animals. Percent completion and response latency also did not differ between groups. There was no evidence of memory impairment in the AβO-treated animals. Preliminary results indicate increased p-tau (AT-8 antibody) in AβO-treated brains at 8 months, suggesting early histological evidence of AD-like pathology may not manifest as cognitive deficits detectable by established testing paradigms.

Disclosures: I. Castro Colmenares: A. Employment/Salary (full or part-time):; Virscio, Inc. **S. Butler:** A. Employment/Salary (full or part-time):; Virscio, Inc. **J.D. Elsworth:** A. Employment/Salary (full or part-time):; Virscio, Inc. **M. Lawrence:** A. Employment/Salary (full or part-time):; Virscio, Inc. **M. Weed:** A. Employment/Salary (full or part-time):; Virscio, Inc. 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/NIA.

Poster

PSTR061: Alzheimer's Disease: Abeta Pathway

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR061.17/B131

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH RF1AG077772
NIH T32AG029796
University of Minnesota College of Pharmacy SURRGE Award Program

Title: The effects of SARS-CoV-2 infection on cognitive function and Alzheimer's disease-related pathology in APP/PS1 mice

Authors: *H. KORTHAS[1], V. D KRISHNA[2], A. CHANG[3], M. C. CHEERAN[2], W. C. LOW[4], L. LI[3];
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Abstract: Alzheimer's disease is the most common type of neurodegenerative disease, characterized by the buildup of toxic beta amyloid plaques and neurofibrillary tau tangles, leading to cognitive decline. The COVID-19 pandemic, caused by the SARS-CoV-2 virus, has

infected over 775 million people across the globe. Interestingly, dementia is a significant risk factor for COVID-19 infection severity and outcomes, and aged COVID-19 survivors have been shown to have an increased chance of a first dementia diagnosis compared to those who did not have a COVID-19 infection. Furthermore, it is now widely known that SARS-CoV-2 is not just a respiratory virus, but can cause numerous cognitive and neurological symptoms, some of which persist far beyond the acute stage of infection. Given this information, this project seeks to understand the mechanisms linking SARS-CoV-2 infection with the development and progression of Alzheimer's disease. To accomplish this, age and sex-matched APP/PS1 mice were infected with the beta variant of SARS-CoV-2 at five months old, then aged the infected mice alongside uninfected littermate controls to 8 months of age. These mice then underwent behavioral/cognitive testing via T-Maze and nest building assessment, followed by euthanasia and tissue collection for virological, biochemical and pathological analyses. Consistent with our previous findings in young wild type mice, no body weight loss was observed in these young APP/PS1 mice post infection. Importantly, despite the mild infection and non-detectable viral RNA in the brain, behavioral testing results showed that SARS-CoV-2 infected APP/PS1 mice exhibited significantly reduced spontaneous alternation and working memory in the T-Maze compared to the uninfected APP/PS1 controls, while there was no difference in the nest building ability between infected and uninfected mice. Immunohistochemical and biochemical analyses of brain tissue are underway to assess the long-term impact of SARS-CoV-2 infection on the progression of β-amyloidosis and associated neuroinflammation. RNA sequencing analyses are also in progress to evaluate transcriptomic changes associated with SARS-CoV-2 infection in the context of amyloid deposition. The results of this study using an interdisciplinary approach are expected to provide novel insights into the underlying mechanisms connecting SARS-CoV-2 infection and Alzheimer's disease.

Disclosures: H. Korthas: None. **V. D Krishna:** None. **A. Chang:** None. **M.C. Cheeran:** None. **W.C. Low:** None. **L. Li:** None.

Poster

PSTR061: Alzheimer's Disease: Abeta Pathway

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Program #/Poster #: PSTR061.18/B132

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH Grants R21AG061674-01
Garrison Family Foundation

Title: The autophagy/mitophagy system and their receptors in Alzheimer's disease progression in APP23 and Tau-P301L transgenic mouse models

Authors: *M. MANCZAK, X. L. YIN, Y. CHEN, J. J. LAWRENCE, V. NEUGEBAUER; Texas Technol. Univ. Hlth. Sci. Ctr., Lubbock, TX

Abstract: Alzheimer’s disease (AD) is the most common form of dementia and is characterized by a progression from episodic memory problems to severe cognitive decline and complete dependence of the patient on caregivers. AD is characterized by the accumulation of dysfunctional mitochondria and misfolded proteins. Autophagy and mitophagy are highly conserved processes in eukaryotic cells, playing critical roles in cellular homeostasis by delivering misfolded, ubiquitinated proteins, and damaged mitochondria to lysosomes for selective degradation. These pathways are particularly crucial in various neurodegenerative diseases, where defects in selective autophagy have been implicated in disease pathogenesis.We investigated two groups of autophagy receptors in APP23 mice carrying the human Swedish double mutation (APP751*K670N/M671L) and in Tau mice carrying the human TauP301L mutation, at both early onset and late stages of Alzheimer's disease (AD). The first group, which includes NDP52, p62, NBR1, and OPTN, is involved in Ubiquitin (Ub)-dependent pathway. These receptors possess two domains: an LC3-binding domain (LIR motif) and a ubiquitin binding domain (UBD). The second group includes BNIP3, NIX/BNIP3L and FUN14, is involved in Ubiquitin (Ub)-independent pathway. These receptors are located in the outer membrane of mitochondria and can directly bind to LC3 without ubiquitination.Our study employed real-time PCR, immunoblotting, immunostaining, and co-immunoprecipitation analyses to measure gene expression, protein levels, localization, and interactions between these proteins. At 12 months of age, both APP23 and Tau mice exhibited significant deficiencies in BNIP3 and Nix/BNIP3L suggesting a potential correlation with the autophagy/mitophagy pathway. The down-regulation of BNIP3 which plays the role in the induction of autophagy suggests dysregulation in the autophagic pathway, which may contribute to the accumulation of misfolded proteins, a hallmark feature of Alzheimer's disease (AD) pathology. The down-regulation of Nix/BNIP3L, responsible for mediating the recruitment of dysfunctional mitochondria to the autophagosome, may contribute to the failure in removing damaged mitochondria.The function and regulation of autophagy/mitophagy receptors in neurodegenerative diseases require further investigation to discovery of potential key regulators and novel therapeutic targets for AD disease.

Disclosures: M. Manczak: None. **X.L. Yin:** None. **Y. Chen:** None. **J.J. Lawrence:** None. **V. Neugebauer:** None.

Poster

PSTR061: Alzheimer’s Disease: Abeta Pathway

Location: MCP Hall A

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Program #/Poster #: PSTR061.19/B133

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: T32HL007778
HL118334
GM127584
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HL66299

HL148069
HL140182

Title: Pseudomonas aeruginosa bacterial infection induces cleavage of the amyloid precursor protein in lung endothelium

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Abstract: Cognitive deficits and end-organ damage are associated with pneumonia, particularly hospital-acquired pneumonia. Pneumonia elicits the production of peripheral cytopathic amyloid and tau species detectable in different biofluid compartments, including bronchoalveolar lavage fluid and plasma. Previous studies have shown that an elevation of beta-amyloid 42 in bronchoalveolar lavage fluid is associated with intensive care unit patient survival, whereas an elevation of beta-amyloid 40 in plasma is indicative of sepsis and end-organ injury. Single-cell RNAseq studies have revealed that many lung cell types, including endothelial cells, express amyloid precursor protein (APP). In the brain, proteolytic cleavage of the amyloid precursor protein by alpha- and gamma-secretases is a physiological, non-amyloidogenic process. However, sequential cleavages by beta- and gamma-secretases result in the production of beta-amyloid species, which negatively impact neural function and may also possess antimicrobial activity. The three amino acid differences between rodent and human APP around the beta-secretase cleavage site reduce the amyloidogenic beta-amyloid production in rodents.
In this study, amyloid precursor protein isoforms were quantified in rat lung endothelial cells. Amyloid precursor protein was knocked out of these cells. The predominant lung isoform, with the three amino acid modifications mimicking the human APP770 isoform, was stably re-expressed in the knockout cells, and the proteolytic cleavage was quantified in the presence and absence of *Pseudomonas aeruginosa* bacteria. Results showed alpha-secretase predominantly cleaved APP under both control and infection conditions. In addition, *P. aeruginosa* activated proteases and caspases, increasing the amount of beta-amyloid 40 in the cell medium. Interestingly, the C-terminal fragment of APP, the APP intracellular domain or AICD, was detectable in the cell medium under control and infection conditions, and infection increased its release from endothelial cells. These results elucidate the previously unappreciated role of lung endothelial APP and its proteolytic cleavages that may impact the health, survival, and end-organ dysfunction of bacterial-infected patients.

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Poster

PSTR061: Alzheimer's Disease: Abeta Pathway

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Topic: C.02. Alzheimer's Disease and Other Dementias

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COLE Neuroscience Research Awards
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Title: Burst Suppression Pattern under Isoflurane-induced Anesthesia in APP23 mice and Primary Cilia cKo Mice

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Abstract: Learning and memory formation is not only essential for individuals to acquire knowledge and acquisition, but also linked to a range of severe brain diseases, including Alzheimer's Disease (AD). Establishing methods for early diagnosis of AD could give patients the opportunity to slow disease progression. Previous AD research has examined the brain activity of affected individuals when they are awake or asleep; however, brain activity under anesthesia remains essentially unstudied. Using anesthetics to block all external sensory stimuli, electroencephalography (EEG) recording of the mouse brain at the lowest basal level, which may reflect intrinsic backbone circuitry for cognition, learning and memory formation. We recently revealed that burst synchronization of primed hippocampal neurons is key for trace memory formation. WT controls, Amyloid Precursor Protein 23 transgenic mice (APP23, an AD mouse model), and Ift88 flox/flox, Camk2a-Cre/ERT2 knockouts (forebrain-specific inducible cilia cKOs) were used in our study. Mice were exposed to 3% isoflurane until reaching a coma-like activity level where burst suppressions can be detected. Based on numerical analysis of burst suppression patterns, we hypothesize that the EEG waveform pattern under isoflurane in WTs, APP23, and cilia cKO will display distinct characteristics, and that if the alteration of burst suppression patterns correspond with effects on cognitive capacity. Our approach allows us to quantify frequency patterns of burst suppression occurrence in the control and two transgenic strain's waveforms, while removing the influence of their outside environment. Using a two-point code in combination with double log-normal curves, we will calculate the probability of burst suppressions happening at any point during isoflurane exposure, ideally projecting a unique pattern across genotypes. Ongoing analyses based on the burst suppression frequencies, visibility, and patterns are used to calculate the probability of their occurrence. Our preliminary results suggest that WTs, APP23, and cilia cKO mice exhibit different temporal dynamics of activity: burst suppression activity starts earlier in APP23 and cilia cKO mice than controls. These observations suggest that this waveform pattern analysis may prove useful in identifying an early biomarker for AD.

Disclosures: S.M. Walsh: None. **L. Wang:** None. **L. Qiu:** None. **M. Lyon:** None. **X. Chen:** None.

Poster

PSTR061: Alzheimer's Disease: Abeta Pathway

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Program #/Poster #: PSTR061.21/B135

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIA R44 AG084491
NIA U54 AG054345

Title: Characterization of the APP ^{SAA} mouse as a useful model for preclinical testing for Alzheimer's disease

Authors: A. P.-Y. TSAI[1], D. GARCEAU[2], R. CHIDAMBARAM[4], P. B.-C. LIN[5], G. E. LANDRETH[6], B. T. LAMB[7], G. W. CARTER[3], T. RAGAN[8], S. J. SUKOFF RIZZO[9], A. OBLAK[7], ***M. SASNER**[3];
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Abstract: The APP^{SAA} model was developed to provide an animal model of early onset, familial Alzheimer's disease (AD) that is accessible for preclinical research without licensing restrictions or artifacts due to transgenic overexpression (Xia et al, 2022). In order to establish the APP^{SAA} model as a useful model for translational research, we have characterized numerous clinically relevant phenotypes throughout aging. These include: quantification of amyloid deposition by brain region using the TissueCyte Serial Two-Photon Plus imaging platform; -omics including brain transcriptomics and proteomics; biochemistry of Aβ species; neuroinflammation and synaptic markers as assayed by immunohistochemistry; fluid biomarkers; spatial transcriptomics; electrophysiology and touchscreen-based cognitive tasks and cortical electroencephalography (EEG). Amyloid plaque pathology begins at cortical regions by 4 months of age and progresses rapidly throughout the forebrain to 12 months, then increases only gradually. Plaques are parenchymal at early stages, with vascular amyloid detected after ~15 months of age. Bulk brain transcriptomics exhibits age-dependent correlations to all AMP-AD differentially regulated pathways, with strongest correlation to immune modules. Hippocampal synaptophysin levels and LTP at the Schaffer collateral-CA1 synapse are reduced at 7.5 months of age. Prior to 12 months of age, there were no differences in cognitive function as measured by hippocampal-mediated pattern separation task in APPSAA relative to hAPP littermate controls, despite significant amyloid accumulation. Handing-induced seizures were observed during daily cognitive training in subjects after 12 months of age but not at younger ages. Cognitive assessments and EEG

analysis are in progress in aged animals. This model improves upon historical transgenic overexpression models for studying early onset amyloidosis and microglial activation.

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Poster

PSTR061: Alzheimer's Disease: Abeta Pathway

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR061.22/B136

Topic: C.02. Alzheimer's Disease and Other Dementias

Title: Activity-dependent regulation of amyloid precursor protein cleavage and developmental implications

Authors: *Z. SMITH, F. J. VONHOFF;
Dept. of Biol. Sci., Univ. of Maryland, Baltimore County, Baltimore, MD

Abstract: Despite the association of the Amyloid Precursor Protein and its orthologs with aging and degeneration shown in Alzheimer's disease, this family of proteins has been implicated in many developmental processes such as regulation of neuronal outgrowth and synaptic stabilization. Early studies suggest interplay between neuronal activity and Amyloid Precursor Protein-Like (APPL) function in Drosophila melanogaster. Our current work clarifies the interplay between these processes and suggests that neuronal activity regulates synaptic architecture during early development through differential processing of APPL. Using Eag1 Sh120 hyperexcitable mutants we were able to show a decrease in full length APPL protein in young animals compared to W1118. However, APPL transcript levels in both groups are not significantly different suggesting an increase in APPL processing. Using a double fluorescently tagged APPL construct containing both c-terminal and n-terminal fluorescent tags we observed localization differences in hyperexcitable animals at the neuromuscular junction of Drosophila larvae. We are in the process of validating these findings with proteomics data on the hyperexcitable animals. These findings suggest neuronal activity may regulate the cleavage of APPL and the formation of both C-terminal fragments (CTF) and the intracellular domain (AICD), a domain that is important in the regulation of epigenetic status and expression of synaptic plasticity genes. This work highlights a novel mechanism through which the Amyloid Precursor Protein family may influence neuronal anatomy in an activity-dependent manner during development.

Disclosures: Z. Smith: None. **F.J. Vonhoff:** None.

Poster

PSTR061: Alzheimer's Disease: Abeta Pathway

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Topic: C.02. Alzheimer's Disease and Other Dementias

Support: R01AG079257, R01DK093953, R01DK132088

Title: Sterile alpha and TIR motif containing 1 NADase plays a key role in driving amyloid-β pathology and synapse degeneration in Azheimer's disease

Authors: F. FAN[1], P. JOSHI[1], X. LIU[2], S. KOTTURU[3], Q.-S. LIU[2], ***X. LOU**[4];
[1]Cell Biol., Neurobio. and Anat., Med. Col. of Wisconsin, Milwaukee, WI; [2]Dept. of Pharmacol. and Toxicology, Med. Col. of Wisconsin, Milwaukee, WI; [3]Cell Biol., Neurobio. and Anat., Med. Col. of Wisconsin, MILWAKEE, WI; [4]Med. Col. of Wisconsin, Milwaukee, WI

Abstract: Alzheimer's disease (AD) is the most generic form of neurodegenerative disease, affecting millions of people worldwide. Among three pathological hallmarks (extracellular amyloid β plaques, intracellular Tau tangles, and synapse loss), synapse loss is the major correlate most robustly linked with cognitive decline and other symptoms. While Aβ pathology has been a leading cause of AD, the underlying molecular pathways driving synapse loss remain incompletely understood. Using genetics, high-resolution imaging, electrophysiology, molecular tools, and behavioral analysis, we investigated the molecular mechanism of synapse degeneration. We find that a new class of NADase, encoded by sterile alpha and TIR motif containing 1 (Sarm1), is crucial in driving AD pathogenesis. As an evolutionarily conserved member of the Toll/Interleukin receptor-1 family, Sarm1 contributes to Wallerian degeneration following peripheral nerve injury via its NAD+ hydrolase activity. We find that in AD brains, Sarm1 is highly enriched in some dystrophic axons and synapses, and these structures are often seen adjacent to amyloid plaques. Accordingly, Sarm1 gene deletion in 5xFAD mice significantly alleviates axon and synapse dystrophy as compared to the age- and sex-matched 5xFAD mice. Further electrophysiology studies at hippocampal neurons reveal a beneficial role of Sarm1 inactivation in preserving short-term and long-term synaptic plasticity. Moreover, Sarm1 inactivation protects AD brains from Aβ-induced pathology, including plaque accumulation, glia activation, and memory and cognition deficits. This protection is attributed to reduced synapse degeneration and neuroinflammation. Together, this work identifies Sarm1 as a key player in driving Aβ-associated core pathology and cognitive decline in AD, and these findings support a novel strategy to treat AD and protect memory by targeting Sarm1 NADase activity.

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Poster

PSTR061: Alzheimer's Disease: Abeta Pathway

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Program #/Poster #: PSTR061.24/B138

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: Swedish Research Council
Swedish Alzheimer Foundation
Swedish Brain Foundation
Krembil Foundation

Title: The Uppsala APP deletion promotes wildtype amyloid-beta aggregation and deposition

Authors: *M. INGELSSON[1], M. PAGNON DE LA VEGA[2], J. GE[4], S. KOUTARAPU[5], S. ZAMPAR[1], L. WU[6], P. E. FRASER[7], V. GIEDRAITIS[3], S. SYVÄNEN[8], L. LANNFELT[8], J. HANRIEDER[10], D. SEHLIN[9];
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Abstract: The *Uppsala* mutation in the gene for the amyloid precursor protein (*APPUpp)*, causing early onset familial Alzheimer's disease (AD), leads to an amyloid-β (Aβ) peptide that lacks six amino acids ($A\beta Upp_{\Delta 19\text{-}24}$). Our original study indicated that the pathogenic effects of this deletion result from increased β-secretase cleavage and decreased α-secretase cleavage together with an increased aggregation behavior of the Aβ mutant. Moreover, we recently described that $A\beta Upp1\text{-}42_{\Delta 19\text{-}24}$ form aggregates aggressively in transgenic mice (tg-UppSwe). However, as this mouse model only features AβUpp, it does not truly recapitulate the condition in the human *APPUpp* brain where AβUpp and wild-type Aβ (Aβwt) co-exist. Here, we aimed to investigate how the two Aβ peptides affect each other by crossing tg-UppSwe with Aβwt expressing tg-Swe mice (tg-UppSwe/Swe). Results from ELISA, histochemistry and MALDI imaging of such mice indicate that the previously reported properties of $A\beta Upp42_{\Delta 19\text{-}24}$ change the aggregation behavior and deposition of both Aβwt40 and Aβwt42in the brain, probably by acting as a seed for their aggregation. Accordingly, plaques containing Aβwt were formed earlier in tg-UppSwe/Swe compared to tg-Swe mice. It could also be observed that plaques containing Aβ38 were more abundant in tg-UppSwe/Swe compared to both tg-UppSwe and tg-Swe mice. These data illustrate a potential interplay between Aβwt and AβUpp, which could determine the structure of Aβ plaques in mutation carriers. Ongoing *in vitro* studies of co-aggregation and co-seeding between Aβwt and AβUpp will shed additional light on how they interact in the formation of aggregates.

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AB. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); BioArctic AB. **J. Hanrieder:** None. **D. Sehlin:** None.

Poster

PSTR061: Alzheimer's Disease: Abeta Pathway

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Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR061.25/B139

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: FDOH 21A04
NIH R15GM147912

Title: Spatiotemporal correlation between cholesterol dysregulation and AD pathologies

Authors: *H. MESA[1], Q. ZHANG[2];
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Abstract: Spatiotemporal correlation between cholesterol dysregulation and AD pathologies
Haylee Mesa, Jonathan Meade, Elaine Zhang, Qi Zhang
Abstract:
Alzheimer's disease (AD) is the most common and most studies dementia in the elderly. Despite decades of investigation, its true cause remains controversial. Amyloid hypothesis postulates that the generation and aggregation of beta-amyloid causes neurodegeneration. While genetic evidence from the inheritable form of AD supports that, the investigation of the more common form, sporadic AD points to membrane trafficking and cholesterol (Chol) metabolism. In fact, the greatest genetic risk factor is ApoE4, an isoform of ApoE that affects the metabolism of membrane lipids, especially Chol. Our previous findings have shown that APP regulates the homeostasis of neuronal membrane Chol (mChol), especially at axon terminals where membrane lipid turnover is the most frequent and profound. It is well known that the unbalance of mChol impairs synaptic transmission, axon integrity, and eventually neuronal survival. Notably, brain Chol metabolism is autonomously and decreased by aging, the primary AD risk factor. So, we speculate that age-dependent brain Chol reduction along with the deficiency in Chol regulation collaboratively leads to synaptic dysfunction and neurodegeneration. To test our hypothesis, we used APP-null mice, excluding the involvement of Abeta. For age-dependency, we collected brains from 12- and 24-month-old mice. For brain region susceptibility, we employed iDISCO and light-sheet imaging. Our analyses indicated that there are age-dependent, region-specific, and cell type-related changes in Chol regulation (measured by SREBP2, the master Chol regulator in the brain). More importantly, we detected spatiotemporally correlated differences in gliosis and Tau hyper-phosphorylation. With the ability to reach subcellular resolution, we also examine nuclear SREBP2 and axon integrity. Together, our results suggest a close tie between Chol abnormality and AD pathology in old APP-null mice. Our cell-based tests also support the

notion that Chol unbalance, especially at axon terminals, are causative to synaptic dysfunction, axon disintegration, and neurodegeneration. So, presynaptic Chol dysregulation is pathogenic for neurodegenerative diseases like AD.

Disclosures: H. Mesa: None. **Q. Zhang:** None.

Poster

PSTR061: Alzheimer's Disease: Abeta Pathway

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR061.26/B140

Topic: C.02. Alzheimer's Disease and Other Dementias

Title: Analysis of Biomarkers in Transgenic Cynomolgus Monkeys Overexpressing APP with Familial Alzheimer's Disease Mutations

Authors: D. YANAGISAWA, T. MORIMURA, M. NISHIMURA, M. EMA, I. TOOYAMA, ***S. ISHIGAKI**;
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Abstract: Alzheimer's disease (AD) is the most common form of dementia, characterized by neurodegeneration and the formation of senile plaques and neurofibrillary tangles, comprised of amyloid β (Aβ) and phosphorylated tau, respectively. While various mouse models have been developed to grasp AD's etiology, none have precisely mirrored its clinical and pathological traits, hinting at the potential utility of nonhuman primate models. In a previous study, we engineered transgenic cynomolgus monkeys overexpressing amyloid precursor protein (APP) with three familial AD mutations (Swedish, Arctic, Iberian mutations) (Seita et al., J Alzheimers Dis, 75:45-60, 2020). Our current investigation delves into changes in cerebrospinal fluid (CSF) biomarkers—Aβ40, Aβ42, tau, and phosphorylated tau at T181—in wild-type and APP-Tg cynomolgus monkeys. CSF samples were obtained from wild-type (n = 8) and APP-Tg cynomolgus monkeys (n = 7) aged 4 years and older under anesthesia with ketamine and xylazine. The levels of Aβ40, Aβ42, tau, and phosphorylated tau at T181 were quantified using the MILLIPLEX MAP Human Amyloid Beta and Tau Magnetic Bead Panel. Some APP-Tg cynomolgus monkeys exhibited age-related decreases in Aβ40 and Aβ42 levels; however, no significant differences were observed in comparison with wild-type cynomolgus monkeys. In contrast, the ratio of Aβ42 to Aβ40 (Aβ42/Aβ40) in APP-Tg cynomolgus monkeys was significantly lower than that in wild-type cynomolgus monkeys. There were no significant differences observed in the levels of tau and p-tau181 between the two groups. These CSF biomarkers hold promise for tracking AD pathology progression in the brain, prompting our commitment to ongoing data collection. Additionally, future analyses will encompass amyloid and tau PET, MRI, and brain biopsy.

Disclosures: D. Yanagisawa: None. **T. Morimura:** None. **M. Nishimura:** None. **M. Ema:** None. **I. Tooyama:** None. **S. Ishigaki:** None.

Poster

PSTR062: Non-AD Dementias

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR062.01/B141

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH/NINDS/NIA R01 NS131122

Title: Endothelial Krüppel-like factor 11 ameliorates neuropathological outcomes and cognitive dysfunction in vascular cognitive impairment and dementia

Authors: *N. QIU[1,2], S. LI[1,2], C. ZHOU[1], T. XIONG[1], X. HUANG[1], J. XUE[1,2], L. M. FOLEY[3], K. T. HITCHENS[3], K. YIN[1,2];
[1]Dept. of Neurol., Univ. of Pittsburgh Sch. of Med., Pittsburgh, PA; [2]Geriatric Research, Education and Clinical Center, Veterans Affairs Pittsburgh Healthcare System, Pittsburgh, PA; [3]Animal Imaging Ctr., Dept. of Neurobio., Univ. of Pittsburgh Sch. of Med., Pittsburgh, PA

Abstract: Vascular cognitive impairment and dementia (VCID), the second most common cause of dementia after Alzheimer's disease, primarily results from chronic cerebral hypoperfusion (CCH)-induced brain injury. This condition significantly hampers the daily functioning of elderly individuals. As a member of the zinc-finger transcription factor family, Krüppel-like transcription factor 11 (KLF11) is enriched in vascular endothelial cells (ECs) and has been implicated in multiple pathophysiological processes associated with neurological disorders. However, the function and molecular mechanism of KLF11 in VCID are still unknown. In this study, experimental VCID was induced in KLF11 knockout mice (KLF11 KO), endothelial cell-selective KLF11 transgenic mice (EC-KLF11 Tg), and their corresponding controls by bilateral common carotid artery stenosis (BCAS) surgery with microcoils on CCAs for five weeks. Cognitive and sensorimotor neurobehavioral deficits were assessed, and white matter injury and neuronal loss were examined. We found that mice underwent BCAS for 5 weeks developed remarkable cognitive impairments, myelin loss, and axonal damage in the corpus callosum and external capsule, and neuronal death in the hippocampal CA1 region and cerebral cortex. Compared to WT controls, KLF11 KO mice exhibited significantly severe cognitive and sensorimotor deficits following VCID. Genetic deletion of KLF11 in mice also significantly aggravated demyelination, axonal injury, and neuronal loss in response to CCH. In contrast, endothelial-selective transgenic overexpression of KLF11 in mice significantly alleviated cognitive and sensorimotor dysfunction, reduced demyelination, and ameliorated white matter injury and neuronal loss in comparison with their WT controls. To further explore the underlying mechanisms of KLF11 in the regulation of the pathogenesis of VCID, especially in ECs, we conducted RNA-seq analysis using FACS-sorting ECs from VCID mouse brains and sham controls. The biological functions implicated by analysis of the differential expression genes showed that many functional genes related to angiogenesis and vasculature development were strongly activated. Our results suggest that endothelial KLF11 promotes the recovery of sensorimotor and cognitive functions, and protects against cerebral white and grey matter injury

in mice after VCID through regulation of cerebrovascular structure and function. Endothelial KLF11 may serve as a novel therapeutic target for the treatment of VCID.

Disclosures: N. Qiu: None. **S. Li:** None. **C. Zhou:** None. **T. Xiong:** None. **X. Huang:** None. **J. Xue:** None. **L.M. Foley:** None. **K.T. Hitchens:** None. **K. Yin:** None.

Poster

PSTR062: Non-AD Dementias

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR062.02/B142

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: the National Health and Medical Research Council of Australia (Grant Identification Number 2019100)

Title: Effect of intermittent fasting on synaptic dysfunction and synaptic loss in a mouse model of vascular dementia

Authors: *N. I. TABASSUM[1], T. ARUMUGAM[2], M. EBRAHIMI[3];
[1]Microbiology, Anatomy, Physiol. and Pharmacol., [2]MAPP, La Trobe Univ., Bundoora, Australia; [3]Microbiology, anatomy, physiology and pharmacology, Latrobe Univ., Bundoora, Australia

Abstract: Synaptic dysfunction and loss represent critical pathological features in Alzheimer's and Parkinson's Diseases; however, their characterization in Vascular dementia (VaD) remains incomplete. Here, we investigated the spatiotemporal dynamics of synaptic dysfunction and loss using the bilateral common carotid artery stenosis (BCAS) model of VaD, inducing chronic cerebral hypoperfusion (CCH). Intermittent fasting (IF) was explored as a potential therapeutic strategy, given its promising outcomes in ameliorating neurological and age-related disorders. Male C57BL/6 mice were randomly assigned to ad libitum (AL) or IF (16 hours fasting and 8 hours eating periods) groups. Regular assessments of body weight, blood glucose, and ketone levels were conducted. Expression levels of synaptic markers, synaptic count, and neuronal structural integrity were evaluated at days 1, 7, 14, 21, and 30 post-BCAS using immunoblotting, immunohistochemistry, transmission electron microscopy (TEM), and quantitative proteomics. Cognitive function was assessed using the Barnes Maze Test. IF mice exhibited significantly lower body weight and glucose levels, along with elevated ketone levels ($n=10$, $p<0.05$) compared to AL mice. IF mice subjected to BCAS demonstrated improved cognitive learning ability and memory ($n=12$-15, $P<.05$), alongside reduced neuropathological alterations, such as white matter lesions (luxol fast blue staining, $n=6$, $p<.05$) and neuronal loss, relative to AL BCAS mice (cresyl violet staining, $n=6$, $p<.05$). Immunoblot analyses revealed no significant differences in several pre- and postsynaptic protein levels in the cortex between AL BCAS and sham groups ($n=8$). However, TEM analysis unveiled significant CCH-induced synaptic loss in the cortex ($n=3$, $p<.05$) from 7 days post-BCAS in AL mice, whereas IF preserved synaptic

density. Proteomics data demonstrated that IF upregulated proteins involved in Ca^{2+} signaling, NMDA receptor expression, neuronal growth, and synaptic plasticity, while downregulating inflammatory proteins. These findings mechanistically elucidate how IF may confer neuroprotection and hold promise for alleviating neuropathology in VaD.

Disclosures: N.I. Tabassum: None. **T. Arumugam:** None. **M. Ebrahimi:** None.

Poster

PSTR062: Non-AD Dementias

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR062.03/C1

Topic: C.02. Alzheimer's Disease and Other Dementias

Title: Argyrophilic grain disease does not show the “sloping shoulders sign”

Authors: *T. IWASE;
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Abstract: The “sloping shoulders sign” is seen in moderate to severe Alzheimer's disease (AD). It is characterized by the hippocampus on both sides smoothly descending outward in axial CT / MRI. We found the “sloping shoulders sign” by 2018 and reported that the sign is helpful to differentiate argyrophilic grain disease (AGD) from AD (Sakurai K, Iwase T, Kaneda D, Hashizume Y, et al. J Alzheimers Dis 2021). In this study, brains and spinal cords from centenarians were studied. The formalin-fixed paraffin-embedded sections stained with hematoxylin and eosin (HE), Klüver-Barrera (KB), Gallyas-Braak and immunostainings for amyloid-β (Aβ), phosphorylated tau (p-tau), α-synuclein, and phosphorylated transactivation response DNA-binding protein of 43 kDa (p-TDP-43) were used. In the first part of this study, we investigated the neuropathological changes of a centenarian with severe dementia who did not show the “sloping shoulders sign”. Numerous argyrophilic grains were found under the microscope. The distribution of argyrophilic grains corresponded to Saito's stage III, and the density of argyrophilic grains was very high. Spongiform changes were observed in the superficial cortical layer in areas rich in argyrophilic grains. The distribution of neurofibrillary tangles (NFTs) was limited to the medial temporal lobe, corresponding to Braak stage III and Braak AT8 immunohistochemistry stage III. The level of AD-related neuropathologic change was intermediate. These findings led to the awareness of hippocampal morphological difference between AGD and AD and the practical use of “sloping shoulders sign”. In the second part of this study, two centenarians with moderate to severe AGD and mild AD neuropathologic change were selected. We found that their axial CT did not show the “sloping shoulders sign”. Our findings indicate that AGD does not show the “sloping shoulders sign”.

Disclosures: T. Iwase: None.

Poster

PSTR062: Non-AD Dementias

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR062.04/C2

Topic: C.02. Alzheimer's Disease and Other Dementias

Title: Trem2 agonism enhances microglial survival in models of csf1r-dependent adult-onset leukoencephalopathy

Authors: *A. MARTINS[1], K. C. LARSON[2], F. GERGITS[1], A. RENOUX[1], E. WEISMAN[1], B. DEJANOVIC[1], E. A. THACKABERRY[4], D. GRAY[3], C. MIRESCU[2];
[2]Discovery Biol., [3]Res., [1]Vigil Neurosci., Watertown, MA; [4]Early Develop., Vigil Neurosciences, Watertown, MA

Abstract: Microglia dysfunction is implicated in several neurodegenerative disorders, including a rare microgliopathy: adult-onset leukoencephalopathy with axonal spheroids and pigmented glia (ALSP). ALSP is caused by heterozygous loss-of-function mutations in the colony stimulating factor 1 receptor (CSF1R) gene, which encodes a receptor required for the differentiation of myeloid cells, as well as for microglial survival and proliferation. Similar functions have also been ascribed to triggering receptor expressed on myeloid cells 2 (TREM2), which shares a similar microglia enrichment profile and converging intracellular signaling pathway mediated by spleen associated tyrosine kinase (SYK) and phosphoinositide-3-kinase (PI3K). To explore the therapeutic hypothesis that loss of CSF1R signaling and related microglial hypofunction can be circumvented via activation of TREM2, we evaluated the potential that VGL101 (Iluzanebart), a human monoclonal TREM2 agonist antibody under development for treatment of ALSP, can compensate for CSF1R loss-of-function. Herein, we demonstrate that Iluzanebart is a potent, dose-dependent, and specific activator of TREM2 signaling in human cells. Iluzanebart treatment rescued viability of induced pluripotent stem cell (iPSC)-derived human microglia (iMGL) in multiple in vitro models of ALSP, including in iMGLs carrying the heterozygous I794T mutation found in ALSP patients. Additionally, Iluzanebart treatment in iMGLs directly increased surface levels of CSF1R, which further translated to increased activation of signaling as measured by phosphorylation of CSF1R. Differentially expressed genes identified in the brains of mice treated with Iluzanebart were exemplary of TREM2-dependent activation of microglia. Changes in protein levels of specific chemokines identified by gene expression analysis were also confirmed in vivo. These findings demonstrate Iluzanebart is a potent and selective TREM2 agonistic antibody, align with the hypothesis that TREM2 activation can compensate for CSF1R dysfunction, and support continued clinical development of Iluzanebart in individuals with ALSP.

Disclosures: A. Martins: A. Employment/Salary (full or part-time):; Vigil Neuroscience. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Vigil Neuroscience. **K.C. Larson:** A. Employment/Salary (full or part-time):; Vigil Neuroscience. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Vigil Neuroscience. **F. Gergits:** A. Employment/Salary (full or part-time):; Vigil

Neuroscience. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Vigil Neuroscience. **A. Renoux:** A. Employment/Salary (full or part-time):; Vigil Neuroscience. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Vigil Neuroscience. **E. Weisman:** A. Employment/Salary (full or part-time):; Vigil Neuroscience. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Vigil Neuroscience. **B. Dejanovic:** A. Employment/Salary (full or part-time):; Vigil Neuroscience. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Vigil Neuroscience. **E.A. Thackaberry:** A. Employment/Salary (full or part-time):; Vigil Neuroscience. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Vigil Neuroscience. **D. Gray:** A. Employment/Salary (full or part-time):; Vigil Neuroscience. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Vigil Neuroscience. **C. Mirescu:** A. Employment/Salary (full or part-time):; Vigil Neuroscience. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Vigil Neuroscience.

Poster

PSTR062: Non-AD Dementias

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR062.05/C3

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: CIHR CGS-D, NO
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Nancy and Buster Alvord Endowment, CDK

Title: Lipid oxidation as a novel underlying mechanism driving white matter devastation in adult-onset leukoencephalopathy with axonal spheroids and pigmented glia

Authors: *N. OLLEN-BITTLE[1], M. FRANK[1], C. D. KEENE[3], E. FINGER[2], Q. ZHANG[4], S. N. WHITEHEAD[1];
[1]Anat. and Cell Biol., [2]Western Univ., London, ON, Canada; [3]Pathology, Univ. of Washington, Seattle, WA; [4]Dept. of Pathology and Lab. Med., London Hlth. Sci. Ctr., London, ON, Canada

Abstract: Background: Adult-onset leukoencephalopathy with axonal spheroids and pigmented glia (ALSP) is a rare, early onset, neurodegenerative disease associated with mutations in the colony-stimulating factor 1 receptor (CSF1R) gene and white matter wasting. The white matter lesions in ALSP can result in a range of devastating symptoms including major personality

changes, cognitive dysfunction, loss of motor function and decline to vegetative state. In the brain, CSF1R is enriched in microglia and is highly connected to their function[1]. Previous work has described lipid laden cells in ALSP tissue and lipid-droplet-accumulating microglia represent a known dysfunctional phenotype that accumulate in other neurodegenerative diseases and produce high levels of reactive oxygen species (ROS)[2]. ROS mediate cellular damage through a wide range of mechanisms including lipid oxidation. Phosphatidylcholines are a predominant lipid within biological membranes and are particularly susceptible to lipid oxidation due to their unsaturated fatty acid residue. Oxidized phosphatidylcholines (OxPCs) have been shown to exert neurotoxic effects both *in vitro* and *in vivo,* and are known to drive pathogenesis in other neurodegenerative conditions[3]. In post-mortem ALSP brain tissue we elucidate the *in situ* relationship of OxPCs and lipid-droplet-accumulating microglia.
Methods: We employed a multi-modal digital pathology workflow to co-register magnetic resonance imaging (MRI) of white matter lesions in post-mortem CSF1R mutation positive ALSP brain tissue with histological staining and positive mode matrix-assisted laser desorption/ionization mass spectrometry imaging (MALDI-MSI). Regions of interest within white matter lesions and normal appearing white matter from ALSP donors were compared to each other as well as to non-ALSP age and sex-matched controls (n=3).
Results: For the first time we demonstrate OxPCs co-localize with MRI confirmed white matter lesions and histologic evidence of intracellular lipid droplet accumulation in CSF1R mutation positive ALSP.
Conclusion: Lipid oxidation and intracellular lipid droplet accumulation may contribute to ALSP progression and may serve as a novel therapeutic target.
References:1.Chitu, V. *et al. Cell Rep.* **30**, 3004-3019.e5 (2020).2.Marschallinger, J. *et al. Nat. Neurosci.* **23**, 194–208 (2020).3.Dong, Y. *et al. Nat. Neurosci.* **24**, 489–503 (2021).

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Poster

PSTR062: Non-AD Dementias

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR062.06/C4

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH Grant AG060731
MSU- Department of Translational Neuroscience

Title: Alpha-synuclein and amyloid co-pathologies combined with nigrostriatal degeneration in a novel rat model of Dementia with Lewy bodies

Authors: *M. HORE[1], C. J. KEMP[1], J. PATTERSON[1], J. R. HOWE[1], M. KUBIK[1], M. GIFANI[1], C. E. SORTWELL[2], S. E. COUNTS[3];

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Abstract: Dementia with Lewy Bodies (DLB) is the second most common neurodegenerative cause of dementia after Alzheimer's disease (AD). DLB is characterized by: 1) Aggregates of alpha-synuclein (α-syn) Lewy bodies (LBs), amyloid-beta peptides as plaques and, to a variable extent, hyperphosphorylated tau protein as neurofibrillary tangles (NFTs); 2) Nigrostriatal degeneration; and 3) DLB-relevant behavioral symptomatology including cognitive fluctuation, spontaneous parkinsonism, rapid eye movement sleep disorder and recurrent visual hallucinations. LB and amyloid plaque co-pathologies in DLB have been replicated in rodent models, but none has recapitulated the full spectrum of DLB. Thus, we are developing a novel DLB rat model by combining the transgenic Tg344-19 rat model of AD with staged intracerebral injections of mouse α-syn preformed fibrils (PFFs). The Tg344-19 AD rat model expresses mutant human amyloid precursor protein and presenilin 1 genes resulting in age-dependent accumulation of plaques and NFTs, cortical and hippocampal neurodegeneration, and cognitive disturbances. Nigrostriatal α-syn PFF injections result in accumulation of pathological α-syn in cortical, limbic and nigrostriatal regions, followed by nigrostriatal degeneration and motor deficits. To develop this model, male and female F344 wildtype (WT) and AD Tg rats received bilateral intranigral injections of α-syn PFFs (WT PFF n = 13, AD PFF = 8) or α-syn monomer control (WT monomer n = 11, AD monomer = 10) at 6 months of age. Four months later, all rats received additional bilateral intrastriatal injections of α-syn PFFs or monomers. Rats were then euthanized at 12 months of age. This surgical strategy, overlaid upon the specific age of the Tg344-19 AD rat, will result in peak PFF-induced nigrostriatal degeneration and optimal accumulation of α-syn inclusions and plaque co-pathologies in the cortex and amygdala. Ongoing postmortem assessments are currently examining: 1) Extent of nigrostriatal degeneration; 2) Impact of co-occurring proteinopathies on plaque and α-syn inclusion burden in the amygdala and multiple cortical regions; 3) Neuroinflammatory markers in the amygdala and multiple cortical regions; and 4) Impact of sex on these outcome measures. A rodent model that integrates the entire repertoire of DLB co-pathologies will increase understanding of the proteinopathy in DLB and facilitate preclinical assessment of novel disease modifying therapies.

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Poster

PSTR062: Non-AD Dementias

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR062.07/C5

Topic: C.02. Alzheimer's Disease and Other Dementias

Title: In vitro disease modeling of FTLD using patient-derived iPSCs identified potential therapeutic agent and mechanism.

Authors: *H. KOKUBU[1], S. HAYASHI[2], K. FUKUSHIMA[2], H. OKANO[3];
[1]Regenerative Med. and CNS drug discovery, R&D, K Pharma Lab., Fujisawa, Japan; [2]K Pharma, Inc., Tokyo, Japan; [3]Keio Univ., Tokyo, Japan

Abstract: Introduction: Frontotemporal Lobar Degeneration (FTLD) is a neurodegenerative disorder that primarily affects the frontal and temporal lobes. FTLD is clinically characterized by behavioral abnormalities, language problems, and/or movement deficits, and no drug is currently available. Most cases of the FTLD cases are sporadic, but several gene mutations are linked to FTLD including *GRN*, *MAPT*, *TARDBP* and *C9ORF72* mutations. FTLD is pathologically classified into four different types such as FTLD-TDP and FTLD-Tau, based on the type of protein aggregation that accumulates in the patients' brains. The purpose of this study is to find out therapeutic agents from existing drugs using patient-derived induced pluripotent cells (iPSCs). Method: Using Tet-On Ngn2 expression system and Fgf8 treatment, we efficiently generated frontal lobe-type cortical neurons from FTLD patient-derived iPSCs. To screen drug candidates for disease modification, commercially available compound library was employed. The drugs that can improve cell death (LDH leakage) and lysosomal deficit (abnormally abundant lysosome/Lamp1), both of which are hallmarks of FTLD, was selected as potential FTLD drugs. One of these drugs was examined if this compound was also effective to sporadic FTLD cases. Result: To identify therapeutic candidate for FTLD, we performed a phenotypic screen using neurons differentiated from FTLD patient-derived iPSCs which harboring the *GRN* S116X mutation. Patient-derived neurons exhibited accelerated cell death and enlarged lysosomes compared to neurons from healthy donors. Of 1,269 compounds screened, three were effective in suppressing cell death and lysosomal enlargement. Based on their properties, one molecule, compound X, was selected for further analysis. Next, we analyzed whether compound X could suppress other cases of FTLD including three familial FTLD cases such as *GRN* mutant iPSCs (M1L and R493X;FTLD-TDP) and *MAPT* iPSCs (R493W ; FTLD-Tau) as well as four sporadic cases, all of which showed accelerated cell death. Again, Compound X suppressed neuronal cell death in all familial cases and three out of four sporadic cases, indicating that Compound X is effective in majority of FTLD cases. Conclusion: This study identified Compound X as a drug candidate for FTLD drug candidate and will contribute to clarify mechanisms underlying FTLD as well.

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Poster

PSTR062: Non-AD Dementias

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR062.08/C6

Topic: C.02. Alzheimer's Disease and Other Dementias

Title: Investigating Non-Canonical SUMF1 in Alzheimer's Disease with Psychosis

Authors: *S.-H. KU[1], V. C. KODAVALI[2], S. L. ERICKSON[2], R. A. SWEET[2];
[1]Univ. of Pittsburgh Med. Ctr., Pittsburgh, PA; [2]Dept Psychiatry, Univ. of Pittsburgh Dept. of Psychiatry, Pittsburgh, PA

Abstract: Problem statement: In Alzheimer's disease (AD), genetic factors play a crucial role in the development of psychotic symptoms, as demonstrated by a recent Genome-Wide Association Studies linking an alternate (non-canonical) transcript of sulfatase modifying factor 1 (*SUMF1*) to AD with psychosis. This alternate *SUMF1* is predicted to be non-translated due to nonsense-mediated decay (NMD). However, the alternate transcript is abundant and uniformly identified in DLPFC gray matter from healthy adults and from individuals with AD. In addition, a protein isoform corresponding to its open reading frame is annotated in Uniprot (Q8NBK3-3). The objective of this study is to uncover the function and expression pattern of non-canonical *SUMF1* in neurons and explore its potential involvement in AD with psychosis.**Methods:** Overexpression in HEK293T cells of mRNA corresponding to the open reading frame of the *SUMF1* alternate transcript terminating at the first stop codon and of a longer mRNA for the alternate transcript including additional terminal exons with multiple stop codons was studied. SUMF1 protein expression was detected by western blot. We further conducted qPCR of canonical and non-canonical *SUMF1* during neuronal maturation in hiPSC-derived neurons and evaluated multiple ASOs for effects on *SUMF1* canonical and non-canonical transcript levels. Sumf1+/- mice were crossed with mice containing a humanized Tau gene (hTau) that promotes recapitulates neuronal pathologies of AD and the resulting progeny evaluated for psychosis-associated behaviors.**Results:** Expression of both the alternate transcript ORF and longer mRNA resulted in SUMF1 protein expression. The longer transcript yielded proteins of varying molecular weights, consistent with escape from NMD. In the context of neuronal maturation from iPSCs, our findings showed that the non-canonical SUMF1 exhibited its peak expression around day 54, and it expressed in a higher level compared to the canonical form. Two ASOs were identified that selectively knock down the non-canonical *SUMF1* while not affecting the canonical form (ASO1, p=0.01; ASO2, p=0.000002). Behavioral testing of Sumf1x hTau mice is ongoing and results will be presented.**Conclusions:** We confirmed the translation of non-canonical SUMF1 through western blotting, indicating that it can escape NMD. The discovery that non-canonical SUMF1 is not subject to NMD suggests a novel avenue for research into the molecular mechanisms underlying pathogenesis in AD with psychosis. Future studies will evaluate the effects of selective knockdown of non-Canonical mRNA on neuronal development and in models of AD disease pathologies.

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Poster

PSTR062: Non-AD Dementias

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Program #/Poster #: PSTR062.09/C7

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NHGRI Intramural Research Program 1ZIAHG000068-16
NICHD Intramural Research Program ZIAHD008988
NIH Grant R01NS114413
NIH Grant R01NS124784
Ara Parseghian Medical Research Foundation at the University of Notre Dame

Title: Optimization of Systemic AAV9 Gene Therapy in Niemann Pick Disease Type C1 Mice

Authors: *A. MYLVARA[1], A. L. GIBSON[3], C. DAVIDSON[1], C. VENDITTI[2], F. PORTER[1], W. PAVAN[2];
[1]NICHD, [2]NHGRI, NIH, Bethesda, MD; [3]UCSD, La Jolla, CA

Abstract: Niemann-Pick disease, type C1 (NPC1) is a rare, fatal neurodegenerative disorder caused by pathological variations in the *NPC1* gene, which encodes a lysosomal cholesterol transport protein. Despite extensive research, there are currently no approved treatments for NPC1 in the US. Recent gene therapy studies involving both systemic and direct central nervous system delivery of AAV9-*hNPC1* have demonstrated significant disease alleviation in murine models. To investigate the effect of dose on gene therapy efficacy in Npc1 mice, we administered three different doses of AAV9-*hNPC1* at a clinically relevant, juvenile age. The medium dose was further examined to assess a window of treatment at pre-, early, and post-symptomatic time points. Our findings demonstrate increased doses administered systemically and earlier in the disease course lead to longer lifespans, slower disease progression, and reduced brain pathology in a null Npc1 mouse model. Examination of viral distribution of AAV9-*hNPC1* shows that earlier treatment results in greater transduction of the central nervous system. These results have important implications for designing clinical trials, suggesting that intervention with high dose gene therapy at early stages of the disease will offer the best outcome for NPC1 individuals.

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Poster

PSTR062: Non-AD Dementias

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Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH R61NS115161

Title: Loss of TDP-43 in neurons exacerbates neurodegeneration and accelerates tauopathy through caspase 3-mediated tau cleavage in a mouse model of mixed etiology dementia.

Authors: *M. BAGHEL[1], X. CHEN[2], G. BURNS[3], A. PEETHAMBARAN MALLIKA[4], T. LI[5], P. C. WONG[6];
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Abstract: Alzheimer's disease (AD)-Related Dementias is a group of progressive neurodegenerative disorders with mid to late life onset, including Lewy body dementia, frontotemporal dementia (FTD) or mixed etiology dementia (MED) such as AD exhibiting TDP-43 pathology. Recent studies indicate that TDP-43 proteinopathy, initially associated with amyotrophic lateral sclerosis and FTD, is also found in 30-60% of AD cases and correlated with worsened neurodegeneration and cognitive functions. How TDP-43 pathology contributes to neuron loss and cognitive deficits remains elusive. Our previous work supporting the view that loss of TDP-43 splicing repression of cryptic exons underlies neurodegeneration led us to hypothesize that in MED, loss of such TDP-43 function exacerbates AD pathologies and/or neuron loss. To address this question, we generated a mouse model for MED (*APPswe/PS1ΔE9;Tau4R;CaMKIIα^{ER};TDP-43$^{F/F}$*) by a crossbreeding strategy with induciblelacking TDP-43 in forebrain neurons (*CaMKIIα^{ER};TDP-43$^{F/F}$*) and inducible tau (*Tau4R*) and β-amyloidosis (*APPswe/PS1ΔE9*) mouse models. To test the influence of TDP-43 on tauopathy-dependent neurodegeneration, we deleted TDP-43 temporally in excitatory hippocampal neurons through oral administration of tamoxifen citrate for 4 weeks in 12 month-old "MED" mice as well as *CaMKIIα^{ER};TDP-43$^{F/F}$* and *APPswe/PS1ΔE9;Tau4R* control littermates and these mice were subsequently sacrificed and analyzed at 20-month of age. As expected for *CaMKIIα^{ER};TDP-43$^{F/F}$*, we observed selective vulnerability of CA2/3 neurons. As compared to control mice, such vulnerability is exacerbated in MED model. Interestingly, we found loss of TDP-43 led to marked loss of granule neurons in the dentate gyrus and CA1 subregion of hippocampus of MED mice. We characterized the pathological conversion of endogenous tau and found that, as compared to control littermates, TDP-43 loss in MED mice accelerated the pathological conversion of endogenous tau. Mechanistically, we show that when TDP-43 is depleted caspase 3 mediated cleavage of endogenous tau is markedly elevated in the presence of a Tau4R seed and β-amyloid plaque leading to exacerbated tauopathy and neuronal loss. Thus, these intriguing observations are consistent with the idea that loss of TDP-43 function accelerates tauopathy-dependent neuron loss in AD exhibiting TDP-43 pathology. Thus, our work discloses novel mechanistic insights and therapeutic targets for MED harboring co-pathology of TDP-43 and provides a new MED model for testing therapeutic strategies.

Disclosures: M. Baghel: None. **X. Chen:** None. **G. Burns:** None. **A. Peethambaran Mallika:** None. **T. Li:** None. **P.C. Wong:** None.

Poster

PSTR062: Non-AD Dementias

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR062.11/C9

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH NINDS R56NS117465
Aligning Science Across Parkinson's disease 020616 through Michael j fox foundation

Title: Lewy pathology and neurofibrillary tangles show distinct localization in temporal cortex of Dementia with Lewy Bodies

Authors: *O. ABDELAZIZ[1], L. A. VOLPICELLI-DALEY[3], T. G. BEACH[4], G. E. SERRANO[5], D. FISCHER[6], R. KENNEDY[2];
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Abstract: Pathologic aggregates of alpha-synuclein and tau, called Lewy pathology and neurofibrillary tangles, respectively, associate with cognitive decline in Parkinson’s disease dementia. Over half of individuals with Lewy body disease also harbor neurofibrillary tangles. Recombinant α-synuclein and tau proteins interact *in vitro*. Previous electron microscopy studies of postmortem brains show that Lewy bodies and neurofibrillary tangles can co-exist in the same cells. We analyzed the potential interactions between α-synuclein and tau by performing dual label immunofluorescence in temporal cortex tissue from human individuals with Dementia with Lewy Bodies. The cortex showed abundant pathologic tau and α-synuclein inclusions in all DLB cases analyzed. None of the control cases showed neurofibrillary tangles but did show a small amount of diffuse, cytosolic alpha-synuclein. Notably, the tau and α-synuclein aggregates, particularly those in neurites, were almost completely distinct. Rarely, in some soma, neurofibrillary tau appeared to wrap around the perimeter of Lewy bodies. Thus, the data suggest that within the temporal cortex, pathologic α-synuclein and pathologic tau do not co-assemble in the same inclusions. The aggregates of α-synuclein and tau may contribute to DLB phenotypes by affecting independent neurons and disrupting circuitry.

Disclosures: O. Abdelaziz: None. **L.A. Volpicelli-Daley:** None. **T.G. Beach:** None. **G.E. Serrano:** None. **D. Fischer:** None. **R. Kennedy:** None.

Poster

PSTR062: Non-AD Dementias

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR062.12/C10

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: DC Center for AIDS Research (DC-CFAR)
Georgetown-Howard Universities Center for Clinical and Translations Science (GHUCCTS)
Artificial Intelligence/Machine Learning Consortium to Advance Health Equity and Researcher Diversity (AIM-AHEAD)

Title: Limbic and Whole-Brain Functional Connectivity in Non-Substance Abusers with HIV

Authors: *S. WASHINGTON[1], A. S. VANMETER[2], M. C. GONDRE-LEWIS[3];
[1]Howard Univ., Washington, DC; [2]Georgetown Univ. Med. Ctr., Washington, DC, ; [3]Col. of Med., Washington, DC.

Abstract: Human immunodeficiency virus (HIV) negatively impacts behavioral health and is co-morbid with neurocognitive and psychiatric disorders, including substance use disorder (SUD). Neuroimaging studies repeatedly show diminished functional connectivity in people infected with HIV. However, previous studies appear to disregard any potential for HIV/SUD co-morbidities, an oversight that represents a potential confound in HIV-related neuroimaging literature. Further, the functional connectivity of limbic neural substrates underlying reward and SUD (e.g., nucleus accumbens, amygdala, and hippocampus) remain unexplored in people living with HIV (PLWH). Here, we obtained resting-state functional magnetic resonance imaging (rsfMRI) data from a small population (N=7) of PLWH who have no history of SUD. Functional connectivity in PLWH had generally reduced functional connectivity relative to healthy controls (N=14), with the greatest differences occurring between visual cortex and cerebellum. Seed-based analyses of left and right nucleus accumbens and hippocampus yielded robust connections with the default mode network in controls. Similar seed-based analyses of the amygdala in controls yielded robust connections with inferior temporal lobe regions rather than the default mode network. Connectivity between corresponding regions in PLWH was reduced but recruited the default mode and inferior temporal networks. Our results suggest that (1) PLWH who do not have SUD show reduced overall functional connectivity relative to controls, consistent with previous rsfMRI studies of PLWH, and (2) this reduced connectivity in PLWH extends to limbic structures underlying reward, even in the absence of SUD.

Disclosures: S. Washington: None.

Poster

PSTR062: Non-AD Dementias

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR062.13/C11

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH R01 DC018797
Alzheimer's Association 23AARG-NTF-1026470

Title: Central auditory deficits in the pathogenesis of Alzheiemer’s Disease

Authors: *J. PARK, J. H. KIM;
Kresge Hearing Res. Inst., Univ. of Michigan, Ann Arbor, MI

Abstract: Hearing loss, a prevalent symptom in the aged population, is associated with an increased risk for Alzheimer’s disease (AD). Intriguingly, hearing loss also precedes cognitive deficits in AD. There is an association between auditory dysfunction and cognitive decline; however, the nature of this relationship and the underlying mechanism linking these two diseases are unclear. Here, we aim to use the auditory nervous system as a model for understanding how sensory deprivation - specifically hearing loss - leads to circuit disruption and causes cognitive decline in AD. Using the 5X FAD mouse model of AD, genetically engineered mice with five AD-linked mutations in amyloid precursor protein and presenilin 1, we investigated how modification of auditory inputs impacts auditory functions and AD-related pathology. We tested how sound deprivation (ear-plugging for two months from 2 months to 4 months old) at the pre-symptomatic stage impacts auditory functions in AD mice. After sound deprivation using earplugs, we examined *in vivo* auditory functions using auditory brainstem responses (ABRs) in 5X FAD mice at 4 months old. Although the sound-blocking effect due to the earplug was similar, after experiencing sound deprivation, the hearing ability of WT returned to normal, but 5xFAD disability. Furthermore, we observed amyloid-beta, pathological markers of AD, in the auditory signaling pathway by immunofluorescence. The 5x FAD mice had increased amyloid beta expression in the auditory cortex and inferior colliculus compared to WT, but not in MNTB. Notably, sound deprivation facilitates this accumulation in 5xFAD mice with earplugs. The results suggest that hearing loss could aggravate the pathophysiological features of AD including amyloid beta accumulation.

Disclosures: J. Park: None. **J.H. Kim:** None.

Poster

PSTR062: Non-AD Dementias

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR062.14/C12

Topic: C.02. Alzheimer's Disease and Other Dementias

Title: Specificity of thalamic nuclear atrophy in frontotemporal dementia subtypes

Authors: *A. BANERJEE[1], F. YANG[2], M. HORNBERGER[3], J. DUTTA[4], M. SARANATHAN[5];
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Abstract: Frontotemporal dementia (FTD) is a progressive neurodegenerative brain disorder marked by changes in behavior, personality, and language with three clinical phenotypes-behavioral variant (BV), non-fluent aphasia (PNFA), and semantic variant (SV). Thalamic atrophy has been observed across FTD subtypes, but the involvement of specific thalamic nuclei has not been well characterized. A very recent method for thalamic nuclei segmentation from standard T1 MRI called Histogram-based Polynomial Synthesis - Thalamus Optimized Multi Atlas Segmentation (HIPS-THOMAS) was shown to be significantly more accurate and more sensitive compared to standard THOMAS and FreeSurfer segmentation. In this cross-sectional study, we demonstrate the utility of HIPS-THOMAS for thalamic nuclei volumetry in FTD patients (total n=266, BV= 64, PNFA=33, SV= 37 and healthy controls (HC)= 132) from T1 MRI data from the Frontotemporal Lobar Degeneration Neuroimaging initiative (NIFD). ANCOVA was used to characterize atrophy of thalamic nuclei with age, gender, and intracranial volume as covariates and Cohen's d was used as a standardized measure to quantify effect sizes. Our analysis revealed an increasing gradient of atrophy across FTD subtypes. Specifically, we observed bilateral atrophy (Cohen’s d 0.8-1.2 with a 10-20 % volume reduction) in anteroventral, mediodorsal and pulvinar in SV compared to HC. In PNFA, this expanded to include centromedian and ventral lateral posterior nuclei (Cohen’s d 0.9-1.2 with a 15-25 % volume reduction). All nuclei were significantly atrophied in BV with anteroventral, mediodorsal, and pulvinar (Cohen’s d 1.8 – 2.0 with a 40-50 % volume reduction) compared to HC. No gender differences were observed except for bilateral pulvinar atrophy in males compared to females in PNFA, left ventral anterior in case of males and ventral posterior lateral nuclei in case of females, both in BV. Atrophy was largely bilateral and symmetric when males and females were combined. Partial correlation analysis between nuclear volumes and neuropsychological test scores revealed a significant positive correlation (0.4-0.6) between the anteroventral, mediodorsal and pulvinar (all left) with Boston Naming Test, ventral lateral anterior and ventral lateral posterior nuclei (bilateral) with Backwards Digit Span in case of BV. Correlations were limited to just left mediodorsal with Peabody Picture Vocabulary Test: Inanimate in PNFA and none in SV. In conclusion, our study found that HIPS-THOMAS segmentation provided insights into differences in thalamic nuclear atrophy patterns in FTD subtypes with progressive involvement of thalamic nuclei in FTD from SV to PNFA to BV.

Disclosures: A. Banerjee: None. **F. Yang:** None. **M. Hornberger:** None. **J. Dutta:** None. **M. Saranathan:** None.

Poster

PSTR062: Non-AD Dementias

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR062.15/C13

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: T32NS095775
T32GM008361
F30AG085889
R01NS128031

Title: Progranulin insufficiency and TDP-43 overexpression interact to worsen phenotypes in a mouse model of Frontotemporal Dementia

Authors: *A. COOK[1], A. K. KAPLELACH[4], K. M. GREATHOUSE[6], B. LIN[2], A. HOWARD[1], N. COOPER[7], G. VOLLMER[1], A. R. HAKIM[5], R. MILLER[1], J. H. HERSKOWITZ[3], A. E. ARRANT[8];
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Abstract: Frontotemporal dementia (FTD) is a common form of dementia and patients typically present with language or behavioral impairments such as social withdrawal, disinhibition, or word finding difficulties. Heterozygous loss-of-function mutations in the progranulin (*GRN*) gene, resulting in haploinsufficiency of the protein, are a major cause of FTD with TDP-43 pathology. TDP-43 pathology is characterized by TDP-43's mislocalization from the nucleus to the cytoplasm and the formation of TDP-43 aggregates. $Grn^{+/-}$ mice are the genetic model of FTD due to progranulin mutations, but do not develop TDP-43 pathology. However $Grn^{-/-}$ mice, the genetic model of Neuronal Ceroid Lipofuscinosis type 11 (CNL11), an adolescent onset lysosomal storage disorder, develop mild thalamic TDP-43 aggregates at advanced ages. To investigate how progranulin insufficiency exacerbates development of FTD-relevant phenotypes, we crossed $Grn^{+/-}$ mice with transgenic mice expressing wild-type human TDP-43 under the Thy1 promoter (Jackson Lab #012836). We analyzed homozygous transgenic mice (hTDP++) for TDP-43 pathology and neuroinflammation, and hemizygous transgenic mice (hTDP+) for FTD-related social deficits and pathology. Analysis of homozygous hTDP++ mice showed that $Grn^{+/-}$:hTDP++ mice had more cortical immunoreactivity for markers of reactive glia than $Grn^{+/+}$:hTDP++, but a Nanostring neuroinflammation panel showed little difference between the two groups. In contrast, $Grn^{-/-}$:hTDP++ mice had dramatic transcriptional changes consistent with greater inflammation. Analysis of hemizygous hTDP+ mice revealed more severe social dominance deficits in $Grn^{+/-}$:hTDP+ mice than either $Grn^{+/-}$:hTDP- or $Grn^{+/+}$:hTDP+ mice. This occurred in the absence of detectable TDP-43 pathology or inflammation. Dendritic spine analysis revealed that $Grn^{+/-}$:hTDP+ mice had lower mushroom spine density on basal dendrites of layer II/III pyramidal neurons in the medial prefrontal cortex, neurons involved in social dominance behavior. These data show that progranulin insufficiency and human TDP-43 overexpression interact to worsen inflammatory and social phenotypes, without worsening TDP-43 pathology. $Grn^{+/-}$:hTDP+ mice have fewer mushroom spines, a potential cause of low social dominance behavior.

Disclosures: A. Cook: None. **A.K. Kaplelach:** None. **K.M. Greathouse:** None. **B. Lin:** None. **A. Howard:** None. **N. Cooper:** None. **G. Vollmer:** None. **R. Miller:** None. **J.H. Herskowitz:** None. **A.E. Arrant:** None.

Poster

PSTR062: Non-AD Dementias

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR062.16/C14

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIDCD DC008552
NIH Federal Grant SP0069419

Title: Within-individual estimation of the distributed language network in patients with primary progressive aphasia.

Authors: *A. Y. SHINN[1], J. SALVO[2], N. L. ANDERSON[1], L. SHI[1], A. M. HOLUBECKI[1], J. BEHN[3], S. SIMON[3], J. SRIDHAR[3], E. BARBIERI[3], M.-M. MESULAM[3], R. BRAGA[2]; [1]Neurol., Feinberg Sch. of Med., Northwestern Univ., Chicago, IL; [2]Neurol., Northwestern Univ., Chicago, IL; [3]Mesulam Ctr. for Cognitive Neurol. and Alzheimer's Dis., Northwestern Univ., Chicago, IL

Abstract: Primary progressive aphasia (PPA) is a neurodegenerative syndrome characterized by brain atrophy alongside progressive cognitive impairment that is initially restricted to language function (Mesulam et al. 2014). Although atrophy patterns can inform the likely pathology and symptom progression, patients with atrophy in the same anatomical region (e.g., the temporopolar region) can exhibit different symptoms (e.g., anomia vs. agnosia). This may be because different functional networks are impacted in different patients, however, establishing this requires mapping of networks within individuals, respecting variability in the topography of functional regions.
Here, we conducted an individual-level investigation of how the language network is affected by atrophy in PPA. We collected magnetic resonance imaging (MRI) data from patients with a diagnosis of PPA who were assessed for language ability using a battery of standardized assessments (e.g., Kaplan, Goodglass, & Weintraub, 1983; Weintraub et al. 2009; Thompson et al. 2012; Cho-Reyes & Thompson 2012; Kertesz 2007; Kay, Lesser & Coltheart 1996). Anatomical T1 images allowed estimation of atrophy using voxel-based morphometry (Ashburner & Friston 2000; Jenkinson et al. 2012). Repeated runs of a functional MRI task were used for mapping the distributed language network. Patients listened to excerpts of speech and unintelligible (filtered) speech (Scott et al. 2016), and pressed a button after each trial following a cue tone. Participants (n = 16) provided 18 to 42 mins of functional MRI (fMRI) data. Data passing quality control (n = 10, 18 - 42 mins) were analyzed in two ways: (1) a task contrast map was calculated comparing unfiltered and filtered speech conditions, and (2) vertex-wise product-moment correlations were computed for functional connectivity (FC)-based estimation of the

language network (Braga et al. 2020) using the task data. This combined approach allowed for mapping of the language network in patients with language difficulties. Maps from each approach were similar in all patients. Data were projected and analyzed in each individual's native cortical surface (FreeSurfer; Fischl 2012) to account for differences in brain morphology due to atrophy. Preliminary analyses suggest that the language network can be defined using task- and FC-based approaches, in some cases even in areas that show significant atrophy. Ongoing analyses are exploring the boundary conditions under which atrophy impacts functional organization.

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Poster

PSTR062: Non-AD Dementias

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR062.17/C15

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH Grant R00 HD096117
NIH Grant 5K12GM093857

Title: 1-deoxysphingolipids implicated as mediators of neurotoxicity in niemann-pick type c disease

Authors: *E. MALAUGH, I. KLIMEK, M. MACZIS, J. NEWTON;
Virginia Commonwealth Univ., Richmond, VA

Abstract: Niemann-Pick Type C disease (NPC) is a lysosomal storage disorder caused by a mutation in *NPC1* or *NPC2* genes encoding lysosomal cholesterol transport proteins. Symptoms include ataxia, psychological disorders, and progressive neurodegeneration associated with increased cholesterol and other lipid types, including sphingolipids. Sphingolipids are fatty acyl amino alcohols essential in membrane structure and signaling. They can be derived from the diet or synthesized *de novo* by serine palmitoyl transferase (SPT), which catalyzes palmitoyl CoA's and serine's condensation at the ER. While others have studied accumulation of diet-derived sphingolipids in NPC, this research investigates whether *de novo* sphingolipid biosynthesis contributes to NPC pathology. We performed lipidomics on the brain and cerebellum from male and female $NPC^{(I1061T)}$ mutant mice at p105 (end-stage disease). We found significantly increased sphinganine (SA), an indicator of *de novo* synthesis, in $NPC^{(I1061T)}$ mice. These results suggest increased *de novo* sphingolipid biosynthesis. We then questioned whether increased *de novo* sphingolipid biosynthesis would also increase 1-deoxysphingolipids (doxSL), atypical neurotoxic metabolites formed via the *de novo* pathway when alanine is used as an SPT substrate rather than serine. Elevated doxSL have been identified in multiple neurodegenerative diseases,

including Type 2 diabetes, aging, Parkinson's, and now NPC. Though the neurotoxicity of doxSL is well demonstrated, the mechanisms driving doxSL-induced neurotoxicity remain unknown. Others have shown that doxSL accumulates in mitochondria and causes mitochondrial dysfunction. Our analyses found significantly increased doxSL, specifically deoxysphinganine and deoxyceramides, a sphingolipid sub-class, in $NPC^{(I1061T)}$ brain and cerebellum. We further investigated ceramide and deoxyceramide at the species level and found significant differences in deoxyceramide but not canonical ceramide species in $NPC^{(I1061T)}$. These data suggest a role for specific deoxyceramide species in NPC pathology.

Disclosures: E. Malaugh: None. **I. Klimek:** None. **M. Maczis:** None. **J. Newton:** None.

Poster

PSTR062: Non-AD Dementias

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR062.18/C16

Topic: C.02. Alzheimer's Disease and Other Dementias

Title: Decreased brain pH correlated with progression of Alzheimer’s disease neuropathology: a systematic review and meta-analyses of postmortem studies

Authors: *H. HAGIHARA, T. MIYAKAWA;
Ctr. for Med. Sci., Fujita Hlth. Univ., Toyoake/Aichi, Japan

Abstract: Background: Altered brain energy metabolism is implicated in Alzheimer’s disease (AD). Limited and conflicting studies on brain pH changes, indicative of metabolic alterations associated with neural activity, warrant a comprehensive investigation into their relevance in this neurodegenerative condition. Furthermore, the relationship between these pH changes and established AD neuropathological evaluations, such as Braak staging, remains unexplored. Methods: We conducted quantitative meta-analyses on postmortem brain and cerebrospinal fluid pH in patients with AD and non-AD controls, using publicly available demographic data. We collected raw pH data from studies in the NCBI GEO, PubMed, and Google Scholar databases. Results: Our analysis of 17 datasets (457 patients and 315 controls) using a random-effects model showed a significant decrease in brain and cerebrospinal fluid pH in patients compared to controls (Hedges’ g = -0.54, $p < 0.0001$). This decrease remained significant after considering postmortem interval, age at death, and sex. Notably, pH levels were negatively correlated with Braak stage, indicated by the random-effects model of correlation coefficients from 15 datasets (292 patients and 159 controls) (adjusted r = -0.26, $p < 0.0001$). Furthermore, brain pH enhanced the discriminative power of the *APOE*ε4 allele, the most prevalent risk gene for AD, in distinguishing patients from controls in a meta-analysis of four combined datasets (95 patients and 87 controls). Conclusions: The significant decrease in brain pH in AD underlines its potential role in disease progression and diagnosis. This decrease, potentially reflecting neural hyperexcitation, could enhance our understanding of neurodegenerative pathology and aid in developing diagnostic strategies.

Disclosures: H. Hagihara: None. **T. Miyakawa:** None.

Poster

PSTR062: Non-AD Dementias

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR062.19/C17

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: 001546 - CONACYT

Title: Cognitive impairment in the type 2 diabetes model (DM2)

Authors: *M. BECERRIL CAVAZOS[1], F. PEREZ[2], A. SANCHEZ-MENDOZA[3], L. CERVANTES-PEREZ[3], E. GONZALEZ-GUEVARA[2];
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Abstract: Diabetes is a chronic disease of glucose metabolism with a high mortality rate. It has been described that patient with type 2 diabetes mellitus (DM2) presents progressive cognitive deterioration for which the mechanisms involved are unknown. In diabetes condition, the increased insulin can modify the expression levels of the NMDA type glutamatergic receptor which participate in physiological process involved in the memory and the neuronal communication. The aim of this protocol is to determinate the mechanisms by which changes in memory can occur in DM2 rats. To perform the objective Male neonates (postnatal 2 days) were grouped into: Group 1 Control rats (0.1M citrate buffer, pH 4.5 i.p. vehicle). Group 2: Diabetic rats (single dose of STZ 70 mg/kg i.p.). Rats were grooming and feed by their moms until 21 days. The evaluation of cognitive damage was performed with the novel object test also the evaluation of oxidant damage with lipid peroxidation and reactive oxidative species (LP and ROS) were done. After 8 weeks of the STZ administration, the determination of glucose tolerance levels was done, when glucose levels where above 150 mg/dL after 30 min and maintained until 60-, 90- or 120-min rats were considered diabetics. After verifying the diabetic groups, the evaluation of short- and long-term memory was carried out in the two different groups at the ages of 8, 14 and 20 weeks with the novel object test. Significant differences were found in short- and long-term memory of diabetic rats compared to control rats at the different ages (n=8 in each group). The evaluation of the oxidative damage shows a significant increase of ROS in the hippocampus and motor cortex in rats with DM2. Rats with DM2 present the increment on oxidative damage can modify the functionality of NMDA receptor then the short- and long-term memory, however, this possibility will be evaluated by expression of the NR1A and NR2B subunits of NMDA receptor to determinate in diabetic rats the NMDA participation in memory impairment of diabetic rats.

Disclosures: M. Becerril Cavazos: None. **F. Perez:** None. **A. Sanchez-Mendoza:** None. **L. Cervantes-Perez:** None. **E. Gonzalez-Guevara:** None.

Poster

PSTR062: Non-AD Dementias

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR062.20/C18

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: Iowa Neuroscience Institute

Title: Evaluating sleep, mood and arousal in mild- to late-stage dementia patients using a novel timing task in conjunction with at-home activity tracking

Authors: A. BERTOLLI, C. HARRINGTON, K. DENIZ, J. SIMMERING, M. M. HEFTI, *G. M. ALDRIDGE;
Univ. of Iowa, Iowa City, IA

Abstract: Dementia with Lewy Body (DLB) and Parkinson's disease dementia (PDD) are common forms of dementia and often overlap with Alzheimer's disease and other dementias. DLB is diagnosed by the presence of four core symptoms. One of these symptoms, cognitive fluctuations, is difficult to quantify and diagnose. During fluctuations, cognition and alertness fluctuate from baseline levels to mild or profound difficulty when performing daily tasks. Spontaneous fluctuations can happen at any point during the day and can last minutes, hours, or even days. In order to better understand these fluctuations and what may trigger them, we designed a pilot study within our registry: Sleep, Mood, and Arousal brain-Stem Hypothesis (SMASH) Dementia: Healthy Aging and Disease Registry (SMASH Dementia!). The goal is to determine how changes in sleep, mood, and arousal correlate with cognition and alertness using objective measures. Patients with mixed dementias are often excluded from research, hindering our ability to understand the experience of a typical patient. Thus, a major goal of the pilot study is to define what at-home research tasks patients with dementias across the spectrum can tolerate. To accomplish these goals, we designed several tasks that can be completed daily: 1) a novel interval timing task they do daily, 2) a simplified mood rating scale and 3) speech tasks. Method: The timing task is an app-based game where participants fill a cup with water to a specific height and toast a piece of bread to a specific color (with a short and long time interval, 16 trials total). This allows calculation of a participants' coefficient of variation (CV) which can be correlated with measures of mood and sleep. Outcomes: As an initial validation, we found that the CV between patients correlated with scores on the Montreal Cognitive Assessment (MOCA). Secondly, the majority of participants were able to answer mood questions and tolerate wearing two different commercial actigraphy devices. Those that dropped out reported feeling overwhelmed and further adjustments were made based on feedback. Participants across the spectrum of disease were able to interact with the timing task, though some with severe dementia could interact with the screen but not the game. Six participants repeated the timing task multiple

times, demonstrating feasibility. Importantly, individual session CV between the two tasks was correlated within-patients, providing evidence that the task quantifies variability between sessions, a potential novel method to quantify cognitive fluctuations.

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Poster

PSTR062: Non-AD Dementias

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Program #/Poster #: PSTR062.21/C19

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: SMASH Dementia! Program of Excellence: Iowa Neuroscience Institute/Roy J. Carver Charitable Trust

Title: Exploring the synaptic burden of co-pathological proteins in neurodegenerative disease

Authors: *Y. LIU[1], P. ALDER[1], R. THANGAVEL[1], K. DENIZ[1], K. FIOCK[2], M. HUNTER[2], M. M. HEFTI[2], G. M. ALDRIDGE[1];
[1]Neurol., Univ. of Iowa, Iowa City, IA; [2]Pathology, Univ. of Iowa, Iowa City, IA

Abstract: Neurodegenerative disorders, including Alzheimer’s disease, Lewy body dementia, and Frontotemporal dementia, are characterized by cognitive decline and the loss of neurons, neuron structure and neuronal function. Several brain pathological markers are used to diagnose these diseases, including the presence of misfolded protein aggregates containing amyloid, tau, alpha-synuclein and TDP-43. Studies have shown that these proteins often co-occur in the same patients, with combinations of protein pathologies being the norm rather than exception. Although protein aggregates and cell loss are used for clinical staging and pathological diagnosis, evidence suggests cognitive decline is more strongly associated with synapse loss. However, the relative influence of individual protein pathologies on synaptic loss is unknown and previous studies have often not accounted for potential co-morbid protein pathology. We hypothesized that the regional burden of phosphorylated-tau would correlate inversely with the density of dendritic spines, small protrusions that represent the major site of excitatory post-synaptic contact. To test this hypothesis, we collected fresh tissue from the anterior cingulate during brain autopsy of consecutive neurodegenerative disease donors and control autopsies. Tissue was stained using the Golgi method to visualize dendritic spine morphology and changes in dendritic complexity. In this pilot study, we demonstrate feasibility in identifying a consistent population of layer II/III and layer V neurons in the cingulate cortex. We performed immunofluorescence on adjacent sections using strategic dual-immunostaining, showing significant evidence of co-pathologies in this region. Finally, we evaluate the relationship between spine density, morphology and dendritic complexity to better understand potential consequences of localized and remote protein aggregation.

Disclosures: Y. Liu: None. **P. Alder:** None. **R. Thangavel:** None. **K. Deniz:** None. **K. Fiock:** None. **M. Hunter:** None. **M.M. Hefti:** None. **G.M. Aldridge:** None.

Poster

PSTR062: Non-AD Dementias

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR062.22/C20

Topic: C.02. Alzheimer"s Disease and Other Dementias

Support: SMASH Dementia! Program of Excellence: Iowa Neuroscience Institute/Roy J. Carver Charitable Trust

Title: Neuropsychiatric Profile of Neurodegenerative Dementias: Potential Role of Noradrenergic Dysfunction

Authors: *K. DENIZ, R. THANGAVEL, Y. LIU, K. FIOCK, M. HUNTER, G. SCHOENING, M. M. HEFTI, G. M. ALDRIDGE;
Univ. of Iowa, Iowa City, IA

Abstract: Diagnosis of dementia brings a significant burden on the healthcare system with the aging population. Neuropsychiatric symptoms (NPS) constitute a significant portion of this stress on the caregiver, patient and society. Even though NPS are recognized as early indicators of potential neurodegeneration and a risk factor for dementia progression, the correlation between symptom and specific pathology remains unclear. Alzheimer’s Disease neuropathological change (ADNC) is a prevalent post-mortem finding in dementia autopsy registries. It is not yet clear if risk for NPS is modified by presence of individual co-pathologies or multiple-pathologies. In this autopsy case series, we attempted to bridge this gap through detailed neuropathological assessment of pathological aggregates (beta-amyloid, tau, alpha-synuclein and TDP-43 immunohistochemistry) of well characterized tertiary care center dementia clinic patients. We first hypothesized that the presence of any secondary co-pathology would be associated with increased risk of NPS. Contrary to our hypothesis, we found no clear association between overall co-pathology presence and NPS. Next, we evaluated an individual brain region, the locus coeruleus (LC) in a subset of autopsy subjects, with the premise that LC is one of the earliest structures involved in neurodegenerative proteinopathies and thus potentially associated with early psychiatric features. We hypothesized that evidence of alpha-synuclein co-pathology in Locus Coeruleus (LC) would result in more NPS as clinical studies have indicated more prevalent NPS in Lewy body dementia and Parkinson’s disease dementia. Interestingly, our initial analysis instead suggests a potential association between markers of anxiety and the presence of tau in the soma of tyrosine hydroxylase positive cells in LC. By contrast, the presence of alpha-synuclein in neurites within LC was associated with hallucinations. To assess association of individual neuropathology burden and neurodegeneration of cell populations relevant to NPS, we are quantifying cell number and cell morphology in LC using unbiased stereology methods. We find striking examples of co-pathology both in neighboring cells as well

co-existing within individual neurons in the LC. Our findings emphasize the potential importance of brainstem localization of NPS in dementias and the need to explore potential impacts of diverse and overlapping neurodegenerative proteinopathies.

Disclosures: K. Deniz: None. **R. Thangavel:** None. **Y. Liu:** None. **K. Fiock:** None. **M. Hunter:** None. **G. Schoening:** None. **M.M. Hefti:** None. **G.M. Aldridge:** None.

Poster

PSTR062: Non-AD Dementias

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR062.23/C21

Topic: C.01. Brain Wellness and Aging

Support: UK Med Research MR/X021149/1
NIA R01AG032282

Title: Early-life and adult neighborhood deprivation: Association with midlife markers of dementia risk and antecedents

Authors: *D. S. SHAH;
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Abstract: Neighborhoods are the primary context in which people live, work, and socialize and are key arenas for the social determinants of health. Residents of socioeconomically disadvantaged neighborhoods appear to face heightened risks for age-related brain diseases like dementia. The causal timing of risk associations remains unclear. Our investigation, utilizing the Dunedin Longitudinal Cohort Study—a population representative birth cohort of 1,037 individuals born in New Zealand in 1972 and followed to midlife—combined lifespan area measures of socioeconomic disadvantage with midlife indexes of dementia risk. Our measure of dementia risk included the CAIDE, LIBRA, ANU-ADRI, and the comprehensive Dunedin Alzheimer's Disease and Related Dementias Risk Benchmark, which is comprised of 48 risk indicators grouped into 10 conceptually distinct domains (e.g., cardio-metabolic risk, inflammatory risk, and lifestyle risk). We observed midlife clustering of dementia risk factors among individuals living in disadvantaged neighborhoods during childhood, adulthood, and both when considered together. Neighborhood deprivation in adulthood ($\beta = 0.36$, $p < .001$) was a stronger predictor of midlife dementia risk than neighborhood deprivation in childhood ($\beta = 0.10$, $p < .001$). When both childhood and adult neighborhood deprivation are tested simultaneously, each remains unique predictors of midlife dementia risk. Individuals living in disadvantaged neighborhoods across the lifespan demonstrated increased dementia risk by midlife, but adult exposures are a more robust predictor. Neighborhood assessment could contribute to better identification of individuals at risk for dementia, for primary and secondary prevention.

Disclosures: D.S. Shah: None.

Poster

PSTR063: Parkinson's Disease: Neuroprotective Mechanisms

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR063.01/C22

Topic: C.03. Parkinson's Disease

Support: DST-PURSE Project (SR/Purse/2021/77)

Title: Tyrosine, Tryptophan and dopamine synthesized gold nanozymes for potential treatment of neurological disorders.

Authors: *A. SHARMA[1], H. K. DAIMA[2], D. NATHURAM[3], S. KOTHARI[1], S. SRINIVAS[4]; [1]Amity Inst. of Biotech., Amity Univ. Rajasthan, JAIPUR, India; [2]Biochem., Central Univ. of Rajasthan, Ajmer, INDIA, Kishangarh, Ajmer, India; [3]Dept. of Biotech., JECRC Universit, Jaipur, Jaipur, India; [4]Sch. of Optometry, Indiana Univ., Bloomington, Bloomington, IN

Abstract: Abstract: The appropriate treatment of neurological disorders possesses several challenges, owing to the intricate anatomy of neuronal circuits and presence of blood brain barrier (BBB), blood-cerebrospinal fluid (CSF) barrier. Nevertheless, peroxidase and glutathione peroxidase enzymes, play pivotal roles in neuro-regeneration and neuroprotection. Therefore, these enzymes are gaining significance attention to meet neurodegenerative disorder challenges.[1] In the present study, the smart design of gold (Au) nanozymes using tyrosine (Tyr, amino acid), tryptophan (Trp, amino acid) and dopamine (Dop, neurotransmitter) is achieved, wherein Tyr,Trp and Dop acts as reducing and capping agent. After thorough physicochemical characterization, the Au^{Tyr} Au^{Trp} and Au^{Dop} nanozymes are assessed for their inherent peroxidase enzyme-mimicking properties. The minute size, of Au nanozymes demonstrate the ability to efficiently traverse the BBB, thus facilitating the delivery of therapeutic agents.[2] Reportedly the reduction in peroxidase activity in Parkinson's disease-affect brains, thus the prepared Au nanozymes with essential biomolecules (dopamine, tryptophan and tyrosine) with peroxidase-mimicking activity may play an important role in the treatment of neurological disorders like Parkinson's.[3] Moreover, the advanced research findings can provide a potential breakthrough in the development of targeted therapies for neurological disorders.
References: 1.Feng, W., et al., *2D vanadium carbide MXenzyme to alleviate ROS-mediated inflammatory and neurodegenerative diseases.* Nature communications, 2021. **12**(1): p. 2203.2.Teleanu, D.M., et al., *Blood-brain delivery methods using nanotechnology.* Pharmaceutics, 2018. **10**(4): p. 269.3.Zhou, Z.D., et al., *The role of tyrosine hydroxylase-dopamine pathway in Parkinson's disease pathogenesis.* Cellular and Molecular Life Sciences, 2022. **79**(12): p. 599.

Disclosures: A. Sharma: None. **H.K. Daima:** None. **D. Nathuram:** None. **S. Kothari:** None. **S. Srinivas:** None.

Poster

PSTR063: Parkinson’s Disease: Neuroprotective Mechanisms

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR063.02/C23

Topic: C.03. Parkinson’s Disease

Support: FAPESP Grant 2020/09015-4
CNPq Grant 408377/2021-6

Title: Eugenia uniflora: A Potential Neuroprotective Agent in Parkinson's Disease Models

Authors: *P. S. C. LOPES[1], G. AZEVEDO[1], B. SILVA[1], G. PEREIRA[1], M. VIDAL GUTIERREZ[3], G. PEREIRA[2], W. VILEGAS[3], R. SILVA[2], J. R. SANTOS[4], A. RIBEIRO[1]; [1]Biosci., Federal Univ. of São Paulo, Santos, Brazil; [2]Pharmacol., Federal Univ. of São Paulo, São Paulo, Brazil; [3]Biosci., São Paulo State Univ., São Vicente, Brazil; [4]Biosci., Federal Univ. of Sergipe, Itabaiana, Brazil

Abstract: Parkinson's disease (PD) is a progressive and neurodegenerative pathology characterized by the death of dopaminergic neurons. Natural products offer promising sources of novel therapeutic substances. *Eugenia uniflora* L. commonly known as Pitangueira is a Brazilian native tree, belonging to the Myrtaceae family. According to popular medicine, this species exhibits various therapeutic activities such as antimicrobial, antidiarrheal, diuretic, antirheumatic, and anti-inflammatory properties. This study aimed to conduct a phytochemical and analytical investigation of the ethanolic extract of *Eugenia uniflora* L. EEu on reserpine (RES)-induced parkinsonism in mice. The phytochemical screening EEu of dry leaves was conducted according to British and Brazilian Pharmacopeia, while antioxidant properties were assessed using the DDPH and ABTS assay. In the *in vivo* experiment, male mice (6-7 months) were treated with a low dose of RES (0.1 mg/kg, s.c.) every other day for 28 days, with or without daily treatment of EEu (3 mg/kg, o.r.). Immunochemistry for tyrosine hydroxylase (TH) was performed. Phytochemical screening indicated the presence of saponins, anthraquinones, hydrolyzable tannins, and flavonoids. EEu exhibited antioxidant activity, with DDPH and ABTS radical scavenging of 12,86% and 38,13%, respectively, relative to trolox. The analysis of immunoreactivity for TH demonstrated effects on the dorsal striatum, the CTR-EEu and RES-EEu groups showed greater TH+ fiber density compared to the CTR-CTR and CTR-RES groups ($p < 0.05$). These data allow us to confirm that *Eugenia uniflora* L. has a therapeutic potential for the treatment of PD.

Disclosures: P.S.C. Lopes: None. **G. Azevedo:** None. **B. Silva:** None. **G. Pereira:** None. **M. Vidal Gutierrez:** None. **G. Pereira:** None. **W. Vilegas:** None. **R. Silva:** None. **J.R. Santos:** None. **A. Ribeiro:** None.

Poster

PSTR063: Parkinson’s Disease: Neuroprotective Mechanisms

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR063.03/C25

Topic: C.03. Parkinson's Disease

Support: NIH Grant NS123405

Title: DJ-1 chaperone function delivers ATP synthase β subunit to the distal neurites to regulate local protein synthesis

Authors: *R. CHEN[1], P. LICZNERSKI[2], J. CHEN[3], W. J. MANDEMAKERS[4], E. A. JONAS[5]; [2]Intrnl. Medicine/Section Endocrinol., [1]Yale Univ., New Haven, CT; [3]yale school of medicine, New Haven, CT; [4]Erasmus MC, Rotterdam, Netherlands; [5]Yale Univ. Sch. Med., Hamden, CT

Abstract: Parkinson's disease (PD) is characterized by the loss of dopaminergic neurons in the midbrain. Dopaminergic neurons releasing dopamine in the striatum are thought to require mitochondria and mitochondrial energy production, but not a lot is known about the function of mitochondria in this specialized cell. DJ-1 protein is encoded by PD gene PARK-7. DJ-1-/- mouse mesencephalic dopaminergic neuron culture (mesDA) provides a model of early pathological changes in PD patients' brains. We have shown previously that the number of dendrites initiated directly from DJ-1-/- tyrosine hydroxylase + (TH+) neuronal somata, overall neurite length and number of branch points are all reduced compared to those of the WT TH+ neurons. We previously also reported binding and functional interaction between DJ-1 and ATP synthase (F1) β subunit (ATP-β) protein, and we reported that, in the absence of DJ-1, ATP synthase is partially disassembled to favor free (FO) c-subunit leak channel (ACLC) activity and inefficient ATP production. We now find DJ-1 serves as a chaperone for ATP-β mRNA as well as for ATP-β protein. ATP-β is the key component of the enzymatic soluble portion of the ATP synthase, and its synthesis is correlated with ATP synthase assembly, so we set out to determine if ATP-β mRNA was locally synthesized in the distal dendritic tree, whether this was affected by DJ-1 loss or mutation, and to determine if we could effect a rescue with overexpression (OE) of ATP- β. First, we tested the effects of specific inhibition of mitochondrial ATP synthesis with oligomycin in WT. These experiments demonstrated almost complete absence of protein synthesis in the neuronal processes, confirming the requirement for mitochondrial ATP production. We found that DJ-1-/- cells have less ATP- β mRNA in the neurites compared to that in the soma or compared to WT neurites, suggesting a difficulty in ATP-β mRNA localization related to DJ-1 loss. Nevertheless, we showed that over-expression of ATP-β improves the overall protein synthesis rate in DJ-1-/- neuronal culture and the neurite length in DJ-1-/- mesDA neurons. However, over-expression (OE) of ATP- β fails to restore the number of neurites or neurite branches, raising the possibility that ATP- β cannot rescue fully without DJ-1 as its key chaperone. Our findings uncover novel molecular mechanisms for the ATP- β and the stoichiometry of F1 to FO and demonstrate a crucial role for DJ-1 chaperone function in optimizing the stoichiometric structure of the ATP synthase.

Disclosures: R. Chen: None. **P. Licznerski:** None. **J. Chen:** None. **W.J. Mandemakers:** None. **E.A. Jonas:** None.

Poster

PSTR063: Parkinson's Disease: Neuroprotective Mechanisms

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR063.04/C26

Topic: C.03. Parkinson's Disease

Support: CAPES - 88887.684788/2022-00
FAPESP - 2021/08562-4
CEUA - 1342290421

Title: Physical Exercise Prevents Neurodegeneration In Cardiorespiratory Nuclei And Breathing Deficits In The 6-OHDA Model Of Parkinson's Disease

Authors: *P. O. S. MEDEIROS[1], L. F. A. T. PEDRAO[2], B. FALQUETTO[2];
[1]Dept. of Pharmacol., Univ. de Sao Paulo, São Paulo, Brazil; [2]Dept. of Pharmacol., Univ. of Sao Paulo, Sao Paulo, Brazil

Abstract: Introduction: Parkinson's disease (PD) is a neurodegenerative disease with death of dopaminergic neurons in the Substantia Nigra (SN). It presents classic symptoms, and respiratory problems. There is neurodegeneration in cardiorespiratory regions such as nucleus of solitary tract (NTS), retrotrapezoid nucleus (RTN), preBötzinger complex (preBötC), rostral ventral respiratory group (rVRG) and nucleus ambiguus (NA), noted in 6-hydroxydopamine (6-OHDA) PD animal model, causing a high loss in cardiorespiratory function. **Aim:** Evaluate the effects of the physical exercise (EX) preventing the neurodegeneration of cardiorespiratory nuclei and the cardiorespiratory deficits in 6-OHDA animals. **Methods:** 6-OHDA (24µg/µl) or vehicle was injected into male adult rat's striatum. EX was performed 12 days after PD induction (n=42), for 28 days. On the 40th day, the animals were submitted to whole-body plethysmography, perfusion, and brain dissection to perform immunohistochemistry. All animals were submitted to tyrosine hydroxylase (TH)-immunoreactivity (ir) to evaluate SN to confirm the PD model, and phox2b, NK1R and ChAT-ir to evaluate cardiorespiratory nuclei degeneration. Two-way ANOVA followed by Newman Keuls was applied with $p<0.05$. **Results:** 6-OHDA reduced TH^+ neurons in SN and EX did not reverse it as expected, confirming the PD model (p<0,0001). At normoxia, 6-OHDA animals showed reduced respiratory frequency (f_R), prevented with EX (vehicle: 98,8±5,6; 6-OHDA: 60,9 ± 3,3; vehicle + EX: 87,9±12,5; 6-OHDA + EX: 85,9±9,3 bpm; p<0,0001); as well during hypercapnia (f_R: vehicle: 150,1±17,9; 6-OHDA: 125,3±4,0; vehicle + EX: 159,1±13,3; 6-OHDA + EX: 154,7±14,3 bpm; p=0,0062). We observed a reduction in phox2b neurons in cNTS (vehicle: 135±20; 6-OHDA: 52±7; vehicle + EX: 124±23; 6-OHDA + EX: 87±13 neurons, p<0,0001), iNTS (vehicle: 917±128; 6-OHDA: 548±64; vehicle + EX: 1009±229; 6-OHDA + EX: 744±42 neurons, p<0,0001) and RTN (vehicle: 52±7; 6-OHDA: 21±12; vehicle + EX: 57±16; 6-OHDA + EX: 44±4 neurons; p=0,0003) in sedentary groups and this was prevented with EX. The same was observed in NK1R-expressing neurons in rVRG (vehicle: 104,7± 19,9; 6-OHDA: 68,1± 7,3; vehicle + EX: 104± 22,8; 6-OHDA + EX: 97,5± 7,1) and preBötC (vehicle: 108± 31,1; 6-OHDA: 64,8± 3,9; vehicle + EX: 103,9± 24,6; 6-OHDA + EX: 101,2± 4,5). Neurodegeneration was also seen in ChAT neurons in NA, prevented with EX (vehicle: 61± 10; 6-OHDA: 34± 7; vehicle + EX: 74± 14; 6-OHDA + EX: 48± 13 neurons;

p<0,0001). **Conclusion:** All the respiratory impairments and neurodegeneration were prevented after EX in the 6-OHDA PD model.

Disclosures: P.O.S. Medeiros: None. **L.F.A.T. Pedrao:** None. **B. Falquetto:** None.

Poster

PSTR063: Parkinson's Disease: Neuroprotective Mechanisms

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR063.05/Web Only

Topic: C.03. Parkinson's Disease

Support: Augusta University Startup

Title: Investigating Opposing Effects of Gut Microbiome Species Levilactobacillus brevis on Motor Function and Behavior in Aging and Parkinson's Disease

Authors: *N. J. JOHNSON[1], D. E. MOR[2];
[1]Neurosci. and Regenerative Med., Augusta Univ., Augusta, GA; [2]Dept. of Neurosci. & Regenerative Med., Augusta Univ., Augusta, GA

Abstract: The gut microbiome is a growing field of interest in both aging and age-related neurodegenerative diseases, including Parkinson's disease (PD), yet the role of host-microbiota interactions remains poorly understood. Lactic acid bacteria (L.A.B) are known constituents of the human gut microbiome and are generally thought to be uniformly beneficial leading to their widespread use in fermented foods and consumable probiotics. However, the complexity of the mammalian gut microbiome in conjunction with slow aging and low tractability of rodent models has led to an oversimplification of how L.A.B. influence host physiology. While L.A.B. are among the bacterial species altered in PD and normal aging, further research is necessary at the singular species level to elucidate mechanisms linking gut microbiota to aging and age-related disease. In PD, L.A.B. species including *Levilactobacillus brevis* (*L. brevis*), are increased in the gut microbiome, yet the relationship between *L. brevis* and the PD hallmarks of α-synuclein (α-syn) pathology, dopamine neuron degeneration, and motor dysfunction remains unknown. Similarly, effects of *L. brevis* on motor decline during aging are not known. *C. elegans* is a well-established aging model system in which to answer these questions, given they feed on singular bacterial species, have a rapid lifespan of 2-4 weeks, share orthologs for 60-80% of human genes, and are highly genetically tractable. Using established behavioral assays, data from healthy non-transgenic worms fed *L. brevis* show an age-dependent decline in motor function along with a decrease in synaptic transmission of acetylcholine - prompting further investigation of the cholinergic motor neurons and muscle cell structure with age through fluorescence microscopy. Paradoxically, preliminary data with *L. brevis*-fed PD models expressing human α-syn showed a potential protective effect against dopaminergic neurodegeneration suggesting dopamine-dependent behaviors might also be improved. A decrease in large α-syn aggregates in muscle accompanied by an increase in soluble α-syn also

suggests a protective effect of *L. brevis* against PD pathology. Intriguingly, results reveal that *L. brevis* appears to mediate opposing effects in normal aging and PD, signifying the need for further understanding its context-dependent mechanisms.

Disclosures: N.J. Johnson: None. **D.E. Mor:** None.

Poster

PSTR063: Parkinson's Disease: Neuroprotective Mechanisms

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR063.06/C27

Topic: C.03. Parkinson's Disease

Support: UAEU research grant (UPAR, Grant code: 12M104)
Zayed Center for Health Sciences Research grant (Grant code: 31R234)

Title: Ellagic Acid Promotes the Autophagic Fluxand Alleviates Alpha synuclein Propagation and Toxicityin an Animal Model of Parkinson's Disease

Authors: *M. HAQUE;
UAE Univ., Al Ain, United Arab Emirates

Abstract: Parkinson's Disease (PD) ranks as the second most prevalent neurological disorder, characterized by a deficiency of dopamine in the nigrostriatal pathway due to the loss of dopaminergic neurons in the Substantia Nigra pars compacta (SNc). Abnormal aggregation of α-synuclein (α-syn) has been identified as a primary contributor to PD, leading to the formation of Lewy bodies, a hallmark of the disease. Ellagic Acid (EA), a well-known dietary supplement found in pomegranates, berries, and nuts, has demonstrated efficacy in preventing the toxicity of α-syn aggregates in cellular PD models. This study aims to investigate whether EA can impede the spreading of α-syn and its associated toxicity in an animal model of PD. Male C57BL/6 mice underwent intrastriatal injections of α-syn Preformed Fibrils (PFF), followed by intraperitoneal administration of 1-Methyl-4-Phenyl-1,2,3,6-Tetrahydropyridine (MPTP) on the sixth week post-surgery for five consecutive days. EA-treated animals received intraperitoneal injections of EA for twelve consecutive days starting from the day after surgery, with adjunct administration of EA alongside MPTP (one hour prior to MPTP) continuing through the sixth week. At the end of the eighth week, animals were sacrificed, and brain samples were subjected to immunohistochemical and western blot analysis. The study revealed that intraperitoneal administration of EA significantly reduced the spread of endogenous α-syn from the injection site (striatum) to the SNc area compared to the PFF + MPTP group. Additionally, EA treatment prevented the loss of dopaminergic neurons in the SNc area and preserved nerve terminal density in the striatum. TUNEL assay results indicated a significant decrease in apoptotic neurons in the SNc of the EA-treated group, consistent with reduced α-syn spreading and toxicity. Furthermore, the assessment of autophagy markers in TH-expressing cells in the SNc suggested that EA enhanced autophagic flux in the PD animal model. These findings suggest that EA treatment

facilitates a restorative mechanism of autophagic flux, thereby inhibiting toxic α-syn spreading and preserving dopaminergic neurons in a male mouse model of PD.

Disclosures: M. Haque: None.

Poster

PSTR063: Parkinson's Disease: Neuroprotective Mechanisms

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR063.07/C28

Topic: C.03. Parkinson's Disease

Title: GT-02287, a clinical stage GCase regulator, improves mitochondrial function and provides a neuroprotective effect in GBA1-Parkinson's disease models

Authors: N. PEREZ[1], B. GUZMAN[2], A. M. GARCIA COLLAZO[1], *J. TAYLOR[3];
[1]Gain Therapeutics, Sucursal en España, Barcelona, Spain; [2]Gain Therapeutics, SA, Lugano, Switzerland; [3]Gain Therapeutics, Inc., Bethesda, MD

Abstract: Heterozygous mutations in the GBA1 gene encoding lysosomal enzyme glucocerebrosidase (GCase) are the major genetic risk factor for the development of Parkinson's disease (PD). In addition to its function in the lysosome, GCase is imported into mitochondria where it promotes the function of mitochondrial complex 1 and GCase mutations that impair its function lead to an increase in mitochondrial oxidative stress. Another pathophysiological process affecting the mitochondria is dysregulation of mitochondrial Rho GTPase 1 (Miro1), an outer mitochondrial membrane protein that mediates mitochondrial axonal transport. Miro1 is removed from depolarized mitochondria, which facilitates removal of damaged mitochondria via mitophagy. PD patient-derived cells are unable to remove Miro1 from depolarised mitochondria. Experimental reduction of Miro1 expression in mitochondria has been shown to rescue the neurodegeneration phenotype in various PD models. Gain Therapeutics applied its proprietary drug discovery platform Magellan™ to the discovery of small-molecule structurally targeted allosteric regulators (STARs) that bind to GCase, stabilize it, and restore its function. One such compound is GT-02287, an orally bioavailable, brain penetrant, clinical candidate currently in a Phase 1 study in healthy volunteers. In cultured rat mesencephalic dopaminergic neurons, conduritol beta epoxide (CBE), an irreversible GCase inhibitor, was used to cause a partial knockdown of GCase activity comparable to that seen in PD patients carrying heterozygous GBA1 mutations. In this model, CBE induced a progressive cytotoxicity associated with increased production of mitochondrial reactive oxygen species (ROS), in addition to causing lysosomal pathology and increasing aggregation of α-synuclein. Treatment with GT-02287 not only ameliorated lysosomal pathology and reduced α-synuclein aggregation, but also reduced the level of mitochondrial ROS, along with improved neurite network and increased neuronal survival. In an *in vivo* study, mice were chronically injured with CBE and subjected to intra-striatal injection of α-synuclein preformed fibrils (PFFs). Delayed administration of GT-02287 reduced the levels of Miro1 in the substantia nigra and plasma levels of emerging

neurodegeneration biomarker neurofilament light chain (NfL) as well as completely restoring motor function to control levels. These data highlight the ability of GT-02287 not only to repair lysosomal dysfunction, but also to alleviate mitochondrial dysfunction which adds to the body of evidence supporting GT-02287 as a potential disease-modifying therapy for Parkinson's disease.

Disclosures: N. Perez: A. Employment/Salary (full or part-time):; Gain Therapeutics. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Gain Therapeutics. **B. Guzman:** A. Employment/Salary (full or part-time):; Gain Therapeutics. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Gain Therapeutics. **A.M. Garcia Collazo:** A. Employment/Salary (full or part-time):; Gain Therapeutics. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Gain Therapeutics. **J. Taylor:** A. Employment/Salary (full or part-time):; Gain Therapeutics. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Gain Therapeutics.

Poster

PSTR063: Parkinson's Disease: Neuroprotective Mechanisms

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR063.08/C29

Topic: C.03. Parkinson's Disease

Support: Parkinson's Foundation Center Grant PF-RC-936279
NIH T32 Training Grant 5T32AG049688-09

Title: Characterization of a novel vulnerable neuron type in Parkinson's disease

Authors: *M. LIANG[1], M. WANG[1], W. WANG[2], I. CHOI[1], K. FARRELL[1], C. DE SANCTIS[1], J. F. CRARY[1], J. W. BLANCHARD[1], N. YANG[1], Z. WU[2], B. ZHANG[1], Z. YUE[1];
[1]Icahn Sch. of Med. At Mount Sinai, New York, NY; [2]Cornell University: Weill Cornell Med. Col., New York, NY

Abstract: Parkinson's disease (PD) is the second leading neurodegenerative disorder characterized by degeneration of neuromelanin-containing dopaminergic (DA) neurons in the substantia nigra (SN). Whether non-DA neurons are vulnerable in PD is poorly understood. We previously generated snRNAseq data from human SN including 9 healthy controls and 23 idiopathic PD. A combination of immunostaining and validation against datasets from independent cohorts resulted in the identification of molecularly distinct subtypes of DA-related neurons, including a RIT2-enriched population in aged human SN. RIT2 variants have previously been linked to PD. Validation in mouse and human SN identifies a RIT2 population that partially overlaps with TH, a marker for DA neurons, and the subpopulation (RIT2+/TH-) was found to be vulnerable in PD. By using a novel Rit2-Cre dependent reporter mouse, we

investigate distinct RIT2 neuronal subpopulations including its distribution, morphology, cell identity by snRNAseq, and vulnerability to α-synuclein. Our analyses suggest that this novel vulnerable population in PD may be interneurons at the SN. Our study highlights the need to study non-DA neurons in PD.

Disclosures: M. Liang: None. **M. Wang:** None. **W. Wang:** None. **I. Choi:** None. **K. Farrell:** None. **C. De Sanctis:** None. **J.F. Crary:** None. **J.W. Blanchard:** None. **N. Yang:** None. **Z. Wu:** None. **B. Zhang:** None. **Z. Yue:** None.

Poster

PSTR063: Parkinson's Disease: Neuroprotective Mechanisms

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR063.09/C30

Topic: C.03. Parkinson's Disease

Title: Translational regulation of the bcl2 survival factor mcl1 in dopamine neurons

Authors: *M. VAN DER VLAG[1], M. SMIDT[2], L. P. VAN DER HEIDE[3];
[1]Swammerdam Inst. for Life Sci., Amsterdam, Netherlands; [2]MNS, Uva, Amsterdam, Netherlands; [3]Swammerdam Inst. for Life Sci., Univ. of Amsterdam, amsterdam, Netherlands

Abstract: Parkinson's disease is characterized by a progressive loss of dopamine neurons in the Substantia Nigra pars compacta. This in turn causes a deficiency in dopamine output to the striatum, underlying the motor symptoms of this disease. Current treatments aim to alleviate these symptoms by restoring dopamine levels, most commonly by supplementing patients with levodopa, the precursor to dopamine. However, there is currently no treatment available that halts the loss of dopamine neurons. Previous work has has shown that the Bcl2 factor Mcl1 is essential for the survival of midbrain dopamine neurons in mice. Thus, boosting Mcl1 could prove an interesting approach to boost resilience of dopamine neurons against cell death-inducing stressors. Using the dopaminergic MN9D cell line as a model we demonstrate that Mcl1 is rapidly induced upon addition of the amino acid L-glutamine. Utilizing cycloheximide to block translation and actinomycin D to inhibit transcription, we show that L-glutamine boosts Mcl1 in a translation-, but not a transcription-dependent manner. Interestingly, L-glutamine treatment in combination with mTORC1 inhibition only revealed a partial effect suggesting that besides mTORC1 other pathways must also contribute. Lastly, while investigating potential interaction effects of L-glutamine and levodopa on Mcl1, we observed none. However, we did notice an effect of levodopa on the phosphorylation state of Creb, an important transcription factor in dopamine neurons. Interestingly, this effect was only observed in the absence of L-glutamine. Through AADC inhibition we show that this effect is dependent on the conversion of levodopa to dopamine. This effect in our model, cannot be attributed to catecholamine receptor signaling and the exact mechanism currently remains a subject of investigation. Taken together, our results show we can use a common amino acid to boost Mcl1 translation. Importantly, this effect persists in co-treatment with levodopa, which is commonly used for symptomatic

treatment in Parkinson's Disease patients. Although, we did observe a differential effect on Creb phosphorylation that requirers further inquiry. Increasing Mcl1 levels in such a manner may provide a novel method for improving the resistance of dopamine neurons to cell death in Parkinson's Disease.

Disclosures: M. van der Vlag: None. **M. Smidt:** None. **L.P. Van Der Heide:** None.

Poster

PSTR063: Parkinson's Disease: Neuroprotective Mechanisms

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR063.10/C31

Topic: C.03. Parkinson's Disease

Title: Ath-1020, a novel small-molecule positive modulator of neurotrophic HGF system, is neuroprotective and improves motor function in preclinical models of Parkinson's disease

Authors: *W. WU[1], S. REDA[2], A.-A. BERTHIAUME[4], S. SETTI[4], J. JOHNSTON[4], R. TAYLOR[3], K. CHURCH[5];
[1]Athira Pharma Inc., Bothell, WA; [3]Discovery Biol., [2]Athira Pharma, Inc., Bothell, WA; [4]In Vivo Pharmacol., [5]Athira Pharma, Bothell, WA

Abstract: The neurotrophic hepatocyte growth factor (HGF) system represents a promising therapeutic target for neurodegenerative diseases including Parkinson's disease (PD) due to its multimodal, neurotrophic, neuroprotective, and anti-inflammatory effects. We have developed a series of small molecule positive modulators of the neurotrophic HGF system to explore the potential of this therapeutic strategy. Here, we assess the effects of ATH-1020 on critical components of PD pathology including neurodegeneration, inflammation, and motor deficits in preclinical models.
To assess the effect of ATH-1020 on HGF-mediated MET receptor activation and downstream signaling, HEK293 cells treated with ATH-1020 were evaluated for MET activation via ELISA, and ERK activation via HTRF. To evaluate neurotrophic effects, neurite length, dendritic branching, and synaptic count were measured in rat primary neurons treated with ATH-1020. The neuroprotective effects of ATH-1020 were assessed by evaluating neuronal survival (via CellTiter-Glo®) in rat primary neurons subjected to neurotoxic insults including 1-methyl-4-phenylpryidinium (MPP+), glutamate, lipopolysaccharide (LPS), or H2O2. Anti-inflammatory effects of ATH-1020 were evaluated by measuring secreted proinflammatory cytokines (IL-1β, IL-6, and TNF-α) in LPS-challenged THP-1 differentiated macrophages. To determine if the effects observed in vitro translated to an in vivo setting, we evaluated the impact of ATH-1020 in a 6-hydroxydopamine (6-OHDA) rat model of PD. ATH-1020 was orally administered daily for 6 weeks, starting 2 weeks after 6-OHDA injection into the striatum. Motor function was assessed using rotarod and grip strength tests.
ATH-1020 enhanced HGF-mediated MET phosphorylation and activated the ERK intracellular signaling cascade, an effect which was abolished by the MET inhibitor capmatinib. Treatment

with ATH-1020 increased neurite outgrowth, dendritic branching, and synaptic count as well as protected against all cytotoxic insults in primary neurons. THP-1 differentiated macrophages treated with ATH-1020 exhibited a reduction in LPS-induced proinflammatory cytokine release. ATH-1020 treatment in the rat 6-OHDA model of PD improved motor function in rotarod and grip strength tests.
Collectively, these results demonstrate that ATH-1020 positively modulates the neurotrophic HGF system thus inducing neurotrophic, neuroprotective, and anti-inflammatory effects. These cellular changes translated into enhanced motor function in a rat model of PD. These findings highlight the potential of ATH-1020 for the treatment of neurodegenerative diseases including PD.

Disclosures: W. Wu: A. Employment/Salary (full or part-time):; Athira Pharma. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Athira Pharma. **S. Reda:** A. Employment/Salary (full or part-time):; Athira Pharma. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Athira Pharma. **A. Berthiaume:** A. Employment/Salary (full or part-time):; Athira Pharma. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Athira Pharma. **S. Setti:** A. Employment/Salary (full or part-time):; Athira Pharma. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Athira Pharma. **J. Johnston:** A. Employment/Salary (full or part-time):; Athira Pharma. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Athira Pharma. **R. Taylor:** A. Employment/Salary (full or part-time):; Athira Pharma. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Athira Pharma. **K. Church:** A. Employment/Salary (full or part-time):; Athira Pharma. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Athira Pharma.

Poster

PSTR063: Parkinson’s Disease: Neuroprotective Mechanisms

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR063.11/C32

Topic: C.03. Parkinson’s Disease

Support: UGC- Grant
IOE-University Of Delhi

Title: Attenuation of Mitochondrial Dysfunction in Astrocytes is mediated through A_{2A}Receptor via regulating the p-38 MAPK pathway in 6-OHDA-induced model of Parkinson's disease (PD)

Authors: *V. WALECHA[1], P. M. LUTHRA[2];
[1]Dr. B.R. Ambedkar Ctr. for Biomed. Research,University of Delhi, faridabad, India; [2]Dr. B.R. Ambedkar Ctr. for Biomed. Research,University of Delhi, Delhi, India

Abstract: Recent studies suggest that astrocytes impact the loss of dopaminergic neurons(DA) and/or circuits in Substantia Nigra (SNr) leading to Parkinson's Disease (PD) through gain of mitochondrial dysfunction, inflammation, and loss of supportive functions where they are known to eradicate the alpha-synuclein via engulfing it.Existing treatment of PD includes dopmainergics such as pramipexole, rotigotine, L-DOPA, etc. which show astrocytic protection by inhibiting the NLRP3 inflammasome, up-regulating metallothionein and causing GSH release to protect the DA neurons respectively. While these medications effectively alleviate symptoms associated with dopamine deficiency, they are also associated with side effects. Consequently, non-dopaminergic therapies are being explored for the treatment of PD which not only improves dopamine-related symptoms, but also addresses inflammation, oxidative stress, and mitochondrial dysfunction resulting from the complex interplay between neurons and glial cells.Therefore, we hypothesize to investigate the restoration of astrocytic mitochondrial dysfunction through non-dopmainergics such as A_{2A} R antagonists (ZM241385 and IDPU) where we aim to enhance the mitophagy in astrocytes regulated via the p-38MAPK -PARKIN pathway so that it can accelerate the removal of damaged mitochondria leading to restoration of mitochondrial potential /ΔΨ(m) thus, serving as a strategy for protection of DA neurons in 6-OHDA induced model of PD.Astrocytes isolated from P0/P1 pups of SD rats , validated using GFAP marker were used for in-vitro studies. 6-OHDA (100µM) induced astrocytes generated high mean fluorescence intensity using H_2DCFDA and Fluoro-4 AM dye thus demonstrating increased ROS and Ca2+ production respectively, however, treatment with A_{2A} R antagonists attenuated the above effects. ΔΨ(m) loss was found to be restored in 6-OHDA (100µM) induced astrocytes when treated with A_{2A} R antagonists as detected using the Rhodamine fluorescence intensity. Protein isolated from both in-vitro and in-vivo samples for Western blot analysis indicated the reduction of p-38 MAPK while increasing DJ-1 (antioxidant) and PARKIN levels in A_{2A} R antagonists treated groups in comparison to 6-OHDA thus, proving to accelerate mitophagy in astrocytes and promoting DA neuronal survival. Our findings provide the first evidence that treatment with A_{2A} R antagonists can maintain Ca2+ homeostasis, restore the ΔΨ(m) , and accelerate the mitophagy pathways regulated via p-38mapk -PARKIN in 6-OHDA induced astrocytes.

Disclosures: V. Walecha: None. **P.M. Luthra:** None.

Poster

PSTR063: Parkinson's Disease: Neuroprotective Mechanisms

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR063.12/C33

Topic: C.03. Parkinson's Disease

Support: NIH/NINDS grant NS121692

Title: Pkd1 interacts with mtor in compensatory signaling pathway during mitochondrial neurotoxic stress in dopaminergic neurons.

Authors: *A. JANG[1], B. N. PALANISAMY[1], M. AY[2], G. ZENITSKY[1], H. JIN[1], V. ANANTHARAM[1], A. KANTHASAMY[1], A. G. KANTHASAMY[1];
[1]Univ. of Georgia, Athens, GA; [2]Univ. of Rochester Med. Ctr., Rochester, NY

Abstract: Exposure to paraquat (PQ) generates reactive oxygen species (ROS), which are implicated in Parkinson's disease (PD). We previously reported that PKD1 is highly expressed in nigral dopamin(DA)ergic neurons and its PKCδ-dependent activation represents an intrinsic compensatory response in counteracting the early-stage oxidative damage in DAergic neurons. Yet, the downstream molecular mechanisms remain enigmatic. Here, we report that a PKD1-dependent early activation of the mammalian target of rapamycin (mTOR) and the DRP1 pathway may play a critical role in the mitochondria of DAergic system. The mTOR protein regulates cell growth, survival, protein synthesis, and autophagy, and its levels vary in PD. DRP1 regulates mitochondrial fission and its dysregulation impacts PD pathogenesis. First, we found that PQ exposure time-dependently increased oxidative stress, mitochondrial dysfunction, and neurotoxicity in N27 DAergic neuronal cells, as determined by increased ROS, decreased cell viability, and increased mitochondrial fragmentation. We also found that this mitochondrial fragmentation began early during PQ treatment, suggesting the involvement of early mitochondrial dysfunction before cell death. Consistent with our published studies, PQ also induced early compensatory PKD1 signaling in N27 DAergic neuronal cells and human iPSC-derived midbrain DAergic neurons, as determined by enhanced phosphorylation of the Ser744/748 and Ser916. Importantly, this early PKD1 activation was accompanied by rapid phosphorylation of mTOR and DRP1 in DAergic neuronal cells. Immunostaining confirmed the co-localization of PKD1 and mTOR. Our proximity ligation analysis revealed strong interactions of PKD1 and phosphorylated forms of mTOR (S2448, S2481, T2446) in PQ-treated N27 cells, suggesting that PKD1 may directly phosphorylate mTOR in response to PQ in DAergic cells. Western blot analysis confirmed the activation of the PKD1-mTOR pathway in the striatal region of transgenic MitoPark mice, a mitochondrial dysfunction model of PD. Moreover, native PKD1 expression increased in surviving DAergic neurons in both PD animal models as well as postmortem human brain tissues. Furthermore, DRP1 was activated at Ser616 in the early stages of PQ-induced oxidative stress, and the rapamycin-induced inhibition of mTOR decreased DRP1 expression, indicating that DRP1 may act as a downstream mediator of mTOR in pesticide-induced neurotoxicity. Our findings reveal that a novel PKD1-mTOR-DPR1 signaling axis may play a compensatory role during oxidative stress-induced DAergic neurodegeneration in PD (NIH/NINDS grant NS121692).

Disclosures: A. Jang: None. **B.N. Palanisamy:** None. **M. Ay:** None. **G. Zenitsky:** None. **H. Jin:** None. **V. Anantharam:** None. **A. Kanthasamy:** None. **A.G. Kanthasamy:** None.

Poster

PSTR063: Parkinson's Disease: Neuroprotective Mechanisms

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR063.13/C34

Topic: C.03. Parkinson's Disease

Support: This research has been funded in part by the West Virginia University Center for Foundational Neuroscience Research and Education

Title: Exercise impacts sensorimotor coordination in aging adults with and without Parkinson's disease

Authors: *C. BRANDMEIR[1], E. HERRICK[1], S. YAKOVENKO[2];
[2]Human Performance, [1]West Virginia Univ., Morgantown, WV

Abstract: Advanced age and neurological disorders like Parkinson's disease (PD) are often associated with sensorimotor problems of limb control, and the cause of this motor deterioration is obscured by changes in both central and peripheral systems. Lifestyle behavioral modifications that increase mobility through exercise may play a considerable general role in maintaining and even improving the overall capacity of this multisystem function. Yet, the effect of exercise on limb coordination during sensorimotor deterioration in PD is unknown. Using a two-alternative forced choice psychometric task, we have previously discovered a remarkable accuracy of limb speed perception in young adults, supporting the hypothesis that the limb speed variable is controlled in the closed-loop sensorimotor pathways. We expected that people with PD would show a diminished ability to perceive limb speed and, consequently, have a diminished limb function, but exercise may rescue this process. We recruited neurotypical (N=19, 58.6±8.7y) and early-stage PD (N=16, 59.4±8.7y) participants. Inclusion screening included disease severity (Hoehn and Yahr II) and the ability to walk unaided. We excluded those with non-PD neurological diseases, recent or unstable cardiac or pulmonary diagnoses, orthopedic history limiting walking within the past 6-months, joint pain, peripheral neuropathy, or inability to consent. Discrimination of limb speed was tested with a 2-alternative forced-choice method during split-belt treadmill walking. The PD group demonstrated a deficit in limb speed perception accuracy compared to the control group. Age further influenced these outcomes, with older participants showing reduced accuracy irrespective of health status. Regular exercise mitigated the performance decline in both groups, particularly in those over 60. These findings indicate that prior regular exercise may play a protective role in the sensorimotor processing of limb coordination in aging adults with and without PD.

Disclosures: C. Brandmeir: A. Employment/Salary (full or part-time):; West Virginia University. Other; This research has been funded in part by the West Virginia University Center for Foundational Neuroscience Research and Education. **E. Herrick:** None. **S. Yakovenko:** None.

Poster

PSTR063: Parkinson's Disease: Neuroprotective Mechanisms

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR063.14/C35

Topic: C.03. Parkinson's Disease

Title: Development of a PINK1 activator as a first in class, disease modifying drug lead for Parkinson's Disease.

Authors: *S. D. JOHNSTONE;
Medicinal Chem., X-Chem, Montreal, QC, Canada

Abstract: The aim of this work was to identify a tool compound to investigate a potential role for PINK1 activation in Parkinson's Disease. PINK1 (PTEN-induced putative kinase 1) and Parkin (ubiquitin E3 ligase) regulate mitochondrial health through a process called mitophagy, and mutations in PINK1 and Parkin result in impaired mitophagy and early onset Parkinson's Disease (Guerreiro, *Cell*, 2015, 160, 570). In healthy mitochondria, PINK1 is degraded at the inner mitochondrial membrane by protease PARL. When mitochondria are damaged, the membrane depolarizes, and PINK1 becomes stabilized at the outer membrane. Here it recruits and activates Parkin, leading to ubiquitination of outer mitochondrial proteins and degradation of damaged mitochondria. A small molecule that enhances this process in diseased neurons could help to restore mitochondrial health (Hertz, *Cell*, 2013, 154, 737).

Disclosures: S.D. Johnstone: A. Employment/Salary (full or part-time):; X-Chem.

Poster

PSTR063: Parkinson's Disease: Neuroprotective Mechanisms

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR063.15/C36

Topic: C.03. Parkinson's Disease

Support: Michael J. Fox Foundation (MJFF)
The Branfman family Foundation
NIH Grant P50AG005134

Title: Effects of endosulfine-alpha expression on alpha-synuclein pathology and neuronal activity

Authors: *G. DRAFOR[1,2], C. CHANDRASEKARAN[1,2], R. XU[3,2], J.-C. ROCHET[1,2];
[1]Borch Dept. of Medicinal Chem. & Mol. Pharmacol, [2]Purdue Inst. for Integrative Neurosci., [3]Basic Med. Sci., Purdue Univ., West Lafayette, IN

Abstract: A key pathological feature of the brains of individuals with Parkinson's disease (PD) and other synucleinopathy disorders is the presence of aggregates enriched with fibrillar forms of the presynaptic protein alpha-synuclein (aSyn). aSyn undergoes accelerated aggregation in the presence of phospholipid membranes by adopting an exposed alpha-helical structure, a state that favors membrane-induced self-assembly. Endosulfine-alpha (ENSA), a highly conserved

member of the cyclic AMP-regulated phosphoprotein family expressed in the CNS, is a regulator of the ATP-sensitive potassium (K_{ATP}) channel as well a binding partner of membrane - associated aSyn. We hypothesized that ENSA could inhibit seeded aSyn aggregation in neurons exposed to aSyn preformed fibrils (PFFs). To address this hypothesis, rat cortical cultures treated with aSyn PFFs were untransduced or transduced with adenovirus encoding ENSA-WT or the control protein LacZ downstream of the neuron-specific synapsin promoter. After 5 or 6 days, the cells were fixed, stained for pS129-aSyn (a variant enriched in pathological aSyn inclusions), and imaged via confocal microscopy. A subset of cultures were incubated during the fixation step with 1%(v/v) triton X-100 , a treatment that enables the visualization of detergent-resistant pS129-aSyn puncta thought to consist of *bona fide* amyloid-like fibrils while eliminating soluble proteins that contribute to the background. PFF-treated cultures transduced with ENSA virus exhibited a reduced number of pS129-aSyn puncta compared to untransduced cultures or cells transduced with LacZ virus. Conversely, aSyn aggregation was enhanced in rat cortical neurons depleted of ENSA via shRNA-mediated knockdown, and in human cortical neurons derived from iPSCs with an ENSA gene disruption. From these results, we infer that ENSA plays a role in mitigating seeded aSyn aggregation in neurons. Current efforts are focused on determining the impact of ENSA down-regulation (previously observed in the brains of individuals with synucleinopathy disorders, Alzheimer's disease, or Down syndrome) on neuron activity, based on the hypothesis that ENSA stimulates neurotransmitter release by inhibiting K_{ATP} channel function. To this end, we are using assays designed to monitor the firing properties of neurons obtained from embryonic rat brains or generated from human iPSCs via multielectrode array (MEA) recordings and calcium transient imaging. These studies will provide valuable insights into the molecular mechanisms underlying ENSA-mediated neuroprotection and the role of ENSA in regulating neuronal activity, setting the stage for developing new therapies.

Disclosures: G. Drafor: None. **C. Chandrasekaran:** None. **R. Xu:** None. **J. Rochet:** None.

Poster

PSTR063: Parkinson's Disease: Neuroprotective Mechanisms

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR063.16/C37

Topic: C.03. Parkinson's Disease

Support: FCT POCI-01-0145-FEDER-03127
Centro2020 CENTRO-01-0145-FEDER-000008:BrainHealth2020

Title: Role of adenosine A_{2A}receptors in rodent models of the prodrome of Parkinson's disease

Authors: *R. A. CUNHA;
Univ. of Coimbra, Coimbra, Portugal

Abstract: Antagonists of adenosine A_{2A} receptors (A2AR) were introduced as new anti-Parkinson's disease (PD), based on their ability to attenuate motor dysfunction and dampen the

loss of dopaminergic neurons (PMID: 32236790). Motor benefits were assumed to result from A2AR forming heteromers to control dopamine D2 receptor function in striatal neurons (PMID: 31559390). However, A2AR-mediated neuroprotection is observed both in striatum/nigra in models of PD, as well as in different brain areas in different models of other brain diseases (PMID: 27365148), implying a non-dopaminergic mechanism. We now enquired if A2AR play a role in the prodrome of PD to format neurodegeneration, the onset of motor symptoms and non-motor symptoms of PD.In the pre-symptomatic phase of an intra-striatal 6-OHDA rat model of PD, A2AR were up-regulated and played an enhanced role in the control of corticostriatal LTP. This suggests that bolstered A2AR activation might contribute to the abnormal synaptic plasticity in circuits involved in the onset of PD motor symptoms.A slow i.c.v. infusion during 15 days of MPP^+ in rats caused an initial loss of dopamine and glutamate synaptic markers in the striatum within 10 days, followed by a neuronal loss in the substantia nigra after 30 days. Treatment with the A2AR antagonist SCH58261 (0.1 mg/kg, i.p.) in the first 10 days attenuated both the initial loss of striatal synaptic markers and the subsequent loss of nigra dopaminergic neurons. Strikingly, SCH58261 treatment starting 20 days after MPP^+ infusion was less neuroprotective. This suggests that A2AR antagonists may be more effective to counteract the onset rather than the evolution of PD pathology.Rats injected intra-striatally with 6-OHDA and analyzed 20 days after did not display overt motor deficits but were anxious and amnesic. Whereas L-DOPA was ineffective, SCH58261 treatment normalized behavior. Finally, mice subject to intra-nasal MPTP (1 mg/nostril), before the onset of motor symptoms, developed procedural memory deficits that were prevented by SCH58261 (0.5 mg/kg, i.p.) and inexistent in global but not striatal-selective A2AR knockout mice. This indicates an ability of A2AR to control non-motor symptoms in the PD prodrome independently of the dopamine system.

Disclosures: R.A. Cunha: F. Consulting Fees (e.g., advisory boards); RAC is a scientific consultant of the Institute for Scientific Information on Coffee and a member of the scientific board of Bial Foundation.

Poster

PSTR063: Parkinson's Disease: Neuroprotective Mechanisms

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR063.17/Web Only

Topic: C.03. Parkinson's Disease

Support: IoE University of Delhi

Title: A_{2a} r antagonist attenuated the soce mediated calcium homeostasis and impaired mitochondrial membrane potential in 6-ohda induced parkinson's disease

Authors: *J. MISHRA, P. M. LUTHRA;
Dr. B. R. Ambedkar Ctr. for Biomed. Res., Univ. of Delhi, New Delhi, India

Abstract: Parkinson's disease (PD) is a common neurodegenerative disorder that affects approximately 1 -3% of the population over the age of 65 years. While treatment options for PD are limited, Moreover, these treatments do not alter disease progression and do not address the mood, postural instability, or cognitive disturbances that frequently accompany PD. The dopamine replacement therapies have significant limitations which influenced researchers to find non-dopaminergic treatments for PD. One non-dopaminergic approach that has received considerable attention is modulation of adenosine receptors. Previously our lab synthesized and validated various A_{2A} R antagonist (Mishra et al, 2010;2013) in haloperidol induced model in which BBPT possessed numerous pharmacological benefits. This study aimed to investigate the molecular mechanism of BBPT for neuroprotection in 6-OHDA induced Primary neuronal cells isolated from P_0/P_1 pups of SD rats. Our findings reveal that 6-OHDA increases SOCE mediated Ca2+ homeostasis through ER-stress as well as impaired $\Delta\Psi(m)$ generates ROS that causes Ca^{2+} influx simultaneously from the cytosol to mitochondria. As result of which impaired Ca2+ concentration causes neurodegeneration in PMDN cells. A_{2A}R antagonists inhibited the increased Ca2+ concentration, decreases the expression level of SOCE mediated Orai1/STIM-1 protein expression with a significant reduction in $\Delta\Psi(m)$ as well as a significant increase in the expression levels of PD related TH and DJ-1 proteins. However, these effects were significantly attenuated the SOCE mediated Ca2+ homeostasis after treatment with BBPT in 6-OHDA induced PMDN cells. Also, BBPT significantly improved ROS level to protect the PMDN cells from the 6-OHDA induced neurodegeneration. Our findings provide the first evidence on the ability of A_{2A}R antagonist (BBPT) to maintain SOCE mediated Ca2+ homeostasis, inhibited PM-ER stress and protect the $\Delta\Psi(m)$ from 6-OHDA induced neurodegeneration in PMDN cells.

Disclosures: J. Mishra: None. **P.M. Luthra:** None.

Poster

PSTR063: Parkinson's Disease: Neuroprotective Mechanisms

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR063.18/C38

Topic: C.03. Parkinson's Disease

Support: NIH Grant R01NS115809

Title: Cytisine remodels astrocyte reactivity and morphology in the substantia nigra pars compacta of a 6-OHDA mouse model of parkinsonism

Authors: *R. GARCIA[1], G. PANDEY[2,3], S. ZARATE[1], L. KUNAM[1], M. ZENEBE[1], R. SRINIVASAN[1,4];
[1]Dept. of Neurosci. and Exptl. Therapeut., Texas A&M Univ., Bryan, TX; [2]Texas A&M Univ. Inst. For Neurosci., Bryan, TX; [3]Department of Neuroscience and Experimental Therapeutics, Texas A&M University, Bryan, TX; [4]Texas A&M University Institute For Neuroscience, Bryan, TX

Abstract: Parkinson's disease (PD) is the second-most prevalent neurodegenerative disorder globally and is marked by a rising incidence rate. At a cellular level, PD is characterized by the progressive loss of dopaminergic (DA) neurons in the substantia nigra pars compacta (SNc). Current therapeutic approaches predominantly address motor symptoms rather than halting neurodegeneration, highlighting a critical need for neuroprotective strategies. Astrocytes, which are intricately involved in maintaining DA neuron health via direct interactions in the SNc, have emerged as pivotal contributors to PD progression. Consequently, there is an urgent need for interventions targeting astrocyte physiology to mitigate DA neuron loss in PD. Endoplasmic reticulum (ER) stress is a central mechanism driving DA neuron degeneration in PD, offering a promising therapeutic avenue for neuroprotection. Epidemiological evidence has associated chronic tobacco use with decreased PD risk, and our prior studies revealed that nicotine and the smoking cessation drug cytisine attenuate ER stress in DA neurons by acting as pharmacological chaperones for α4β2 neuronal nicotinic acetylcholine receptors (nAChRs) and consequently promoting ER-exit site formation. Furthermore, cytisine exhibits neuroprotection in a sex-specific manner in a 6-hydroxydopamine (6-OHDA) mouse model of parkinsonism. Interestingly, astrocytes in the SNc which ensheathe DA neurons express α4β2 nAChRs, raising the possibility that cytisine may also reduce astrocytic ER stress in this PD-relevant brain region. Therefore, we hypothesized that by attenuating astrocytic ER stress, cytisine reduces astrocyte reactivity and modifies the morphological interactions between astrocytic processes and DA neurons. To test this, we measured GFAP reactivity and S100B-positive process retraction in the SNc of a 6-OHDA mouse model of parkinsonism treated with low-dose intraperitoneal cytisine injections. We found that cytisine induces S100B-positive process retraction in the SNc, suggesting that cytisine alters the morphological relationship between DA neurons and astrocytes. Additionally, cytisine reduces astrocytic GFAP expression in the SNc, suggesting that the drug reduces astrocyte reactivity in this region. Together, these data suggest that in addition to attenuating ER stress in dopaminergic neurons, cytisine reshapes DA neuron-astrocyte interactions by altering astrocytic morphology and reactivity, which has important implications for understanding PD pathogenesis.

Disclosures: R. Garcia: None. **G. Pandey:** None. **S. Zarate:** None. **L. Kunam:** None. **M. Zenebe:** None. **R. Srinivasan:** None.

Poster

PSTR063: Parkinson's Disease: Neuroprotective Mechanisms

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR063.19/C39

Topic: C.03. Parkinson's Disease

Support: NIH R01NS115809

Title: Sex Differences in Novel Transgenic Mice with Constitutively Upregulated Nicotinic Acetylcholine Receptors: Implications for Parkinson's Disease

Authors: *G. PANDEY[1,2], R. GARCIA[3], S. ZARATE[4], R. SRINIVASAN[5];
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Abstract: Parkinson's disease (PD) incidence rates predict a worldwide pandemic that will affect over 12 million people by 2040, underscoring the urgent need for neuroprotective drugs. Unfortunately, no neuroprotective drugs are currently available, and most proposed neuroprotective drugs failed clinical trials because PD is produced by a range of insults not replicated in any one animal model. For this reason, we focus on hyperactivated endoplasmic reticulum (ER) stress, a convergent apoptotic mechanism for multiple PD-related toxicities. Nicotine reduces PD risk; however, nicotine concentrations in tobacco users cannot activate neuronal nicotinic acetylcholine receptors (nAChRs), making this an unlikely mechanism for neuroprotection of dopaminergic (DA) neurons. We have previously shown that nanomolar concentrations of the nicotinic ligand cytisine rapidly chaperone β2-subunit-containing (β2*) nAChRs out of the ER. This directly reduces the ER stress response, which is critical for neuroprotection. To test this hypothesis, we created a novel transgenic mouse line named $\beta2_{\text{enhanced ER export}}$, with enhanced ER export of β2* nAChRs. Surprisingly, $\beta2_{\text{enhanced ER export}}$ mice demonstrate significant increases in Sec24D ER exit sites (ERES) within substantia nigra pars compacta (SNc) DA neurons in only female but not male mice. We also induced parkinsonism in mice by unilateral injection of 6-OHDA in the dorsolateral striatum. Interestingly, the $\beta2_{\text{enhanced ER export}}$ mutations reduced apomorphine rotations only in female mice. This reduction corresponds with a decrease in the loss of TH+ neurons and astrocyte reactivity. Our data suggests the $\beta2_{\text{enhanced ER export}}$ mutation exerts neuroprotection only in female mice. We are also testing the consequences of upregulating β2* nAChRs on striatal dopamine release using the optogenetic sensor GRABDA and on dendritic responses in DA neurons with the genetically encoded calcium indicator, GCaMP6f.

Disclosures: G. Pandey: None. **R. Garcia:** None. **S. Zarate:** None. **R. Srinivasan:** None.

Poster

PSTR063: Parkinson's Disease: Neuroprotective Mechanisms

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR063.20/C40

Topic: C.03. Parkinson's Disease

Support: William C Rowland Jr. Parkinson's Research Fund
NIH R21NS120570

Title: Alterations in the microvascular environment of the SNpc in response to voluntary exercise in a mouse model of Parkinson's Disease

Authors: *T. N. RODRIGUEZ[1], R. J. SMEYNE[2], M. SMEYNE[3];
[1]Neurosci., Farber Inst. of Neurosci. Thomas Jefferson Univ., philadelphia, PA; [2]Dept. of Neurosciences, Farber Inst. of Neurosci. Thomas Jefferson Univ., Philadelphia, PA; [3]Vickie & Jack Farber Inst. for Neurosci., Philadelphia, PA

Abstract: Parkinson's disease (PD) is a debilitating neurological disorder that affects 2% of the population aged 50 and older. Currently, PD symptomology can be addressed with drugs/surgery, but these treatments fail to slow the progression of the disease. Aerobic exercise has been shown to slow or even stop progression of motor symptoms in humans, as well as protect against neuronal pathology in mice. However, the mechanisms underlying exercise-induced neuroprotection remain largely unknown. Characteristic PD pathology includes loss of dopaminergic (DA) neurons in the Substantia Nigra pars compacta (SNpc). Loss of 60-70% of these neurons in the SNpc manifests in PD's motor symptoms: tremor, bradykinesia, and gait disturbances. In addition to physical motor symptoms, PD patients also suffer from cerebrovascular aberrations with disease progression including increased blood-brain-barrier permeability, decreased capillary network density and complexity, and loss of DA neuron to vessel contacts. The goal of this study is to quantify changes to the architecture of the microvasculature and neurovascular unit in the SNpc in response to voluntary exercise and assess the contribution of angiogenesis to exercise-induced neuroprotection. Previous work in our lab has shown that administration of the neurotoxin, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) causes a 40% loss of DA neurons in the SNpc of standard-housed C57BL/6J mice, compared to a 5% loss in exercised mice. We demonstrated that one mechanism underlying this neuroprotection is exercise's ability to cause cellular hypoxia in the SNpc, which induces transcription of target genes, some of which increase angiogenesis. Exercise has profound angiogenic capabilities in the muscular and cardiovascular systems, but exercise-induced microvascular changes have yet to be characterized in the SNpc in the context of neuroprotection. In this study, we analyzed changes to the microvascular network of the SNpc in mice that performed 90 days of voluntary wheel running. We also quantified changes in support cells of the neurovascular unit (NVU) including pericytes and microglia in the SNpc. We reconstructed the microvascular environment of the SNpc using Vesselucida 360 to perform 3-D analysis of vasculature alongside NVU support cells and DA neurons. Future studies to assess biochemical and epigenetic modifications in the SNpc that accompany changes to the NVU in response to exercise are planned.

Disclosures: T.N. Rodriguez: None. **R.J. Smeyne:** None. **M. Smeyne:** None.

Poster

PSTR063: Parkinson's Disease: Neuroprotective Mechanisms

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR063.21/C41

Topic: C.03. Parkinson's Disease

Support: NIH INBRE Pilot Award to HL

Title: A putative neuroprotective strategy against a Drosophila model of Parkinson's disease

Authors: *A. ATHEBY[1], K. ROSIKON[2], H. O. LAWAL[3];
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Abstract: Parkinson's disease (PD) is the second most common neurodegenerative disease. The precise cause of most PD cases remains unknown, however, decades of research have established key environmental and genetic factors as contributors to its etiology. Moreover, despite the advances in our understanding of the possible causes of the disease, a viable treatment remains elusive. Rotenone, a potent laboratory model for sporadic PD has been used to uncover important insights into the etiology of Parkinson's disease. This research aims to test the neuroprotective capability of the small molecule dacarbazine (which we identified in a previous pharmacological screen) and its structural derivative, 5-Amino-4-imidazolecarboxamide (AICA) against rotenone-induced neuronal toxicity. Both compounds have been reported previously to increase synaptic activity in a manner that is dependent on vesicular monoamine release. In this project, we investigated whether both compounds are capable of conferring organismal and/or neuroprotection against rotenone toxicity. We report that dacarbazine confers a small but reproducible protection against organismal toxicity induced by rotenone exposure in both male and female *Drosophila.* These results are all the more remarkable given that dacarbazine is a chemotherapeutic drug with a toxic potential of its own. Crucially, we report for the first time, that consistent with its published role as a VMAT-dependent drug, AICA protects dopamine (DA) neurons against rotenone-induced neuronal toxicity in an assay in which we combined both a pesticide (rotenone) and age as risk factors for PD. We also report effects of AICA on locomotion ability. Together, these findings identify a promising and viable for developing therapeutics against Parkinson's disease.
Student names: Angeline Claudia AthebyD #s: D10687712Contact emails: aatheby20@students.desu.eduGender: FemaleAge group: 30-35Race: Black EthnicityLevel of education attainment:Ph.DPhone #: 3026667609Abstract Title: A dopaminergic release agonist confers neuroprotection against a *Drosophila* model of sporadic Parkinson's disease
Abstract #: See above.

Disclosures: A. Atheby: None. **K. Rosikon:** None. **H.O. Lawal:** None.

Poster

PSTR064: ALS iPSC Models

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR064.01/C42

Topic: C.06. Neuromuscular Diseases

Title: Ferroptosis-dependent neuronal damage induced by oxidative stress and TDP-43 aggregation formation in iPSC-motor neurons as ALS models

Authors: H. KOBAYASHI[1], H. S. MASUYAMA[2], H. TANABE[1], H. KATO[1], ***S. ENDOH-YAMAGAMI**[1];
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Abstract: Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disease characterized by the progressive loss of motor neurons. The approved drugs currently available have limited effects on survival, necessitating the development of new therapeutic agents. To create platforms for drug evaluation, we developed ALS models using motor neurons derived from human induced pluripotent stem cells (iPSCs).
While the molecular mechanisms of ALS are not fully understood, numerous studies suggest that oxidative stress is a central mechanism underlying ALS pathogenesis. In order to establish in vitro ALS models, we exposed iPSC-motor neurons (iCell Motor Neurons from FUJIFILM Cellular Dynamics) to weak oxidative stress, and we successfully induced neuronal damage. Under this stress, the motor neurons exhibited increased neurite degeneration, reactive oxygen species (ROS) production, and neuronal cell death. We found that ferroptosis inhibitors displayed neuroprotective effects in the oxidative stress model, suggesting that the motor neurons undergo cell death via ferroptosis, implicated in ALS and other neurodegenerative diseases. Additionally, edaravone exhibited activity in slowing down neuronal damage in the model. These findings indicate that our model encompasses certain aspects of ALS disease phenotype. To further utilize the model, we evaluated a commercially available small-scale library and identified compounds that showed neuroprotective effects.
The hallmark of ALS is the cytoplasmic mislocalization and aggregation of TDP-43. We have, furthermore, successfully induced TDP-43 aggregation through a combination of oxidative stress and other stressors. Currently, the utility of the TDP-43 aggregation model in drug evaluation is under investigation.
In summary, we have established a model of neuronal damage induced by oxidative stress using iPSC-motor neurons, and this model reflects key features of ALS. Additionally, we have successfully reproduced the TDP-43 aggregation phenotype in iPSC-motor neurons. We expect that these models will be useful for drug development and contribute to a deeper understanding of the underlying mechanisms of ALS.

Disclosures: H. Kobayashi: A. Employment/Salary (full or part-time):; FUJIFILM Corporation. **H.S. Masuyama:** A. Employment/Salary (full or part-time):; FUJIFILM Corporation. **H. Tanabe:** A. Employment/Salary (full or part-time):; FUJIFILM Corporation. **H. Kato:** A. Employment/Salary (full or part-time):; FUJIFILM Corporation. **S. Endoh-Yamagami:** A. Employment/Salary (full or part-time):; FUJIFILM Corporation.

Poster

PSTR064: ALS iPSC Models

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR064.02/C43

Topic: C.06. Neuromuscular Diseases

Title: Measuring activity in human pluripotent stem cell-derived neural organoids for disease modeling and drug discovery

Authors: J. CHAN[1], J. WANG[1], J. BAGLEY[2], L. CHEW[1], A. MACCIONE[3], S. A. LOUIS[1], A. EAVES[1,4], B. M. FONTINHA[2], ***C. MAK**[1], E. KNOCK[1,5];
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Abstract: Neural organoids have emerged as a powerful technology for modeling developmental processes, cell-cell interactions, cytoarchitecture, and disease mechanisms. However, the structural heterogeneity observed between organoids, as well as from a lack of protocol standardization, can complicate functional analysis. To address this challenge, we present standardized workflows for the generation and long-term culture of cerebral and spinal cord organoids. Additionally, we show how to induce disease-related phenotypes in these organoids and measure functional outputs using multielectrode arrays (MEAs). Cervical spinal cord organoids (SCOs) were generated using STEMdiff™ Spinal Cord Organoid Differentiation Kit from 8 different human pluripotent stem cell (hPSC) lines. Three 30-day-old SCOs were adhered to 48-well Axion™ MEA plates within 100% Matrigel® domes and cultured for 40 days in Organoid Maturation Medium or BrainPhys™ Neuronal Medium. These spinal cord organoids were cultured for an additional 40 days and treated with 10 µM MG-132, a compound known to induce aggregation of TAR DNA-binding protein 43 (TDP-43) and used for modeling amyotrophic lateral sclerosis (ALS). In a separate experiment, three 60-day-old hPSC-derived unregionalized cerebral organoids generated using STEMdiff™ Cerebral Organoid Differentiation Kit were plated onto 3D HD-MEA (4096 µpillars, ~90 µm high, size ~12x12 μm^2 - 3Brain), according to the manufacturer's instructions in BrainPhys™ Neuronal Medium + 10 mM glucose. Cerebral organoids were then treated with 100 µM 4-aminopyridine (4-AP) to induce an epileptic phenotype, with reversal of this phenotype modeled by subsequent treatment with 1 mM valproic acid, an anti-epileptic. SCOs cultured in BrainPhys™ Neuronal Medium activated twice as many electrodes and displayed network bursting activity compared to SCOs cultured in Organoid Maturation Medium. Acute treatment of SCOs with MG-132 reduced the number of active electrodes and spikes to 0 and the weighted mean firing rate to 0 Hz. For cerebral organoids, acute treatment with 4-AP resulted in a 10 - 15-fold increase in the mean firing rate compared to the baseline (untreated) rate, resulting in an epileptic-like phenotype. Subsequent treatment with valproic acid resulted in a 3 - 5-fold reduction in the firing rate compared to the untreated baseline rate. These data suggest that organoids generated using STEMdiff™ organoid differentiation kits display robust neural activity after long-term culture in either STEMdiff™ Neural Organoid Maintenance Kit or BrainPhys™ Neuronal Medium, providing a reliable platform for neuronal disease modeling and drug discovery.

Disclosures: J. Chan: A. Employment/Salary (full or part-time):; STEMCELL Technologies Inc. **J. Wang:** A. Employment/Salary (full or part-time):; STEMCELL Technologies Inc. **J. Bagley:** A. Employment/Salary (full or part-time):; a:head Bio AG. **L. Chew:** A. Employment/Salary (full or part-time):; STEMCELL Technologies Inc. **A. Maccione:** A. Employment/Salary (full or part-time):; 3Brain AG. **S.A. Louis:** A. Employment/Salary (full or part-time):; STEMCELL Technologies Inc. **A. Eaves:** A. Employment/Salary (full or part-time):; STEMCELL Technologies Inc. **B.M. Fontinha:** A. Employment/Salary (full or part-

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Poster

PSTR064: ALS iPSC Models

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR064.03/C44

Topic: C.06. Neuromuscular Diseases

Title: In Vitro Systems targeting TDP-43 translocation, aggregation and STATHMIN-2 splicing

Authors: *A. BROWN;
Scantox ApS, Ejby, Denmark

Abstract: IN VITRO SYSTEMS TARGETING TDP-43 TRANSLOCATION, AGGREGATION AND STATHMIN-2 SPLICING Andy Brown[2], Tina Loeffler[1], Irene Schilcher[1], Irantzu Perez Ruiz[1], Igor Cancar[1]; Magdalena Daurer[1], Stefanie Flunkert[1], Manuela Prokesch[1]*[1]Scantox Neuro GmbH, Neuropharmacology, Grambach, Austria*[2]*Scantox Holding Aps,Denmark*TDP-43, a protein expressed by the TARDP gene and linked to RNA processing, is crucial in understanding amyotrophic lateral sclerosis (ALS) and other neurodegenerative diseases, as its mislocalization and aggregation are hallmark features of these diseases, contributing to neurodegeneration and neuronal dysfunction.Evidence suggests that TDP-43 dysfunction correlates with cytoplasmic stress granule (SG) formation, which in turn affects RNA translation during cellular stress. Cryptic splicing and polyadenylation events in genes like stathmin-2 (STMN-2) and UNC13A have been observed in tissues from patients with a diagnosis of ALS, frontotemporal dementia, or Alzheimer's disease and have recently been described as relevant cause for neuronal dysfunction.Recent regulatory approvals underscore the demand for novel translational models utilizing induced pluripotent stem cells (iPSCs) to facilitate drug testing in neurodegenerative disorders.To address this, we developed *in vitro* models mimicking TDP-43 pathology using human TDP-43 overexpressing neuroblastoma cells (SH-TDP43) and iPSC-derived glutamatergic neurons carrying the M337V mutation in the TARDP gene. These models were exposed to the SG inducer sodium arsenite (SA) and treated with potential therapeutic agents such as edaravone and riluzole. TDP43 translocation and SG formation was analyzed using immunocytochemistry. TDP-43 aggregation was evaluated using either automated western blotting (WES™) or HTRF-based assays. Cryptic splicing of POLDIP-3, STMN-2 and UNC13A was assessed using quantitative RT-PCR. Our results demonstrate significant SG formation in SA-treated cells compared to controls using the SG marker G3BP, along with evidence of cryptic splicing in genes such as STMN-2, UNC13A and POLDIP3. Notably, riluzole showed good efficacy in preventing cryptic splicing of STMN-2 in SA-induced SH-TDP43 cells and iPSC-derived glutamatergic neurons, while edaravone did not.The same methods are planned to be applied to primary motor neurons.In conclusion, our *in vitro* models

utilizing SA-induced SGs provide valuable platforms for screening the efficacy of investigational compounds targeting TDP-43-related pathologies and downstream effects.

Disclosures: A. Brown: None.

Poster

PSTR064: ALS iPSC Models

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR064.04/C45

Topic: C.06. Neuromuscular Diseases

Support: IIT Gandhinagar Fellowship

Title: Elucidating Length dependent TDP 43 aggregation and the impact of Post-translational modifications

Authors: *K. BHAVSAR[1], S. GUPTA[2];
[1]Indian Inst. of Technol., Gandhinagar, Gandhinagar, India; [2]Biol. Engin., Indian Inst. of Technol. Gandhinagar, Gandhinagar, India

Abstract: Transactive response DNA-binding protein 43 (TDP-43) is a highly conserved nuclear RNA/DNA-binding protein involved in regulating RNA processing. It has gained significant scientific attention in the pathogenesis of various neurodegenerative diseases (NDs), including amyotrophic lateral sclerosis (ALS), frontotemporal lobar degeneration (FTLD), FTLD-Tau, limbic-predominant age-related TDP-43 encephalopathy (LATE), etc. The aberrant accumulation of TDP-43 in cytoplasmic inclusions is a hallmark of ALS and FTLD, highlighting its role in disease progression. PTMs, such as phosphorylation, acetylation, ubiquitination, and proteolytic cleavage, dynamically regulate TDP43 localization, stability, and toxicity. This study elucidates the involvement of TDP-43 in the pathogenesis of NDs, focusing on the impact of post-translational modifications (PTMs) on its structure. We have synthesized and modified various length-dependent aggregation-prone sequences from RRM1, RRM2, and low-complexity domains of TDP-43. The research work was done using chemical synthesis and analytical techniques like Solid-phase peptide synthesis, RP-HPLC, LC-MS, MALDI/TOF, and an array of biophysical and microscopic analyses, such as ThT kinetic assay, Microscopy, Congo red staining, SEM, and AFM was performed to characterize the fibrils. We have also studied the derived peptides' cellular toxicity in HEK 293 cells. Results and Discussion: With the *Insilico* and experimental approach involving chemical, bio-physical, and imaging techniques, we confirmed the fibrillary amyloid nature of peptide aggregates upon modification. We have demonstrated that charge-neutralizing PTMs can induce aggregation in various unsuspecting peptide sequences derived from RRM1 and RRM2 regions in a length-dependent manner. We found four sets from six sets of peptides that showed an amyloid-forming potential upon acetylation and carbamylation. However, we could not see any significant amyloid-forming ability upon serine phosphorylation. In conclusion, our work depicts the significance of TDP-43

PTMs in neurodegeneration and emphasizes the need for further investigations. Deciphering the molecular mechanisms underlying PTM-mediated TDP-43 Aggregation holds promise for developing novel therapeutic interventions to mitigate neurodegenerative pathology.

Disclosures: K. Bhavsar: None. **S. Gupta:** None.

Poster

PSTR064: ALS iPSC Models

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR064.05/C46

Topic: C.06. Neuromuscular Diseases

Support: NIH Grant 1R21NS123845

Title: Enhanced extracellular vesicle release in a cerebral organoid model with loss of C9orf72

Authors: *I. MARTORELL SERRA, M. CICARDI, M. SINGER, K. KRISHNAMURTHY, D. TROTTI;
Neurosci., Thomas Jefferson Univ., Philadelphia, PA

Abstract: Amyotrophic Lateral Sclerosis (ALS) and Frontotemporal Dementia (FTD), two neurodegenerative disorders on a shared continuum, display progressive pathology that spreads throughout the central nervous system (CNS). This spread is potentially associated with gliosis, indicating that neuroinflammation is a contributing factor. The most common genetic cause of ALS/FTD is a hexanucleotide repeat expansion (HRE) in the *C9ORF72* gene. Three potential pathogenic mechanisms associated with *C9ORF72*-HRE have been identified: reduction of C9orf72 protein (C9) levels, formation of nuclear RNA foci, and aberrant translation leading to toxic dipeptide protein repeats. The precise impact of C9-haploinsufficiency on disease onset and progression is still being investigated. Impaired C9 function induces altered trans-Golgi vesicle trafficking and aberrant extracellular vesicles (EVs) secretion, among other molecular events. EVs, bilayer membrane vesicles released by cells, play critical roles in intercellular communication and inflammation. Our hypothesis posits that C9-haploinsufficiency affects this pathway, leading to abnormal EV production and composition, potentially contributing to neuroinflammation. To test this, we generated cerebral organoids (COs) from iPSC-derived controls ($C9^{+/+}$), C9-linked ALS/FTD patients ($C9^{+/-}$), and engineered C9 KOs ($C9^{-/-}$). As anticipated, the levels of C9 protein were significantly lower in $C9^{+/-}$ COs compared to the controls and were found to be undetectable in $C9^{-/-}$ COs. The growth of COs over time was not affected by C9 haploinsufficiency, as assessed by area measurement. EVs production at 6 months *in vitro* was increased in $C9^{+/-}$ and $C9^{-/-}$ COs compared to control. This increase was not caused by higher basal neural activity in $C9^{+/-}$ and $C9^{-/-}$ COs at 6 months *in-vitro*, as determined by calcium imaging experiments. Our immediate objective is to study neurodegeneration, gliosis, and EV composition/origin in our model. Next, we will infiltrate iPSCs-derived microglia progenitors into the corresponding background COs before maturation. This will help us

investigate the potential involvement of EVs in the initiation and progression of neuroinflammation. Our ultimate goal is to gain a deeper understanding of the role played by C9 in disease progression by combining the findings from these experiments with our current research.

Disclosures: I. Martorell Serra: None. **M. Cicardi:** None. **M. Singer:** None. **K. Krishnamurthy:** None. **D. Trotti:** None.

Poster

PSTR064: ALS iPSC Models

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR064.06/C47

Topic: C.06. Neuromuscular Diseases

Title: Micro-rna mediated direct reprogramming of patient-derived fibroblasts to lower motor neurons as a novel model for amyotrophic lateral sclerosis

Authors: *G. ANEX[1], L. CAPANO[2], B. WAINGER[2];
[1]Neurol., Massachusetts Gen. Hosp., Boston, MA; [2]Neurol., Massachusetts Gen. Hosp., Charlestown, MA

Abstract: Amyotrophic lateral sclerosis (ALS) is a fatal neurodegenerative disease characterized by the degeneration and progressive loss of motor neurons, ultimately resulting in paralysis and death. About 10% of ALS cases show a family history and result from mutations in a range of specific genes, while 90% of cases are non-familial. ALS is an age-associated disorder, with onset usually occurring in mid-adulthood even with genetically inherited cases. Patient-derived human induced pluripotent stem cells (iPSCs) can be used to generate human neurons (iPSC-Ns), providing a valuable tool to model the disease. However, in the process of iPSC generation, the epigenetic feature of cellular age is erased, and the cells are reverted to embryonic. Unfortunately, iPSC-Ns have been unable to consistently recapitulate quintessential ALS pathologies such as the mislocalization and aggregation of the RNA binding protein TDP-43, potentially due to their embryonic state. Instead, we sought a model that maintains the epigenetic age of the starting cell. One such model is microRNA-mediated direct reprogramming of human fibroblasts to create age-maintained human neurons. To do this, microRNAs-9/9* and -124 (miR-9/124) are exogenously expressed in human patient-derived fibroblasts. These microRNAs first erase non-neuronal fate, and second, induce neuronal fate acquisition. As demonstrated in prior published work from Dr. Andrew Yoo's laboratory at Washington University in St Louis, the miRNAs can be combined with the lower motor neuron transcription factors ISL1 and LHX3 to generate motor neurons (moto-miNs).We hypothesize that moto-miNs derived from ALS subject fibroblasts, including both familial and sporadic ALS, will better capture canonical ALS pathologies as compared to iPSC-Ns. We characterize TDP-43 mislocalization and associated aberrant splicing, TDP-43 aggregation, nuclear pore function, mitochondrial dysfunction, and

cell death. We are determining whether this method can better reproduce ALS pathology and thereby elucidate disease mechanisms.

Disclosures: G. Anex: None. **L. Capano:** None. **B. Wainger:** 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.; Lab receives funding from Argenx. F. Consulting Fees (e.g., advisory boards); Scientific Advisory Board for Quralis.

Poster

PSTR064: ALS iPSC Models

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR064.07/C48

Topic: C.06. Neuromuscular Diseases

Support: NINDS/NIA R01 NS104219
NCI R35 CA197532
Les Turner ALS Foundation

Title: Utilizing Physiologic Media to Model ALS Motor Neuron Metabolism

Authors: *E. KASPI, N. CHANDEL, E. KISKINIS;
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Abstract: Amyotrophic Lateral Sclerosis (ALS) is a debilitating neurodegenerative disease which selectively targets upper and lower motor neurons (MNs) of the brain and spinal cord. Mislocalization of RNA-binding protein TDP-43 and mitochondrial dysfunction are two common pathologic hallmarks of degenerating ALS MNs. However limited emphasis has been placed on accurately modeling human MN metabolism *in vitro,* and thus investigating the causal relationship between metabolic dysfunction, the aberrant action of TDP-43, and neurodegeneration. Traditional cell culture media utilized to maintain human neurons is specifically formulated to reduce metabolic stress and is not physiologic. Little is known about how a physiologic metabolic milieu affects MN metabolism, and what metabolic mechanisms in this context contribute to disease. Here, we aim to address this fundamental limitation by utilizing Human Plasma-Like Media (HPLM), which closely approximates the extracellular glucose and small metabolite composition of human plasma & cerebrospinal fluid. In preliminary experiments, we find HPLM can support iPSC-derived MNs and patterns of electrophysiologic activity. Using mass spectrometry analysis, we show HPLM remodels the intracellular polar metabolome of healthy MNs, and severely depletes intracellular glucose and downstream glycolytic metabolites. Additionally, we show that *Phosphofructokinase-P* (PFKP), a rate-limiting glycolytic enzyme, is pathologically mis-spliced in the context of TDP-43 knock down. Together, these results provide a promising platform for further investigation into novel metabolic mechanisms of MN vulnerability in ALS.

Disclosures: E. Kaspi: None. **N. Chandel:** None. **E. Kiskinis:** None.

Poster

PSTR064: ALS iPSC Models

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR064.08/C49

Topic: C.06. Neuromuscular Diseases

Support: Fondecyt Regular 1221147 (FN)
PIA-ANID ECM-12
VRID Nº2022000481INV
Fondecyt Regular 1240486 (KS)

Title: Svct2 over-expression increases arborization and maturation in induced human pluripotential stem cell (ipsc)-derived motor neurons and treated with hsod1-g93a amyotrophic lateral sclerosis (als) mutant.

Authors: *J. SMITH GHIGLIOTTO[1], K. A. SALAZAR[2], E. RAMÍREZ[3], R. MAGDALENA[3], M. A. CARRASCO[4], F. J. NUALART[5];
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Abstract: SVCT2 over-expression increases arborization and maturation in induced human pluripotential stem cell (iPSC)-derived motor neurons and treated with hSOD1-G93A amyotrophic lateral sclerosis (ALS) mutant.
***J. Smith-Ghigliotto[1]**, K. Salazar[1], E. Ramírez[1], R. Magdalena[1], M. Carrasco[2], F. Nualart[1].
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Different studies in animals have established the role of vitamin C and the vitamin C transporter SVCT2 in proliferation, differentiation, and neurogenesis in embryonic and adult brains cells. However, there is no data on its role in differentiation and maturation in induced human pluripotential stem cell (iPSC)-derived motor neurons overexpressing hSOD1wt or hSOD1-G93A, a mutant protein expressed in ALS, a fatal motor neuron disease characterized by progressive degeneration of nerve cells in the spinal cord and brain. AF22 cells (neuralized iPSCs cultures) were characterized by RT-PCR, Western blot and confocal-microscopy analysis to define the expression of vitamin C transporters SVCT2 and GLUT1. These cells were differentiated for 16 days in vitro and additionally, maturated for 19 days to induce motor neurons. The phenotype was confirmed by confocal microscopy, protein markers and RT-PCR. The effect of SVCT2 lentiviral overexpression was evaluated with qRT-PCR to synaptic genes expression, confocal analysis to synaptic proteins and quantitative analysis to neuronal branching. iPSC-derived motor neurons overexpressing hSOD1-wt, or hSOD1-G93A ALS

mutant were also studied. The results indicate that AF22 cells express SVCT2 and GLUT1 transporters as well as induced motoneurons that also showed, the specific cellular markers choline acetyltransferase and the Hb9 expression. SVCT2 overexpression in induced motoneurons overexpressing hSOD1-wt or hSOD1-G93A ALS mutant increase the neuronal branching and the expression and localization of synaptic proteins in dendritic spine is being analyzed. Thus, our results indicate that SVCT2 lentiviral overexpression induced dendritic and axonal branching and increase synaptic formation in human motoneurons generated from neuralized iPS cells overexpressing hSOD1-G93A.
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Disclosures: J. Smith Ghigliotto: None. **K.A. Salazar:** None. **E. Ramírez:** None. **R. Magdalena:** None. **M.A. Carrasco:** None. **F.J. Nualart:** None.

Poster

PSTR064: ALS iPSC Models

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR064.09/C50

Topic: C.06. Neuromuscular Diseases

Title: Enrichment of TDP-43 Fragments in ALS Patient-Derived Fibroblasts

Authors: *R. PRADHAN[1], N. G. KINNEY[2], B. K. JENSEN[1], S. BARMADA[3], H. ILIEVA[1]; [1]Neurosci., Thomas Jefferson Univ., Philadelphia, PA; [2]Thomas Jefferson Univ. Grad. Neurosci. Program, Philadelphia, PA; [3]Univ. of Michigan, Ann Arbor, MI

Abstract: Amyotrophic lateral sclerosis (ALS) is a devastating neurological disorder characterized by progressive muscle weakness, leading to paralysis and ultimately death. Diagnosing ALS is difficult since it presents a wide range of clinical symptoms and there are no reliable biomarkers available. Early diagnosis is critical for timely intervention to slow disease progression. Currently, the diagnosis of ALS primarily depends on the patient's clinical history and examination. This approach often results in delays in confirming the diagnosis, with a median period of 10 to 16 months following the initial appearance of symptoms. Abnormal accumulation of TDP-43 protein is observed in the central nervous system of 98% of ALS cases that makes it a highly promising target for developing a diagnostic biomarker. While postmortem studies have identified TDP-43 abnormalities in ALS brains, limited data exist on the pathological form of TDP-43 in the peripheral cells/biofluids of living patients. Therefore, in the present study we aimed to identify any distinct insoluble fragments of TDP-43 in ALS patient fibroblasts, with a potential to extrapolate in biological fluids. Furthermore, we aimed to determine the source of these fragments by exposing the cells to stressful conditions, such as culturing them in serum-deprived media. Subsequently, we used Bafilomycin, an autophagy inhibitor, to investigate the role of autophagy in the generation of these fragments. Interestingly, In ALS fibroblasts, we identified an enrichment of a specific 35 kDa C-terminal fragment (CTF)

of TDP-43 compared to age-matched controls. Serum deprivation increased production of these fragments in both ALS and control fibroblasts, with an additional 25 kDa fragment observed uniquely in ALS cells at 24 and 48 hours. Immunostaining revealed progressive nuclear loss of TDP-43 over time in the cells cultured in the absence of serum. Bafilomycin effectively blocked the generation of these fragments, indicating the involvement of autophagy in their production mechanism. In summary, our study highlights the presence of distinct insoluble TDP-43 fragments in ALS fibroblasts, particularly under stress conditions. These findings contribute to the potential value of studying TDP-43 fragments in biofluids as diagnostic biomarkers for ALS.

Disclosures: R. Pradhan: None. **N.G. Kinney:** None. **B.K. Jensen:** None. **S. Barmada:** None. **H. Ilieva:** None.

Poster

PSTR064: ALS iPSC Models

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR064.10/C51

Topic: C.06. Neuromuscular Diseases

Title: Functional phenotypic screening with human iPSC derived spinal motor neurons cultures for new amyotrophic lateral sclerosis therapies

Authors: *O. H. SCHROEDER, M. WINKLER, A.-M. KNOSPE, L. SCHULTZ, K. JÜGELT; NeuroProof Systems GmbH, Rostock, Germany

Abstract: Amyotrophic lateral sclerosis, ALS, is a fatal disease with not fully understood disease mechanisms. Therefore, phenotypic disease models are needed for the development of new therapies. The disease occurs in familial and sporadic forms, fALS and sALS. Although only about 10% of cases are familial with a known hereditary origin, they are important for disease modeling. Known fALS forms have mutations in the SOD1, C9orf72, TDP-43, FUS, and other genes. Human-induced pluripotent stem cells with fALS mutations can be differentiated toward spinal motor neurons. They are canonical disease models that reflect phenotypic disease symptoms. In our hands, iPSC-derived spinal motor neurons with a SOD1 D90A, a SOD1 A4V mutation, a C9orf72 mutation, a TDP43-G298S, and a TDP43 A384V mutation could be cultivated on microelectrode array plates for 14 to 28 days. No difference in survivability between diseased and wild-type cells was observed. The first electrophysiological activity can be observed after 7 days and lasts more than 5 weeks. After 14 days in vitro, a reliable hyperexcitation of the disease motor neurons compared to the wild-type neurons can be observed for C9orf72 and SOD1 mutated forms and after 21 days in vitro for the TDP43 mutated forms. The toxin β-Methylamino-L-alanine, BMAA, induced in C9orf72 an increase of hyperexcitated activity. BMAA addition opens the door to also test compounds potentially effective in sporadic forms of ALS. The excitation state of diseased ALS spinal motor neurons is a robust and validated model for potential treatment strategies.

Disclosures: O.H. Schroeder: E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); NeuroProof Systems GmbH. **M. Winkler:** A. Employment/Salary (full or part-time):; NeuroProof Systems GmbH. **A. Knospe:** A. Employment/Salary (full or part-time):; NeuroProof Systems GmbH. **L. Schultz:** A. Employment/Salary (full or part-time):; NeuroProof Systems GmbH. **K. Jügelt:** A. Employment/Salary (full or part-time):; NeuroProof Systems GmbH.

Poster

PSTR064: ALS iPSC Models

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR064.11/C52

Topic: C.06. Neuromuscular Diseases

Support: NIH Grant R01NS122973
NIH Grant R01NS089640

Title: Effect of fatty acid treatment on the inflammatory profile of spinal cord astrocytes

Authors: *D. ESTEVE[1], M. BRESQUE TOLEDO[1], M. PEHAR[2,3], M. R. VARGAS[1];
[1]Neurol., [2]Div. of Geriatrics and Gerontology, Med., Univ. of Wisconsin-Madison, Madison, WI; [3]Geriatric Res. Educ. Clin. Ctr., Veterans Affairs Med. Ctr., Madison, WI

Abstract: Lipid droplets (LDs) are organelles with a core of hydrophobic neutral lipids surrounded by a phospholipid monolayer. These organelles serve as metabolic energy storage and are implicated in different processes such as energy homeostasis and lipid metabolism. LDs are observed under physiological conditions, but their formation appears to be exacerbated in neurodegenerative diseases such as amyotrophic lateral sclerosis (ALS) and Alzheimer's disease. It has been proposed that astrocytes protect neurons from lipid-induced damage by accumulating and storing toxic lipids in LD. However, the role of fatty acid overburden and LD accumulation in the biology of astrocytes and its effect on astrocyte-neuron interaction remains only partially defined. We observed that an excess of fatty acids (oleic and linoleic acid) in spinal cord astrocyte cultures induces the formation of LDs. Our data show that LD accumulation is associated with an NF-κB-driven pro-inflammatory response in astrocytes. LD-containing astrocytes upregulate the expression of several pro-inflammatory markers at mRNA level, while increased levels of CXCL10 and TNFα are observed in the conditioned media of these cells. Moreover, using a co-culture model, we observed that LD accumulation in astrocytes renders these cells toxic to co-cultured motor neurons. In addition, we explored the effect of lactate dehydrogenase A inhibition in the biology of LD-containing astrocytes and its effcts on astrocyte-motor neuron interaction. Taken together, our results highlight the potential role of LD biology in modulating astrocyte-mediated neurotoxicity and neuroinflammation.

Disclosures: D. Esteve: None. **M. Bresque Toledo:** None. **M. Pehar:** None. **M.R. Vargas:** None.

Poster

PSTR064: ALS iPSC Models

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR064.12/C53

Topic: C.06. Neuromuscular Diseases

Support: Fondecyt regular 1221147
Fondecyt Regular 1240486

Title: Impaired vitamin C recycling and DHA accumulation negatively affect neurites in normal and ALS iPSC-derived neurons

Authors: *F. NUALART[1], R. MAGDALENA[2], L. E. FERRADA[1], K. A. SALAZAR[3], J. C. TAPIA[4], M. A. CARRASCO[5];
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Abstract: Neurons oxidize ascorbic acid (AA, reduced vitamin C) into dehydroascorbic acid (DHA), which is released into the extracellular space and taken up by astrocytes. Then, DHA is reduced to AA, thus maintaining its concentrations in brain parenchyma. High oxidative stress may favor DHA accumulation, changing neuronal metabolism and inducing RIPK1-dependent cell death. However, it is unknown whether absence of vitamin C recycling affects neurites, with or without ALS-related mutations.Neurospheres (NE) were formed *in vitro* from NSCs isolated from rat brain and were treated with 100/200/400 µM DHA for 12-24 h with/without 10 µM Necrostatin-1s (Nec-1s). We evaluated neurite length/branching points (IncuCyte®S3) and P-RIPK1 expression (Western Blot). Motor neurons (hiMNs) were generated from hiPSCs-derived AF22 cells or hiPSCs-*C9ORF72*. Varicosities in neurites were analyzed after 400 µM DHA treatment at 12-24 h. SVCT2 (AA transporter) expression was studied SOD1-G93A or WT mice spinal cord sections.Increasing DHA concentrations generate shorter neurites and fewer branching points in NE, effect associated with early RIPK1 phoshorylation and inhibited by early Nec-1s treatment. In hiMNs, DHA induces a greater number of varicosities/neurite versus control, effect that is more prominent in C9-derived MNs. SOD1-G93A spinal cords show high SVCT2 expression in astrocytes, meanwhile neurons show internalization and intracellular aggregation.DHA negatively affects neurites in neurons *in vitro*, effect inhibited by early Nec-1s treatment, suggesting a RIPK1-dependent mechanism. SVCT2 expression in astrocytes and transporter internalization in neurons suggests loss of vitamin C recycling, thus allowing for DHA accumulation and aiding progression of ALS.

Disclosures: F. Nualart: None. **R. Magdalena:** None. **L.E. Ferrada:** None. **K.A. Salazar:** None. **J.C. Tapia:** None. **M.A. Carrasco:** None.

Poster

PSTR064: ALS iPSC Models

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR064.13/C54

Topic: C.06. Neuromuscular Diseases

Support: NIH/NINDS Grant R01NS116143
NIH/NIGMS Grant P20GM103430

Title: Nucleocytoplasmic shuttling of RNA-binding proteins in iPSC-derived ALS neurons is altered under conditions of stress

Authors: *A. COLLINS[1,2], R. SIRTORI[3,4], M. GREGOIRE[3,4], E. POTTS[1,2], C. FALLINI[3,2,4]; [1]Univ. of Rhode Island, Kingston, RI; [2]Interdisciplinary Neuroscience Program, University of Rhode Island, Kingston, RI; [3]Cell and Mol. Biol., Univ. of Rhode Island, Kingston, RI; [4]University of Rhode Island, Kingston, RI

Abstract: Amyotrophic Lateral Sclerosis (ALS) is a progressive neurodegenerative disease that leads to loss of motor function, paralysis, and death within a few years of clinical onset. Nucleocytoplasmic transport (NCT) is an essential function in eukaryotic cells, regulating the dynamic distribution of transcription factors and other regulatory proteins between the nucleus and cytoplasm, particularly in response to cellular stimulation and stress. Interestingly, defects to the nuclear pore complex (NPC) and impaired NCT have been identified as a major disease mechanism in neurodegenerative disorders, including ALS. It is still not known how NCT disruption alters the nuclear and cytoplasmic proteome in neurons, particularly in response to cellular stress. To answer this question, we are testing how NPC injury affects cellular function and resilience in ALS neurons carrying the *C9ORF72* mutation under conditions of cellular stress. Pilot data from label-free proteomics experiments performed on fractionated induced pluripotent stem cell (iPSC)-derived neurons showed that proteins involved in protein transport and localization processes were specifically downregulated in the nuclear fractions of *C9ORF72* mutant neurons compared to isogenic wild type controls. Interestingly, we also found that whole cell lysates from mutant neurons showed downregulation in the cellular and oxidative stress response compared to the controls. When we treated neurons *in vitro* with sodium arsenite, a well-established oxidative agent, we found a similar rate of stress granule formation in both *C9ORF72* mutant neurons and isogenic wild type controls. However, the dissolution of granules occurred with different dynamics in mutant cells, and the overall cellular levels and distribution of many stress granule components in response to stress was altered in *C9ORF72* mutant neurons. Interestingly, these observed changes occurred at an age before neurons developed obvious NPC alterations, suggesting that specific alterations of protein shuttling in ALS neurons may occur at early time points during disease development. Overall, our study suggests that specific downstream cellular pathways that depend on the efficient shuttling of these proteins may be key players in the pathogenic cascade that ultimately leads to neuronal death in ALS.

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Poster

PSTR064: ALS iPSC Models

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR064.14/Web Only

Topic: C.06. Neuromuscular Diseases

Title: Modelling neurodegeneration using a human genetically matched system: a next generation approach to study frontotemporal dementia and amyotrophic lateral sclerosis

Authors: T. SMITH[1], *T. BROWN[2], T. OOSTERVEEN[3], L. FOULSER[1], A. TURNER[1], S. POKORNY[1], S. MILDE[1], O. DOVEY[4], W. BERNARD[1], G. MASTROGIOVANNI[1], H. GARNETT[1], M. KOTTER[1], D. MAGNANI[5], M. IOVINO[6], V. YIANNI[1], P. BALFOUR[1]; [2]Product Mgmt., [3]CTD, [1]bit.bio, Cambridge, United Kingdom; [4]bit.bio, Saffron Walden, United Kingdom; [5]Discovery UK, Charles River Labs., Saffron Walden, United Kingdom; [6]Charles River, Saffron Walden, United Kingdom

Abstract: Development of therapies to treat neurodegenerative diseases is hampered by the limited translatability (<10%) of existing preclinical animal models as well as the lack of reliable and consistent sources of in vitro models. Patient-derived human induced pluripotent stem cells (hiPSCs) enable generation of in vitro models that can recapitulate human disease phenotypes. However, conventional hiPSC differentiation protocols are often lengthy, complex, and difficult to scale. The lack of genetically matched controls for patient-derived models further complicates the investigation of disease phenotypes.

bit.bio has developed opti-oxTM, a deterministic hiPSC programming technology that overcomes these limitations and enables generation of cell types and associated genetically matched disease models. Our objective was to generate disease models for frontotemporal dementia (FTD) and amyotrophic lateral sclerosis (ALS) for use with genetically matched, wild type controls to improve screening specificity and accelerate drug discovery for these neurodegenerative disorders.

We used CRISPR/Cas9 gene editing to introduce the disease-relevant mutations G93A in SOD1 and P525L in FUS in ioMotor Neurons, P301S or N279K in MAPT in ioGlutamatergic Neurons, and M337V in TDP-43 (TARDBP) in both ioGlutamatergic Neurons and ioMotor Neurons. During the pathogenesis of FTD and ALS, mutant TDP-43, FUS, SOD1 and Tau proteins are prone to misfolding, aggregation, phosphorylation and/or mislocalisation, and have been reported to affect a range of neuronal subtypes, including cortical glutamatergic neurons & spinal lower motor neurons.

In this poster we showcase how opti-ox technology has been used to rapidly and deterministically program hiPSCs into motor neurons, termed ioMotor NeuronsTM, which are a homogenous population of defined and functional cells (evaluated by MEA), that express key lower motor neuron marker genes MNX1(HB9), FOXP1, ISL2 and cholinergic markers ChAT and SLC18A3 (VAChT) by day 4. Additional data demonstrates the utilisation of CRISPR/Cas9 gene editing in another neuronal cell type programmed with opti-ox (ioGlutamatergic NeuronsTM) to infer a disease-related phenotype, demonstrating reduced neuronal activity in

TDP-43 M337V/M337V neurons compared to TDP-43 M337V/WT and genetically matched control.

Disclosures: T. Brown: None. **T. Oosterveen:** None. **L. Foulser:** None. **A. Turner:** None. **S. Pokorny:** None. **S. Milde:** None. **O. Dovey:** None. **W. Bernard:** None. **G. Mastrogiovanni:** None. **H. Garnett:** None. **M. Kotter:** None. **D. Magnani:** None. **M. Iovino:** None. **V. Yianni:** None. **P. Balfour:** None.

Poster

PSTR064: ALS iPSC Models

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR064.15/C55

Topic: C.06. Neuromuscular Diseases

Support: PROMETEO CIPROM/2021/018

Title: Neural-like cells derived from ALS adipose mesenchymal cells show ALS specific cellular phenotype

Authors: *M. P. MARTINEZ[1], D. GARRIGÓS[2], E. GEIJO-BARRIENTOS[3], S. MARTINEZ[4]; [1]Inst. de Neurociencias (UMH-CSIC), Alicante, Spain; [2]Univ. Miguel Hernandez, Pinar de Campoverde, Spain; [3]Univ. Miguel Hernandez-CSIC, San Juan, Alicante,, Spain; [4]Inst. de Neurociencias, Inst. De Neurociencias. UMH-CISC, San Juan De Alicante, Spain

Abstract: The primary and progressive degeneration of motor system is the main pathogenic process that characterizes amyotrophic lateral sclerosis (ALS), which is a fatal neurodegenerative disease of motor neurons (MNs) in the primary motor cortex and spinal cord. Patients' death occurs in 3-5 years after the diagnosis due to the progressive palsy and dysfunction of the respiratory system. The overall prevalence and incidence of ALS worldwide is ranging between 4.1-8.4 per 100.000 persons and 0.6-3.8 per 100.000 person-years, respectively. With a global mortality rate of approximately 30,000 patients each year. The etiology is known in most of the patients with the most frequent sporadic ALS (sALS; 90%), and clinical onset and symptoms are highly heterogeneous. Irrespective of the cause and initial onset the ALS is an almost neurodegenerative disease of MNs, in which the factors determining preferential involvement of MN are yet to be fully understood. Therefore, to improve our understanding of ALS selective pathogenesis of human MNs it is necessary to develop more adequate experimental models. Human adipose-derived stem cells (hADSCs) isolated from an sALS donor, and control donors were induced into neural stem cells (iNSCs) using a 3-step NSC induction protocol Park et al. (2017). These iNSCs cells derived from hADSCs develop neuronal morphology and express the Choline acetyltransferase (ChAT), that is a characteristic marker of the spinal cord MNs, in both sALS and control derived neuros. The analysis of pathogenic neurodegenerative markers of ALS-MNS: TDP43 protein localization, to determine the presence of sALS characteristic TDP43 proteinopathy; LAMP2a and LC3 protein expression, to analyze autophagy mechanisms,

revealed that iNSCs cells derived from hADSCs reproduce the selective pathogeny of ALS in motoneurons that have been demonstrated in sALS patients.

Disclosures: M.P. Martinez: None. **D. Garrigós:** None. **E. Geijo-Barrientos:** None. **S. Martinez:** None.

Poster

PSTR064: ALS iPSC Models

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR064.16/C56

Topic: C.06. Neuromuscular Diseases

Support: NIH NIA R01NS104219
NIH NINDS U54 NS108874
Les Turner ALS Foundation
New York Stem Cell Foundation
ALS Scholars in Therapeutics Fellowship

Title: TDP-43 dysfunction triggers exon skipping and aggregation of the epilepsy gene KCNQ2 in ALS/FTD

Authors: *K. A. MARSHALL[1], B. JOSEPH[4], J. R. MANN[2], F. ALESSANDRINI[2], C. VANOYE[3], A. L. GEORGE[3], D. SIMKIN[2], M. PRUDENCIO[5], L. PETRUCELLI[5], E. KISKINIS[2];
[2]Dept. of Neurol., [3]Dept. of Pharmacol., [1]Northwestern Univ., Chicago, IL; [4]Columbia Univ. Irving Med. Ctr., New York City, NY; [5]Mayo Clin., Jacksonville, FL

Abstract: Cortical hyperexcitability is a broadly observed, yet poorly understood clinical feature of familial and sporadic amyotrophic lateral sclerosis (ALS). Nuclear depletion and cytoplasmic aggregation of the RNA splicing modulator TDP-43 is a unifying neuropathological feature identified in most ALS patients. Here, we sought to examine a potential association between TDP-43 dysfunction and neurophysiology. By integrating gene expression datasets from human iPSC-derived neurons depleted of TDP-43 and postmortem ALS tissue we identify spurious skipping of exon 5 of the voltage-gated potassium channel KCNQ2 (Kv7.2). KCNQ2 forms heterotetrameric channels with other Kv7 subunits to conduct M-current and regulate repetitive firing and excitability in neurons. We show that KCNQ2 is sensitive to TDP-43 levels and aberrant pre-mRNA processing yields a non-functional protein that disrupts neuronal excitability, accumulates within the ER in iPSC-derived neurons and forms abundantly present ubiquitinated aggregates in postmortem spinal cord tissue from ALS patients. This event strongly correlates with phosphorylated TDP-43 levels and age of disease onset in patients and can be leveraged as a novel biomarker for TDP-43 pathology and ALS diagnosis. Collectively, our work reveals that nuclear TDP-43 maintains the fidelity of KCNQ2 expression and function in

human neurons and provides a mechanistic link between established excitability disturbances in ALS and TDP-43 dysfunction.

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Poster

PSTR064: ALS iPSC Models

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

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Topic: C.06. Neuromuscular Diseases

Support: Philanthropy

Title: Evaluating TDP-43 Dysregulated RNA Splicing in the Periphery as an ALS Biomarker

Authors: *N. KINNEY[1], B. K. JENSEN[2], H. S. ILIEVA[2];
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Abstract: Amyotrophic Lateral Sclerosis (ALS) is a devastating progressive neuromuscular disease. Current therapies aim to slow progression with limited efficacy and there are no curative drugs. Disease biomarkers are of critical importance for diagnostic (accurate diagnosis of disease), prognostic (determining disease progression), and therapeutic purposes (measuring effect of disease modifying drugs). Elevations in cerebrospinal fluid (CSF) and blood neurofilaments (NF) have begun to be used as a diagnostic biomarker for pre-clinical ALS. Reductions in NFs are also used in clinical trials as a therapeutic outcome measure. However, increases in NF levels are not ALS specific, as they are associated with several other neurodegenerative conditions. Thus, a disease specific biomarker is needed. Cytoplasmic aggregation and subsequent dysfunction of TDP-43, a DNA/RNA binding protein involved in RNA splicing, is a hallmark of ALS pathophysiology. TDP-43 dysregulation can cause non-canonical splicing of various RNA transcripts that can reduce protein expression levels and/or disrupt function. One such abnormal variant which has been detected across animal and cell models is a deletion of exon 3 in the POLDIP3 gene. POLDIP3 encodes for an RNA binding protein which is ubiquitously expressed. In this study, we aimed to determine if POLDIP3 RNA for both the normal and non-canonical variant is detectable in peripheral tissues. To do this, we first knocked down TDP-43 levels to artificially induce alternative splicing of POLDIP3 levels in ALS patient derived fibroblasts and lymphoblasts to determine the level of TDP-43 dysfunction necessary to reveal non-canonical splice variants. We then created a custom panel TDP-43 regulated targets and validated them in our *in vitro* models. We plan to assay our custom panel of TDP-43 regulated RNA targets in human skin and blood in order to query if non-canonical splicing is a viable biomarker target for ALS.

Disclosures: N. Kinney: None. **B.K. Jensen:** None. **H.S. Ilieva:** None.

Poster

PSTR064: ALS iPSC Models

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French Muscular Dystrophy Association
The New York Stem Cell Foundation (NYSCF),
Les Turner ALS Foundation

Title: ALS-linked TDP-43 dysfunction alaters UPF1-mediated mRNA metabolism including alternative polyadenylation and 3'UTR length

Authors: *F. ALESSANDRINI[1], M. WRIGHT[1], T. KUROSAKI[2], L. MAQUAT[3], E. KISKINIS[1];
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Abstract: UPF1-mediated mRNA decay pathways play a crucial role in maintaining cellular homeostasis by surveilling and eventually degrading aberrant transcripts. Moreover, it modulates the expression of 5-10% of physiological genes. However, the precise role of UPF1 in post-mitotic neurons and especially its activity in amyotrophic lateral sclerosis (ALS) remains elusive. The present study focused on defining the role of UPF1 in human MNs, which represent the most vulnerable cellular population in ALS, and understanding the interplay between TDP-43 dysfunction and UPF1-mediated degradation of mRNAs. Utilizing human iPSC-derived spinal motor neurons (MNs), we generated a robust set of UPF1 degradation targets in human MNs by integrating RIP-seq and RNA-seq analysis before and after UPF1 knockdown to identify mRNAs bound by to the phosphorylated active form of UPF1. RNAs targeted by UPF1 in MNs are functionally enriched for autophagy and structurally characterized by highly structured, long 3′-untranslated regions (3'UTRs). We observed that the absence of TDP-43 reduces UPF1 phosphorylation and UPF1-decay efficiency, leading to the accumulation of improperly processed mRNAs. Remarkably, we also found that UPF1 and TDP-43 loss-of-function disrupt alternative polyadenylation (APA) and 3'UTR length of overlapping transcripts, a process that we confirmed to be compromised in neuronal models of ALS *in vitro* and ALS postmortem patient tissue. Our study offers a comprehensive understanding of UPF1-mediated mRNA decay in physiological and diseased motor neurons, highlighting the disruption in APA site selection as a critical neuropathological mechanism in ALS regulated by the both TDP-43 and UPF1.

Disclosures: F. Alessandrini: None. **E. Kiskinis:** None.

Poster

PSTR064: ALS iPSC Models

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR064.19/C59

Topic: C.06. Neuromuscular Diseases

Support: DFG YI 209/1-1, AOBJ 680080
DFG/ANR WE 2791/7-1

Title: Morphological and Transcriptomic Signatures in Patient-derived Motor Neurons carrying ALS causative KIF5A Mutations.

Authors: *I. LOSS[1], R. YILMAZ[1], S. LOGHMANI[1], C. STICHT[2], J. H. WILBERTZ[3], P. KOCH[4], J. WEISHAUPT[1], R. PARLATO[1];
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Abstract: Our group has previously described heterozygous ALS-causing mutations in the *Kinesin Family Member 5A* (*KIF5A*). KIF5A is a kinesin responsible for anterograde transport of proteins, organelles, RNA, and neurofilaments along the neurites. ALS-linked mutations occur in the kinesin's C-terminal cargo-binding domain and are caused by the disruption of exon 27 splicing. In this study we asked what are the consequences of these KIF5A mutations on neuronal morphology and transcription profiles, to identify disease signatures for testing therapeutical approaches. To this end, we generated hiPSCs from one pre-manifest carrier of a heterozygous ΔExon27 mutation (c.3020+2T>C, P1) and from two ALS patients of a family with a c.2993-1G>A heterozygous mutation (P2, P3). cDNA sequencing of *KIF5A* confirmed the skipping of exon 27 in P1, and the shift of its splicing acceptor site in P2 and P3. These mutations alter exon 27 splicing differently, yet both are predicted to lead to the production of a common C-terminal aberrant end. Using a custom antibody targeting the aberrant neopeptide, the endogenous mutant KIF5A expression was detected in hiPSC-derived motor neurons (MNs) from the three patient lines by Western blotting. Immunostaining using an antibody targeting the N-terminal domain of KIF5A, revealed a significant increase in KIF5A inclusions in the neurites of MNs derived from patients compared with controls at day (D) 20. Further analysis of MNs at D35 revealed that the propensity of KIF5A to aggregate is increasing over time in both control and mutant cell lines. These data suggest that KIF5A is aggregation prone per se; however, the presence of the mutation enhances the formation of KIF5A inclusions. Furthermore, immunofluorescence analysis revealed significant morphological changes between control and

patient MNs at D20, such as reduced neurite network but enlarged nuclei and soma. Additionally, bulk RNA sequencing of MNs at D20 and D35 from three healthy individuals and three patients highlighted maturation-dependent alterations in pathways associated with RNA processing, chromatin remodelling, and neuronal projection development. Splicing analysis of the transcriptomic data revealed the GO term vesicle fusion to be significantly upregulated at D20, but not at D35. Taken together, these findings advance our understanding of molecular events occurring at different stages of the disease. Furthermore, they build the foundation for a pre-clinical translational screening platform for the development of new pharmaceutical strategies.

Disclosures: I. Loss: None. **R. Yilmaz:** None. **S. Loghmani:** None. **C. Sticht:** None. **J.H. Wilbertz:** None. **P. Koch:** None. **J. Weishaupt:** None. **R. Parlato:** None.

Poster

PSTR064: ALS iPSC Models

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR064.20/C60

Topic: E.09. Motor Neurons and Muscle

Title: Building a Same Donor Human iPSC-Based Neuromuscular Junction Model from Schwann Cells, Motor Neurons, and Skeletal Muscle for ALS Disease Modeling

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Anatomic Inc., Minneapolis, MN

Abstract: Amyotrophic Lateral Sclerosis (ALS) is a progressive neurodegenerative disease characterized by the loss of motor neurons, leading to muscle weakness and eventual paralysis. Given the critical role of Schwann cells in the maintenance of neuromuscular junctions (NMJs), and the emerging evidence of their involvement in ALS pathology, integrating Schwann cells into NMJ models offers a unique opportunity to study ALS mechanisms and screen for therapeutic agents. This study describes the development of a fully human induced pluripotent stem cell (hiPSC) based NMJ model, incorporating Schwann cell precursors (SCPs), motor neurons, and skeletal myogenic progenitors - all derived from the same donor - to create a promising avenue for studying neuromuscular diseases, drug screening, and tissue engineering applications. Utilizing novel directed differentiation protocols, hiPSCs were efficiently differentiated into SCPs and motor neurons within only 9 and 7 days, respectively, through the exclusive use of growth factors and small molecules to direct cell fate. Skeletal myogenic progenitors were generated from hiPSC-derived teratomas in mice, which were previously shown to possess robust regenerative potency. These differentiated cells were then seeded into commercially available compartmentalized microfluidic devices that separated the muscle cells from neurons/glia to facilitate the formation of functional NMJs. Differentiation efficiency and cell identity were confirmed using specific markers before chips were seeded: S100+/SOX10+/MITF- for SCPs, ISL1+/CHAT+ for motor neurons, and MYOD1+/PAX7+ for

skeletal myogenic progenitors. Both motor neurons and SCPs express TDP43. Motor neurons rapidly extended axons into the skeletal myogenic progenitor compartment, which were successfully timed to terminally differentiate into DESMIN+ myotubes. SCPs were observed aligning with motor neuron axons in the channels as well as migrating towards the end of axon terminals in close proximity to myotubes. Motor neurons were loaded with a calcium dye, and stimulation with the pan-sodium channel activator veratridine showed signal propagation into the muscle chamber and correlated with muscle twitching. The fully hiPSC-based NMJ model, derived from a single donor, offers a new platform for studying neuromuscular diseases and evaluating pharmacological agents. By leveraging this model, we can examine the pathological role of TDP-43 in ALS, including its impact on Schwann cells and NMJ integrity with the aim to advance our understanding of ALS pathology and facilitating the development of targeted therapies for ALS and related neuromuscular conditions.

Disclosures: V. Truong: A. Employment/Salary (full or part-time):; Anatomic Incorporated. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Anatomic Incorporated. **M. Dau:** A. Employment/Salary (full or part-time):; Anatomic Incorporated. **G. McCabe:** A. Employment/Salary (full or part-time):; Anatomic Incorporated. **P. Walsh:** A. Employment/Salary (full or part-time):; Anatomic Incorporated. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Anatomic Incorporated.

Poster

PSTR064: ALS iPSC Models

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR064.21/C61

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: ICMR-CARE II, Government of India (No.5/4-5/Neuro/184/CAR-Phase-II/2018-NCD-I)
NIMHANS, Institute Fellowship (NIMH/A&E-SA3-226/Ph.D/NPHY/NS/2021-22)

Title: Effect of cerebrospinal fluid from sporadic amyotrophic lateral sclerosis patients on kv1.3 channel expression in human microglial cells

Authors: *N. SARKAR[1], D. KRISHNA[1], M. KEERTHIPRIYA[2], S. VENGALIL[2], A. NALINI[2], T. RAJU[3], T. N. SATHYAPRABHA[1], K. VIJAYALAKSHMI[1];
[1]Neurophysiol., [2]Neurol., Natl. Inst. of Mental Hlth. and Neuro Sci. (NIMHANS), Bengaluru, India; [3]Res., Sankara Acad. of Vision, Bengaluru, India

Abstract: Microglia play a vital role in the pathophysiology of Amyotrophic Lateral Sclerosis (ALS) primarily via neuroinflammatory responses. Yet, anti-inflammatory drugs have shown

modest therapeutic response. This is possibly attributed to the complex mechanisms driven by activated microglia ranging from morphological changes, release of inflammatory molecules, abnormal migratory and phagocytic processes to altered expression of ion channels, notably the voltage gated K^+ channel, Kv1.3. Enhanced expression of Kv1.3 is implicated in augmenting neuroinflammatory responses and driving the activated microglia to toxic form by facilitating release of pro-inflammatory mediators and cytotoxic molecules including Reactive Oxygen Species (ROS) and Nitric Oxide (NO). Additionally, it increases Ca^{2+} signaling thereby enhancing their migratory and phagocytic property. Role of Kv1.3 in activating microglia has been documented in animal models of various neurodegenerative diseases including ALS. However, till date there are no studies on human microglial cells, a pressing priority, as the cells of human origin better mimics the patient scenario. To investigate this, a Human Microglial cell line, HMC3 and human microglia-like cells derived from induced pluripotent stem cells of sporadic ALS patients, iMicroglia were exposed to cerebrospinal fluid (CSF) of sporadic ALS patients (ALS-CSF; 10% v/v; n=5 in duplicates) and LPS (10ng/ml) up to 12 hours. Our previous findings on rodent glia demonstrate the toxic effect of ALS-CSF in inducing marked astrogliosis and microgliosis thereby contributing to neuroinflammation. Here, the effect of ALS-CSF on human microglial cells was assessed for expression level of Kv1.3 channel by immunocytochemistry and flow cytometry, morphology changes through live-cell imaging, viability by MTT assay, ROS levels by DCF-DA and NO levels by spectrophotometric assay. Our findings demonstrate up-regulation of Kv1.3 channel alongside increased ROS and NO levels with enhanced viability of the human microglia post ALS-CSF exposure signifying its activated state. Morphologically, transformation of ramified resting form to the phagocytic amoeboid form was prominently seen following exposure to ALS-CSF. Thus, our study demonstrates the toxic effect of ALS-CSF on activation of microglia of human/patient origin too. It emphasizes the possible role of Kv1.3 channel expression in driving microglial activation to the detrimental form. Our ongoing investigations with Kv1.3 channel blockers will provide deeper insights on driving microglial activation to protective form thereby modulating neuroinflammatory responses in ALS.

Disclosures: N. Sarkar: None. **D. Krishna:** None. **M. Keerthipriya:** None. **S. Vengalil:** None. **A. Nalini:** None. **T. Raju:** None. **T.N. Sathyaprabha:** None. **K. Vijayalakshmi:** None.

Poster

PSTR065: Neuroinflammation: Animal Models

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR065.01/C62

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Title: Anti-inflammatory and neurotrophic factor production effects of 3,5,6,7,8,3',4'-heptamethoxyflavone on lipopolysaccharide-induced inflammation model mice

Authors: *T. OMASA, A. SAWAMOTO, S. OKUYAMA;
Matsuyama Univ., Matsuyama, Japan

Abstract: Citrus fruits contain many bioactive components, including polymethoxyflavone. Recently, research on citrus fruits and their effects in the central nervous system have received a lot of attention. We are focusing on 3,5,6,7,8,3',4'-heptamethoxyflavone (HMF) in our research and have revealed many effects in some disease models. In recent years, it has been reported that Inflammation is essentially a type of defense response in the body, but if this response becomes chronic, it can be triggers for many diseases. Furthermore, chronic inflammation in the peripheral tissue spreads to the brain and is thought to be closely related to diseases of the central nervous system. Therefore, in this study, HMF (300 mg/kg) was administered to the 9 weeks old mice of C57BL/6N in which inflammation was induced by lipopolysaccharide (LPS; 2 mg/kg), and its effects were evaluated. HMF improved the amount of spontaneous locomotive activity that was reduced in the LPS group 2 days after LPS administration. Additionally, HMF suppressed activated microglia in the hippocampus, which were increased in the LPS group. Next, to confirm whether HMF suppresses inflammation in the periphery, we assayed serum cytokines in a few hours after LPS administration. However, HMF did not suppress inflammatory cytokines both in the serum and brain. In the experiment of a chronic inflammatory model mice, LPS (5 mg/kg) was administered on day 1, sample administration was started 8 days later, and brains were collected on day 24. The LPS group showed increased spontaneous locomotive activity compared to the CON group, while the HMF group improved to the same level as the CON group. It did not inhibit microglial activation in the hippocampus; meanwhile, activated astrocytes were increased in the LPS group, and further increase in astrocytes activation was observed in the HMF group. In addition, BDNF production and neurogenesis were promoted by HMF in the hippocampus, and excessive phosphorylation of tau protein was inhibited. In the previous studies, we have reported that HMF penetrates into the brain, and these results together suggested that HMF penetrate into the brain and exert anti-inflammatory and neuroprotective effects directly in the hippocampus.

Disclosures: T. Omasa: None. **A. Sawamoto:** None. **S. Okuyama:** None.

Poster

PSTR065: Neuroinflammation: Animal Models

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR065.02/C63

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Title: Rutin attenuates LPS induced cognitive impairments in male rats by suppressing oxidative stress and inflammation in male rats : An in vivo and in-sillico study

Authors: *A. DUBEY;
Biochem., Univ. of Allahabad, Allahabad, India

Abstract: Microglia induced neuro-inflammation significantly influence the pathogenesis and progression of neurodegenerative disorders, such as Alzheimer's disease, Parkinson's disease, and multiple sclerosis.. The drugs used in the treatment of neurodegenerative disorders are often

accompanied by several side effects. In this study, we are investigating the identification of a novel drug against neuro-inflammatory disorders by using phytochemical eugenol. The rats were orally treated with rutin for ten days prior to LPS injection (5mg/kg I.P.) and after the treatment, assessed for neuro-inflammatory markers, Behavioral dysfunction and oxidative end points. Molecular docking and MD simulations study of the rutin against pro-inflammatory enzymes (Cyclooxygenase and Lipoxygenase) and NF-kB was also assessed to understand their modes of action. In rats exposed to LPS, there were significant decrease in the activity of membrane proteins and ion channels, such as acetylcholinesterase, Na^+-K^+ ATPase, and the low level of reduced glutathione, as well as an increase in the amounts of superoxide anions, hydrogen peroxides, and lipid peroxidation. The rats groups received LPS injections showed mild histopathological alterations in their brains. The rat brain after LPS injection had higher levels of NF-kB, IL-6 and TNF-α transcripts. We discovered that LPS treatment causes cognitive decline in rats along with microglia activation and neuronal cell death in the hippocampus. However, rutin administration attenuated the LPS induced neuro-inflammation by reverting the enhanced level of level of IL-6 and TNF-α. The *in sillico* analysis and MD simulation study showed that the rutin provides a low docking energies against these proteins and stability during simulation with least RMSD and RMSF fluctuation. Our study shows the anti-neuro-inflammatory potential of rutin; thus, rutin may have therapeutic potential to improve cognitive and behavioral function in neuro-inflammation-related diseases. And these data may provide additional insight for researchers performing neuro-inflammation research.

Disclosures: A. Dubey: None.

Poster

PSTR065: Neuroinflammation: Animal Models

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR065.03/C64

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Title: Effect of compounds targeting different mechanisms on LPS-induced neuroinflammation

Authors: *C. SIMMONS[1], L. JAGGER[1], M. PEARCE[1], E. MOKORI[1], N. MODY[1], P. MARCELO[1], J. S. DAVIES[1], R. BRAMMER[1], W. PIJACKA[1], Z. TURNBULL[1], S. P. VICKERS[2], N. MIRZA[3], J. UNITT[4];
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Abstract: Accumulating evidence indicates that neuroinflammation is a common underlying mechanism behind neurodegenerative disorders (e.g. Parkinson's and Alzheimer's disease) and might be key to disease progression. Lipopolysaccharide (LPS) is a potent endotoxin used to model aspects of neuroinflammation. Previously we (i) characterized two LPS serotypes (055 and 0111) for their propensity to increase proinflammatory biomarkers in brains of male

C57BL6/J mice up to 24h post-dose; (ii) determined the effects of acute LPS administration (4h) on gene expression; and (iii) determined the effect of pre-administration of Dexamethasone (Dexa: 10, 30 or 50 mg/kg, p.o.) on LPS-induced neuroinflammation (055, 0.3 mg/kg, i.p). Here, we have tested compounds specific to various targets involved in neuroinflammatory pathways. These included HS-276 (TAK1), GSK2982772 (RIPK1), MCC950 (NLRP3), CA-4948 (IRAK4), Tofacitinib citrate (JAK), Psilocybin (5HT2A), and TAK-242 (TLR4). Dexa was included as a reference. Each compound was dosed at a suitable time before LPS injection, and at 4h post-LPS injection mice were terminated, a post-mortem blood sample collected and centrifuged for plasma. Whole brains were collected on dry ice and homogenized with a pestle and mortar in liquid nitrogen. Gene expression was performed using TaqMan assays, with RT-PCR performed using the CFX384 RT-PCR detection system. Levels of IL-1β, IL-6, TNF-α and IFN-γ mRNA were quantified, and values expressed as mean fold change relative to control ± SEM; n = 10-12 per group. Protein expression levels of these cytokines were also analysed using the MSD multiplex system. TAK-242 (10 mg/kg, ip) significantly reduced mRNA and protein expression of IL-1β, IL-6 and TNF-α compared to LPS-treated mice ($p<0.001$ compared to LPS only group for all three cytokines). Dexa was included as a reference (10mg/kg, po) and significantly reduced LPS induced mRNA and protein expression of IL1-β, IL-6 and TNF-α, as seen in our previous study. Expression of IFN-γ mRNA or protein was not increased significantly by LPS and therefore there was no induced response to be ameliorated. All other compounds tested did not reduce levels of cytokine mRNA or protein expression induced by LPS. Our data show that TAK-242 inhibits the LPS-induced increase in cytokine mRNA and protein expression in a similar manner to Dexa. TAK-242 is a TLR4 inhibitor which is a known receptor for LPS so this response further validates this *in vivo* LPS model as a useful approach for testing the efficacy of novel anti-inflammatory agents against neuroinflammation but may only be useful for agents either targeting TLR-4 or its immediate downstream components.

Disclosures: C. Simmons: A. Employment/Salary (full or part-time):; Sygnature Discovery. **L. Jagger:** A. Employment/Salary (full or part-time):; Sygnature Discovery. **M. Pearce:** A. Employment/Salary (full or part-time):; Sygnature Discovery. **E. Mokori:** A. Employment/Salary (full or part-time):; Sygnature Discovery. **N. Mody:** A. Employment/Salary (full or part-time):; Sygnature Discovery. **P. Marcelo:** A. Employment/Salary (full or part-time):; Sygnature Discovery. **J.S. Davies:** A. Employment/Salary (full or part-time):; Sygnature Discovery. **R. Brammer:** A. Employment/Salary (full or part-time):; Sygnature Discovery. **W. Pijacka:** A. Employment/Salary (full or part-time):; Sygnature Discovery. **Z. Turnbull:** A. Employment/Salary (full or part-time):; Sygnature Discovery. **S.P. Vickers:** A. Employment/Salary (full or part-time):; Sygnature Discovery. **N. Mirza:** A. Employment/Salary (full or part-time):; Sygnature Discovery. **J. Unitt:** A. Employment/Salary (full or part-time):; Sygnature Discovery.

Poster

PSTR065: Neuroinflammation: Animal Models

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR065.04/C65

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: MJFF/ASAP

Title: Rgs10 - critical determinant of peripheral immune cell homeostasis and neuroprotection after exposure to systemic chronic inflammation.

Authors: *J. JERNIGAN[1], H. STALEY[1], J. HOLT[2], M. BOLEN[1], C. COLE[1], N. NEIGHBARGER[1], A. MERCHAK[1], K. MENEES[1], M. G. TANSEY[3];
[1]Univ. of Florida, Gainesville, FL; [2]Neurosci., Universtity of Florida, Gainesville, FL; [3]Neurosci., Univ. of Florida, Gainesville, FL

Abstract: Chronic systemic inflammatory diseases (CSID) represent the most significant cause of death in the world. While multiple risk factors that trigger CSIDs (including inflammatory bowel disease, type-2 diabetes, etc.) have been epidemiologically associated with risk for Parkinson's Disease (PD), the role of peripheral immune cell dysregulation in this process has been underexplored. Regulator of G protein signaling - 10 (RGS10) is highly expressed in immune cells and has been implicated in multiple diseases associated with aging and chronic inflammation including PD. Interestingly, subjects with idiopathic PD display reduced RGS10 levels in subsets of peripheral immune cells. Based on these findings, we hypothesize that **RGS10 maintains homeostatic peripheral immune cell effector functions and protects the CNS from chronic systemic inflammation-induced degeneration.** We induced CSI through biweekly intraperitoneal injections of low dose (1X10^6 Eu/Kg) LPS for 6 weeks in 5-7 month-old male and female C57BL6/J WT mice and RGS10 KO mice to investigate peripheral immune cell function and nigrostriatal pathway vulnerability. 24 hours post last injection, tissues were either flash frozen or processed for flow cytometry the same day. Protein and RNA were extracted from frozen tissues for QPCR and immunoblot analyses. Preliminary findings demonstrate that RGS10 KO animals exposed to CSI displayed increased levels of tyrosine hydroxylase (TH) and dopamine transporter (DAT) mRNA and protein in the ventral midbrain along with exacerbated proinflammatory gene expression. Additionally, the induction of neuroinflammation via CSI coincides with increased peripheral immune cells in and around the brain. Further analyses will confirm the induction of neuroinflammation, changes in dopaminergic tone in the ventral midbrain, and the presence/activation status of peripheral immune cells in the brain and the peripheral circulation in both sexes. The observed increase in the level of dopamine-related proteins in RGS10 KO mice triggered by CSI could be due to neuronal stress as a result of increased traffic of peripheral immune cells into the brain, suggesting a regulatory role for RGS10 in peripheral immune cell trafficking during chronic inflammatory stress conditions that compromise neuronal function and survival. Completion of these studies will advance our understanding of protective mechanisms involved in safeguarding the brain against CSIDs and risk for neurodegeneration. Future experimentation will assess the specific impact of the RGS10 deficient peripheral immune cell functions on CSI-induced degeneration via the use of bone marrow chimeras.

Disclosures: J. Jernigan: None. **H. Staley:** None. **J. Holt:** None. **M. Bolen:** None. **C. Cole:** None. **N. Neighbarger:** None. **A. Merchak:** None. **K. Menees:** None. **M.G. Tansey:** 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.; INmune Bio, Biogen/IONIS, Merck,

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Poster

PSTR065: Neuroinflammation: Animal Models

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR065.05/C66

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: NIH Grant AI129198
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Japanese Society for the Promotion of Science
Uehara Memorial Foundation
Astellas Foundation for Research on Metabolic Disorders

Title: Three-dimensional inner ear pathology in mice with audiovestibular dysfunction caused by Lassa virus infection

Authors: *M. H. SAITO[1], R. COOK[1], J. MARUYAMA[2], S. PAESSLER[2], T. MAKISHIMA[1]; [1]Otolaryngology, [2]Pathology, The Univ. of Texas Med. Br., Galveston, TX

Abstract: Purpose: Lassa fever (LF) is a viral hemorrhagic fever caused by infection with Lassa virus (LASV) endemic to West Africa. The audiovestibular dysfunction is a significant sequela of LF survivors. This study explored the 3D cochlear and vestibular pathology in our LF mouse model using tissue clearing techniques with lightsheet microscopy.
Methods: Stat1 knockout mice infected with LASV underwent weekly ABR and DPOAE testing and observation of vestibular behavior. Temporal bones were collected, fixed in 10% formalin > 7 days, and processed for tissue clearing with a modified Sca/e S protocol (Hama et al. Nat Neuosci, 2015. 18(10):1518-1529). The whole temporal bone was labeled with cell-type specific markers and antibodies, imaged using lightsheet microscopy, and reconstructed in 3D for spatial analysis of inner ear cells.
Results: LASV-infected mice showed severe hearing loss and behaviors suggestive of vestibular dysfunction such as head bobbing and tilting. LASV-infected cochlea showed minimal changes to the inner and outer hair cells from apical to basal turn, but showed significant damage to the spiral ganglion cells and neuronal structures along with infiltration of T-lymphocytes. In the vestibule, damage to the neuronal structures and stroma underlying the sensory epithelium was observed while the hair cells were largely unaffected.
Conclusions: The combined application of tissue clearing and labeling with cell-type specific marker antibodies was suitable for 3D imaging of the LF model mice temporal bones at a single-cell resolution. We conclude that direct damage to the inner ear hair cells is not the main mechanism of LASV infection-induced audiovestibular dysfunction.

Disclosures: M.H. Saito: None. **R. Cook:** None. **J. Maruyama:** None. **S. Paessler:** None. **T. Makishima:** None.

Poster

PSTR065: Neuroinflammation: Animal Models

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR065.06/C67

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: ANID-Subdirección de Capital Humano/Doctorado Nacional/2022-21221569
FONDECYT-1210375

Title: Sars-cov-2 spike protein s1 increases the activity of astroglial hemichannels: potential implications for cellular dysfunction and neurocovid

Authors: *J. PRIETO, A. FARÍAS, S. VERGARA, J. A. ORELLANA;
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Abstract: NeuroCOVID refers to neurological symptoms observed in individuals with COVID-19 and Long-COVID, including hypogeusia, hyposmia, headaches, cognitive decline, and encephalitis. However, it remains uncertain whether these symptoms arise from SARS-CoV-2 virus itself, the associated systemic inflammation, or viral proteins (e.g., spike protein S1 [spike S1]). Relevantly, the persistent activation of hemichannels composed by connexin-43 (Cx43) or pannexin-1 (Panx1) plays pivotal roles in amplifying the cellular damage induced by viruses in astrocytes. Moreover, during infection, the spike S1 is cleaved from SARS-CoV-2 and released into the interstitium. From there, it can cross the blood-brain barrier, directly affecting brain cells. The question of whether spike S1 affects the activity of hemichannels and how this modulation might impact astroglial cellular function remains unanswered. In this context, we stimulated primary astrocyte cultures or acute brain slices of mice with spike S1 (10-1000 pM) for 1-72 h or 1-3 h, respectively. By using the technique of dye uptake combined with epifluorescence and confocal microscopy, we found that spike S1 led to a time and concentration-dependent increase in the activity of both Cx43 and Panx1 hemichannels in astrocytes. These responses were sensitive to the inhibition of the metabotropic glutamate receptor, the glutamatergic ionotropic NMDA receptor, and the enzyme cyclooxygenase-2, suggesting the involvement of these pathways in the spike S1-induced activation of astroglial hemichannels. Notably, the opening of hemichannels evoked by spike S1 in astrocytes resulted in the increased production of nitric oxide, a high release of ATP, and exacerbated ATP-induced $[Ca^{2+}]_i$ dynamics, as measured by DAF-FM, luciferin/luciferase, and FURA-2 fluorescent/bioluminescent essays, respectively. We hypothesize that spike S1-induced opening of astroglial Cx43 and Panx1 hemichannels could contribute to the pathogenesis and progression of NeuroCOVID.

Disclosures: J. Prieto: None. **A. Farías:** None. **S. Vergara:** None. **J.A. Orellana:** None.

Poster

PSTR065: Neuroinflammation: Animal Models

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR065.07/C68

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: Fauna Bio and University of Florida Research Agreement AGR00025126

Title: Foreign body response from implanted cortical-neuro probes in the spiny mouse

Authors: J. GAIRE[1], *B. SAJDAK[2], S. PENA[1], P. MCNAMARA[2], C. LOPEZ[2], M. MADEN[1]; [1]Univ. of Florida, Gainesville, FL; [2]Fauna Bio, Emeryville, CA

Abstract: Spiny mice (Acomys species) are remarkable rodents known for their exceptional regenerative abilities. They can perfectly regrow various tissues, such as skin, muscle, kidney, and spinal cord, with minimal or no scarring. This ability is of interest because excessive scarring, known as organ fibrosis, disrupts normal tissue structure and function. This phenomenon shares similarities with the foreign body response (FBR), which occurs when the body reacts to biomedical implants including neural implants, potentially leading to their failure. This study aims to investigate whether the "fibrosis-free" regeneration observed in peripheral organs of Acomys extends to the brain, specifically the cortex. To do so, we implanted intracortical microelectrodes into the cortices of both regenerative Acomys and Mus, a traditional laboratory animal known for healing through scar formation. We euthanized the animals at 4 and 28 days post-implantation (DPI) and examined their brains. Histological assessments were conducted to characterize the FBR, and RNA sequencing was performed to identify differentially expressed genes. Immunostaining of brain sections was carried out using specific markers for microglia/macrophages (Iba1), reactive astrocytes (GFAP), and neuronal nuclei (NeuN), followed by imaging with a confocal microscope. Compared to Mus, we observed fewer Iba1+ cells at 4 DPI and reduced GFAP+ intensity at 28 DPI near the implant site in Acomys. Additionally, there was a higher number of NeuN+ cells around the implant in Acomys, suggesting a diminished glial response compared to Mus. In summary, our findings reveal unique differences in the response of Acomys and Mus to cortical foreign body insult. Further investigations are underway to identify the genes associated with the reduced FBR observed in Acomys.

Disclosures: J. Gaire: None. **B. Sajdak:** None. **S. Pena:** None. **P. McNamara:** None. **C. Lopez:** None. **M. Maden:** None.

Poster

PSTR065: Neuroinflammation: Animal Models

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR065.08/C69

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: Chaire Fondation Caroline Durand en traumatologie aiguë de l'Université de Montréal

Title: Neurochemical Impact of Single and Repeated Concussions: Insights from In Vivo Microdialysis in a Rat Model

Authors: *I. MASSE[1], L. MOQUIN[2], A. P. GRATTON[2], L. DE BEAUMONT[3];
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Abstract: This study utilizes *in vivo* cerebral microdialysis to explore the neurochemical sequelae of single and repeated concussions in a novel rat model, providing a detailed assessment of the acute biochemical responses in the brain. Using a refined weight-drop technique that closely mimics the mechanical forces associated with concussive impacts, we continuously monitored the extracellular levels of critical amino acids in the hippocampus - specifically glutamate, GABA, taurine, glycine, glutamine, and serine - immediately before, during, and after concussive events. Our results indicate a significant increase in the levels of glutamate, the primary excitatory neurotransmitter, and taurine, a neuromodulator known for its neuroprotective properties, following the first concussion. These increases suggest an excitotoxic response potentially leading to neuronal damage. Interestingly, when a second concussion was administered within an hour - prior to the resolution of the neurochemical and metabolic disturbances from the first impact - the subsequent increases in glutamate and taurine were less pronounced. This finding suggests adaptive or protective neurochemical changes that may reduce the vulnerability to subsequent injuries. Moreover, the prolongation of righting times after repeated concussions highlights a cumulative impairment of neurological function, reinforcing the need for adequate recovery time between concussions to prevent long-term neurological deficits. These results are crucial as they contribute to our understanding of the biochemical pathways involved in concussion and provide a basis for developing targeted interventions to prevent or mitigate the effects of repeated brain injuries. This study underscores the importance of monitoring neurochemical changes following concussive impacts and the potential neuroprotective mechanisms that may be activated following repeated injuries. The insights gained from this research are critical for shaping future therapeutic strategies and for informing guidelines on managing concussions to minimize long-term adverse effects.

Disclosures: I. Masse: None. **L. Moquin:** None. **A.P. Gratton:** None. **L. De Beaumont:** None.

Poster

PSTR065: Neuroinflammation: Animal Models

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR065.09/Web Only

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: Turkish Academy of Sciences (TD)

Title: Cortical spreading depolarization induces heightened TSPO expression in dural fibroblasts in a migraine model

Authors: C. CAKIR-AKTAS[1], E. ERDENER[1], M. A. MOSKOWITZ[2], *T. DALKARA[3]; [1]Inst. of Neurolog. Sci. and Psychiatry, Hacettepe Univ., Ankara, Turkey; [2]Dept. of Neurol. and Radiology, Harvard Med. Sch., Boston, MA; [3]Neurosci. and Mol. Biol. and Genet., Hacettepe Univ. Inst. of Neurolog. Sci. and Psychiatry AND Bilkent Univ., Ankara, Turkey

Abstract: Inflammatory processes in the meninges and brain play an important role in the pathogenesis of migraine. Positron emission tomography (PET) with Translocator Protein (TSPO)-binding ligands has revealed increased signals in both meningeal and parenchymal tissues in humans after migraine with aura attacks. TSPO, expressed in the outer mitochondrial membrane, is a marker of activated inflammatory cells. However, the change in meningeal TSPO has not previously been studied in experimental migraine models. In this study, we aim to understand whether there is an increase in meningeal TSPO levels in mice following cortical spreading depolarization (CSD), neurophysiological correlate of aura, and to elucidate cellular origin of the TSPO response. CSD was induced by a single pinprick in Swiss Albino mice and was validated with laser speckle contrast imaging. Mice were transcardially perfused with 4% PFA 24-hours after CSD induction. Whole-mount preparations of dura were immunolabeled for TSPO and the perivascular macrophage marker F4/80. Dural fibroblasts were identified morphologically and distinguished by absence of F4/80 staining. The levels of TSPO in the dura was also quantified by Western blotting in a separate group of mice. Our findings reveal robust baseline TSPO expression in meningeal cells, encompassing vascular smooth muscle, macrophages, and fibroblasts in naive and sham-operated mice. Twenty-four hours after a single CSD, TSPO signal intensity significantly increased in fibroblasts and to a lesser extent in perivascular macrophages ipsilateral to CSD. The increase in dural TSPO was confirmed with Western Blotting. These data show that TSPO exhibits robust baseline expression in meninges, which further increases mainly in fibroblasts 24 hours after CSD. The elevation in TSPO is consistent with PET studies in migraine patients and suggests the impact of intense neuronal activity to changes in an inflammation-related connective tissue protein and its potential involvement in the pathophysiology of dural neurogenic inflammation and headache.

Disclosures: C. Cakir-Aktas: None. **E. Erdener:** None. **M.A. Moskowitz:** None. **T. Dalkara:** None.

Poster

PSTR065: Neuroinflammation: Animal Models

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR065.10/C70

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: Hacettepe University Scientific Research Projects Coordination Unit, TSA-2017-14418
Scientific and Technological Research Council of Turkey (TUBITAK), 118S435

Title: Cortical spreading depolarization induces distinct transcriptomic responses in neurons, astrocytes, and microglia, shifting from pro to anti-inflammatory signaling within 24 hours. A potential mechanism contributing to headache termination

Authors: *Z. KAYA[1,2], N. BELDER[3], M. SEVER-BAHCEKAPILI[3], E. ERDENER[3], B. DONMEZ-DEMIR[3], C. BAGCI[3], M. KÖROGLU[4], K. BILGUVAR[5], T. DALKARA[6]; [1]Hacettepe Univ., Ankara, Turkey; [2]Hacettepe University Institute Of Neurological Sciences and Psychiatry, Ankara, Turkey; [3]Hacettepe Univ. Inst. Of Neurolog. Sci. and Psychiatry, Ankara, Turkey; [4]Biostatistics and Bioinformatics, Acibadem Mehmet Ali Aydinlar Univ., Istanbul, Turkey; [5]Dept. of Genome Studies, Hlth. Sci. Inst., Acıbadem Mehmet Ali Aydınlar Univ., Istanbul, Turkey; [6]Neurosci. and Mol. Biol. and Genet., Hacettepe Univ. Inst. of Neurolog. Sci. and Psychiatry AND Bilkent Univ., Ankara, Turkey

Abstract: Cortical spreading depolarization (CSD), the presumed neurophysiological event underlying aura may trigger migraine headaches through inflammatory signaling originating in neurons and spreading to the meninges by way of astrocytes. The transition from pro-inflammatory to anti-inflammatory mechanisms is pivotal for resolution of inflammation, a process that remains poorly understood in the context of CSD and termination of migraine headaches. This study aims to elucidate the progression of post-CSD inflammatory signaling and its resolution in neurons, astrocytes, and microglia in mouse brains. CSD was triggered optogenetically or by pinprick. The cell-specific distribution of active NF-κB pairs, along with subsequent transcriptomic changes was evaluated using immunofluorescence, western blotting, coimmunoprecipitation, FRET analysis, and cell-specific transcriptomics. Following the transient release of pro-inflammatory mediators high mobility group box 1 (HMGB1) and IL1-β from neurons, we detected the pro-inflammatory NF-κB p65:p50 pairs, alongside the anti-inflammatory cRel:p65 pairs in astrocyte nuclei shortly after CSD. However, 24 hours post-CSD, the former disappeared while the latter persisted, indicating a shift from pro-inflammatory to anti-inflammatory transcriptional activity in astrocytes. Pathway analysis of cell-specific transcriptomic data confirmed NF-κB-related pro-inflammatory transcription in non-neuronal cells 1-hour post-CSD, whereas no such activity was observed in neurons. The analysis with Bayesian cell proportion reconstruction revealed that microglia exhibited transcriptional changes in non-NF-κB inflammatory signaling pathways, indicating that CSD induces segregated transcriptional changes in neurons, astrocytes, and microglia. Consistent with the transcriptional data, no p65 nuclear translocation and inflammatory morphological phenotype were observed in microglia, suggesting that microglia may contribute to synaptic repair by surveilling injured dendrites with their processes, while inflammatory signaling in astrocytes can potentially stimulate/modulate the meningeal nociceptor activity through astrocyte endfeet abutting

subarachnoid and perivascular spaces. In conclusion, following a single CSD, distinct transcriptomic responses occur in neurons, astrocytes, and microglia, suggesting tightly regulated inflammatory signaling, which is largely terminated within 24 hours, thus potentially contributing to headache resolution.

Disclosures: Z. Kaya: None. **N. Belder:** None. **M. Sever-Bahcekapili:** None. **E. Erdener:** None. **B. Donmez-Demir:** None. **C. Bagci:** None. **M. Köroglu:** None. **K. Bilguvar:** None. **T. Dalkara:** None.

Poster

PSTR065: Neuroinflammation: Animal Models

Location: MCP Hall A

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Program #/Poster #: PSTR065.11/C71

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: NIH Grant NS116914

Title: Chronic Poly I:C alters expression of serotonin transporter in discrete brain regions

Authors: *M. S. SCHRIER[1], P. A. GAJEWSKI-KURDZIEL[2], S. J. MCGOVERN[1], Z. FILLIBEN[1], T. ZHANG[1], N. QUAN[1,3], R. D. BLAKELY[1,3];
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Abstract: Serotonin (5-HT) is an essential neuromodulator and its high-affinity transporter (SERT) limits its extracellular accumulation to constrain the actions of 5-HT spatially and temporally. Elevated SERT mRNA outside the raphe nucleus (RN) following immunological challenge has been reported, with SERT immunoreactivity co-localized with astrocytic markers. Astrocyte SERT upregulation has also been implicated in the elaboration of fatigue-like behavior following systemic Poly I:C (PIC) administration. In an effort to better elucidate the localization and regulation of non-neuronal SERT in vivo and the impact of non-neuronal SERT on behavior, we developed a novel chronic PIC paradigm which combines intranasal and intraperitoneal administration. Adult female C57/BL6 mice were individually housed in digital ventilated cages (DVC®) prior to and during a 5 day PIC exposure paradigm to track home cage locomotor activity, defined by total horizontal distance moved. Mice were treated for 5 days with 10 mg/kg intraperitoneal injections of high molecular weight PIC or saline. On days 1, 3, and 5, mice were additionally given 40 ng of PIC or 20 μL saline intranasal drops. Frontal cortex, hypothalamus, both hippocampi, midbrain, olfactory bulb, and cerebellum were collected 5 hours after treatment on the 5th day post PIC administration. RNA analysis revealed that chronic PIC administration led to a 4.6-fold increase in SERT mRNA in the hippocampus, with increases also present in the hypothalamus and olfactory bulb. We additionally found increased inflammatory markers throughout the brain including increases in hippocampal IL-1R1, IL-1β, TNF-α, and IL-

6. SERT and cytokine mRNA in hippocampal tissue were positively correlated with each other, but negatively correlated with mouse locomotor activity. Immunohistochemical studies failed to identify a cellular site of increased SERT in brain parenchyma. However, we found that SERT mRNA elevations were absent if mice were perfused with saline prior to tissue collection, suggesting a peripheral source as responsible for systemic PIC increases in SERT mRNA. Ongoing studies seek to identify the relevant peripheral cell type(s) and evaluate their relevance for neuroinflammation and fatigue-like behavior.

Disclosures: M.S. Schrier: None. **P.A. Gajewski-Kurdziel:** None. **S.J. McGovern:** None. **Z. Filliben:** None. **T. Zhang:** None. **N. Quan:** None. **R.D. Blakely:** None.

Poster

PSTR065: Neuroinflammation: Animal Models

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Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR065.12/C72

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: Baylor University

Title: Using the murine Lewis Lung Cancer model to examine the impact of diet-induced obesity on tumor-associated neuroinflammation

Authors: *C. G. FOWLER, R. RODRIGUEZ, A. G. BEAUDRY, L. E. KUSUMO, A. E. GILLETT, M. P. WIGGS, M. L. LAW, E. G. VICHAYA;
Baylor Univ., Waco, TX

Abstract: In the United States, obesity prevalence is at an all-time high, impacting an estimated 42% of the population. Obesity has been linked to an increased risk of developing certain types of cancers and is also a common co-morbidity in cancer patients. Obesity in these patients can be associated with poor clinical outcomes and increased symptom burden. As cancer-related symptoms and obesity have been associated with alterations in neuroinflammatory processes, we sought to use a murine model to examine the interaction between cancer and obesity-associated neuroinflammation in a murine model. We hypothesized that diet-induced obesity would result in neuroinflammatory priming and exacerbate tumor-associated neuroinflammation within the hippocampus. To examine this interaction, we used two different time courses to induce obesity in C57BL6J mice: (1) 9 weeks of 45% high-fat diet (HFD) and (2) 24 weeks of 45% HFD with 10% fructose water. Following obesity induction, we injected mice with 5 x 105 Lewis Lung Carcinoma (LLC) cells or PBS subcutaneously into the flank. Tumors were grown to maximum tumor burden criteria (19 - 25 days), and tissue was collected. Relative expression of proinflammatory cytokines was measured in the hippocampus via qPCR. Analysis of neuroinflammation in the hippocampus of 9-week diet fed mice demonstrated an expected elevation in Il1b in the tumor-bearing mice, but also lower Il6, Itgam, and Gfap. HFD non-tumor mice exhibited decreased Il1b as compared to control diet non-tumor mice. Following 24 weeks

of diet, we failed to observe the expected tumor-induced increase in Il1b in control mice. This may, in part, be related to increased variability in the control group due to their more advanced age, as well as the early termination time required in the HFD-tumor-bearing mice due to accelerated tumor growth rates. We did observe a significant time-by-diet interaction for Il1b, such that the tumor was associated with lower levels in control mice, but elevated levels in HFD treated mice. A similar trend was observed with Tnf. Overall, the results from our experiments indicate that long-term HFD consumption, at both the 9- and 24-week timepoints, does not prime the neuroinflammatory response to the LLC tumor. Rather, the HFD seemingly induces an anti-neuroinflammatory effect, potentially indicative of an adaptive mechanism to maintain neuronal homeostasis in the context of a chronic disruption. Future research on the intersection between cancer and obesity is necessary to better understand their combined effects on the brain and behavior.

Disclosures: C.G. Fowler: None. **R. Rodriguez:** None. **A.G. Beaudry:** None. **L.E. Kusumo:** None. **A.E. Gillett:** None. **M.P. Wiggs:** None. **M.L. Law:** None. **E.G. Vichaya:** None.

Poster

PSTR065: Neuroinflammation: Animal Models

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR065.13/C73

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: Baylor University

Title: Investigating the Antidepressant and Anti-Inflammatory Effects of Resveratrol in a Mouse Model of Diabetes

Authors: *L. E. KUSUMO, R. L. BONNER, G. M. READ, C. G. FOWLER, E. G. VICHAYA; Dept. of Psychology & Neurosci., Baylor Univ., Waco, TX

Abstract: Depression is the leading cause of disability worldwide, negatively impacting quality of life and lifespan. Emerging evidence indicates that depression occurs at higher rates among individuals with chronic diseases. For example, those living with diabetes are at a twofold increased risk of developing depression than those of the general population. While managing a chronic disease likely contributes to this risk, there is evidence to suggest that immunometabolic factors play an important role in depression, particularly in the context of metabolic and inflammatory diseases. To better understand these mechanisms, we have been working with a mouse model of diabetes pharmacologically induced by administration of streptozotocin (STZ). In the current study, we are evaluating the behavioral and immunomodulatory effects of resveratrol (RSV), a potent antioxidant, on STZ-treated mice. We used 8-week-old male C57BL/6J mice and a 2 (+/- STZ) by 2 (+/- RSV) factorial design (n = 6 mice/group). Mice were dosed with 50 mg/kg/day STZ for 5 days or an equal volume of citrate buffer. The first day of STZ was designated Day 0. On experimental day 13, after confirmation of diabetic status

(defined as a blood glucose level exceeding 250 mg/dL), mice were subjected to 21 consecutive days of RSV (80 mg/kg) or vehicle injections. Behavioral testing began two weeks into RSV administration. As expected, STZ effectively induced hyperglycemia with STZ mice reaching, on average, blood glucose levels of 388 ± 29 mg/dL vs 140 ± 6 mg/dL in control mice. As anticipated, STZ was associated with decreased marble burying, poorer nest building, and increased fear conditioning. RSV did not impact blood glucose levels. While there was a trend toward RSV reversing STZ effects on marble burying and fear conditioning, we were statistically underpowered. Future directions will include an additional cohort of mice as to increase the statistical power for behavioral outcome measures. Ongoing tissue analyses will determine if RSV was able to modify markers of neuroinflammation and brain metabolism.

Disclosures: L.E. Kusumo: None. **R.L. Bonner:** None. **G.M. Read:** None. **C.G. Fowler:** None. **E.G. Vichaya:** None.

Poster

PSTR065: Neuroinflammation: Animal Models

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Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: National Science and Technology Council of Taiwan (NSTC 113-2811-B-002-002, NSTC 111-2218-E-A49-033 and NSTC 111-2314-B-A49-045-MY3)
Cheng Hsin General Hospital Foundation (no. CY11113 and CY11006)

Title: Non-invasive Low-intensity Pulsed Ultrasound Improves Neurological Outcomes and Ameliorates Neuronal Inflammation in Experimental Intracerebral Hemorrhage

Authors: *W.-S. SU[1,2], C.-H. WU[3], N. HSIAU[2], S.-F. CHEN[4,5], F.-Y. YANG[2];
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Abstract: Intracerebral hemorrhage (ICH) presents a critical medical condition associated with elevated rates of illness and death. Inflammation mediated by glial cells substantially exacerbates its severity, yet there is currently no recognized effective treatment for clinical ICH. However, low-intensity pulsed ultrasound (LIPUS) has shown potential as a non-invasive neuroprotective method for mitigating damage associated with neurodegenerative disorders. This study aimed to investigate LIPUS as a potential neuroprotective therapy and explore its mechanisms in reducing neuronal inflammation in ICH. We utilized C57BL/6 male mice to evaluate the effects of LIPUS on ICH. ICH was induced by directly injecting bacterial collagenase into the striatum of the mice. We administered non-invasive LIPUS treatment, simulating clinical conditions, over a

span of 3 to 7 days, with a two-hour delay in the initial intervention. The study encompassed a range of assessments, including the evaluation of neurological function, histological analysis, measurement of brain water content and hemoglobin levels, MRI scans, and the analysis of protein expression associated with neurotrophic factors, inflammatory markers, and apoptosis. In vitro experiments were conducted to investigate glia-mediated inflammation by introducing thrombin or conditioned media into primary and cell line cultures. Furthermore, we delved into the effects of LIPUS treatment on the PI3K/Akt signaling pathway, employing the PI3K inhibitor LY294002 for additional analysis. The application of LIPUS treatment led to substantial enhancements in neurological deficits and a decrease in tissue loss, edema, and neurodegenerative processes after ICH. These protective effects were attributed to the suppression of glia-mediated inflammation through the inhibition of the PI3K/Akt-NF-κB signaling pathway. Consequently, this inhibition resulted in reduced cytokine expression and mitigated damage induced by microglial activation in neuronal cells in vitro. LIPUS offers a promising non-invasive therapeutic approach for managing ICH. It effectively enhances neurological outcomes and alleviates brain inflammation by targeting the PAR4-PI3K/Akt/NF-κB signaling pathway. These findings underscore the potential of LIPUS as a valuable treatment strategy for ICH.

Disclosures: W. Su: None. **C. Wu:** None. **N. Hsiau:** None. **S. Chen:** None. **F. Yang:** None.

Poster

PSTR065: Neuroinflammation: Animal Models

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Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: Neural Therapies SL (Ref NT-202401)
MCIN (project CPP2020-008855)
MEC (grant DIN2018-010144)

Title: Assessing behavioral and molecular responses in ischemic stroke models: implications of the time of ischemia

Authors: *A. PUENTE SANZ[1], A. HERRERO[2], D. PEREZ RODRIGUEZ[3], B. ANUNCIBAY[4], M. LETEK[5], A. FERNANDEZ-LOPEZ[1];
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Abstract: Stroke is a major global health concern with an increasing incidence and significant morbidity and mortality rates, without specific treatment so far. Here, we report behavioral and molecular responses after 15 days of reperfusion in two models of transient middle cerebral artery occlusion (tMCAO), comparing 45 min and 60 min occlusion arbitrarily referred as mild

and moderate ischemia.
Twelve-week-old male Sprague Dawley rats were used in tMCAO as previously described (Santos-Galdiano et al., 2018, J. Pharmacol. Exp. Ther. 367(3):528-542) and three experimental groups were compared: 1) sham animals, 2) mild ischemia and 3) moderate ischemia. Experimental assays included behavioral tests (cylinder, adhesive removal, hanging wire, and apomorphine-induced rotation tests), transcriptomic analysis and western blotting.
A significant decrease in infarct volume was observed after 15 days of reperfusion in both mild and moderate models compared to 48 hours of reperfusion. Significant differences in neurological deficits were observed in moderate compared to mild ischemia, especially in the adhesive removal and the apomorphine-induced rotation tests. Transcriptomic analysis, quantitative real time PCR and Western blot revealed significant differences in gene expression. The comparison of the results in these models supports the presence of an ischemia threshold where the tissue damage reaches levels that distinctly modify both molecular and behavioral responses.
This study was supported by Neural Therapies SL (Ref NT-202401) and forms part of the project CPP2020-008855, granted by MCIN/AEI/10.13039/501100011033 and the European Union "NextGenerationEU"/PRTR. Alba Puente Sanz is granted by DIN2018-010144 and Amanda Herrero is granted by DIN2019-010883.

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Poster

PSTR065: Neuroinflammation: Animal Models

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Program #/Poster #: PSTR065.16/C76

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: NRF of Korea Grant 2018R1A6A1A03025221
NRF of Korea Grant RS-2023-00260439
NRF of Korea Grant RS-2023-00210098

Title: Treatment effects of Aquilariae Lignum pharmacopuncture on pain- and depressive-like symptoms in a reserpine-induced chronic fatigue syndrome mouse model

Authors: *J.-H. SONG;
Daejeon Univ., Daejeon, Korea, Republic of

Abstract: Chronic fatigue syndrome (CFS) is accompanied by various symptoms such as pain, depression, sleep disorder, and orthostatic intolerance etc. Aquilariae Lignum (AL) is used for the treatment of neuropsychiatric symptoms (pain, depression, anxiety, and neuropathic inflammation, etc.) in East Asia. In this study, we investigated the improvement effects of AL pharmacopuncture (PA) on pain- and depression-like behaviors through regulation of neuronal

activity, neuropathic inflammation, and microglial activation in the brain regions of reserpine-induced CFS mouse model. After 10 days of reserpine injection, The AL (PA) was administrated at Joksamri (ST36)·Sameumgyo (SP6) acupoints for 10 days. Improvement effects of AL (PA) treatment on the mechanical allodynia and thermal hyperalgesia were demonstrated in the von Frey test and hot plate test. The immobility time was reduced by AL (PA) treatment in the forced swimming test. The number of c-Fos, p-ERK, p-JNK, and p-p38 positive cells were altered by AL (PA) treatment in 24 brain regions. We derived key brain regions such as Cingulate cortex, Arcuate nucleus, Latelal hypothalamus, and Posterior hypothalamus, where the number of c-Fos, p-ERK, p-JNK, and p-P38 positive cells were changed by more than 20% with AL (PA) treatment compared to reserpine treatment. Changes of ionized calcium-binding adapter molecule 1 and transient receptor potential vanilloid 1 expression were similarly observed in the major brain regions affected by AL (PA). Therefore, AL (PA) could be considered a focused treatment method for pain- and depressive-like symptoms of the CFS.

Disclosures: J. Song: 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.; NRF of Korea Grant 2018R1A6A1A03025221, NRF of Korea Grant RS-2023-00260439, NRF of Korea Grant RS-2023-00210098.

Poster

PSTR065: Neuroinflammation: Animal Models

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR065.17/C77

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Title: Astrocytic DICER deletion induces loss of motor function and degeneration of motor neurons in the spinal cord.

Authors: *K. MAYES;
Neurosci. and Regenerative Med., Augusta Univ., Augusta, GA

Abstract: Mature microRNAs (miRNAs) bind to target mRNAs which typically leads to translational repression and downregulation of gene expression. This makes miRNAs important posttranscriptional regulators of gene expression. To investigate the role miRNAs play in the Central Nervous System (CNS) and more specifically in astrocytes, we used a transgenic mouse line with a GFAP:Cre mediated conditional knockout of the endoribonuclease DICER. Using this DICER Knockout model, we characterized the impact of the reduction of mature miRNAs in astrocytes throughout the CNS in a non-cell-autonomous fashion. Early-stage DICER KO mice exhibited normal motor development and function prior to postnatal week 8, but after week 8, DICER KO mice rapidly declined, resulting in a severe reduction or loss of limb motor function, and premature death. Immunohistochemistry staining and confocal imaging were used to characterize the cell population and cell morphological differences in DICER KO mice

compared to a wild type control. This imaging showed that DICER KO mice have increased cell proliferation, altered astrocyte populations, and increased levels of microglia and macrophages in both brain and spinal cord. The greatest increase in activated microglia was seen in the ventral horns of the lumbar region of spinal cord. Light sheet imaging and electron microscopy were also used to investigate these differing cell populations and whole tissues at the subcellular level, revealing deteriorating nuclear membranes in affected motor neurons, as well as other organelles exhibiting morphology indicative of degeneration. These findings suggest motor neuron degradation in the spinal cord compared to wild type controls, which could contribute to phenotypic ataxia and end-stage symptoms seen in DICER KO mice.

Disclosures: K. Mayes: None.

Poster

PSTR065: Neuroinflammation: Animal Models

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR065.18/C78

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Title: Neuroprotective Action of Thymol in Parkinson's disease: Alleviating Mitochondrial Dysfunction and Oxidative Stress-Induced Apoptosis in rat model

Authors: *A. KUMAR;
Dept. of Biochem., Univ. of Allahabad, Allahabad, India

Abstract: Objective:The objective of this study was to evaluate the neuroprotective efficacy of Thymol in MPTP-induced mice models of Parkinson's disease (PD), focusing on its potential to mitigate mitochondrial dysfunction and oxidative stress, which are key contributors to apoptosis-mediated neuronal senescence.Background:Parkinson's disease (PD) is a prevalent neurodegenerative disorder characterized by the degeneration of dopaminergic (DA) neurons in the substantia nigra pars compacta. Mitochondrial dysfunction and oxidative stress are implicated in the pathogenesis of PD, leading to the activation of complex processes resulting in neuronal apoptosis. While treatments for symptomatic relief exist, a cure for PD remains elusive.Method:In this study, Thymol's neuroprotective effects were assessed in MPTP-induced PD rat models. Thymol, known for its diverse biological properties including anti-inflammatory and anti-viral activities, was administered to evaluate its impact on motor coordination and mitochondrial function in the midbrain of MPTP-intoxicated rats. Various parameters including mitochondrial complex activity, antioxidant enzyme levels, apoptotic protein expression, and inflammatory cytokine levels were analyzed.Result:Thymol treatment significantly improved motor coordination in MPTP-intoxicated rats and enhanced the activity of mitochondrial complexes I, IV, and V. This was accompanied by increased levels of superoxide dismutase and mitochondrial glutathione, indicative of reduced oxidative stress. Furthermore, Thymol inhibited the expression of proapoptotic proteins such as caspase-3 and Bax while promoting the expression of antiapoptotic protein Bcl-2. Thymol supplementation also led to the activation of

pAkt1, which inhibited apoptosis of DA neurons. Additionally, Thymol treatment reduced the expression of proinflammatory cytokines TNF-α and IL-6, indicating its anti-inflammatory effects.Conclusion:Thymol demonstrates promising pharmacological properties as a neuroprotective agent against MPTP-induced toxicity in PD rats. Its mechanism of action involves the phosphorylation of GSK3β via activation of Akt/ERK signaling in the mitochondrial intrinsic apoptotic pathway. These findings suggest that Thymol could serve as a potential treatment option for mitochondrial-mediated apoptotic senescence in Parkinson's disease. Further research is warranted to validate its therapeutic potential and elucidate its molecular mechanisms in clinical settings.

Disclosures: A. Kumar: None.

Poster

PSTR065: Neuroinflammation: Animal Models

Location: MCP Hall A

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Program #/Poster #: PSTR065.19/C79

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: DOD Grant CP200074

Title: The targeted signaling of Tumor Necrosis Factor Receptor 2 (TNFR2) in specific tissue types is essential for the resolution of chronic neuropathic pain

Authors: *S. ARNAB[1], R. FISCHER[2], J. R. BETHEA[3];
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Abstract: Chronic neuropathic pain (CNP) arises from persistent neuroinflammatory cascades and the emergence of maladaptive synaptic plasticity in the brain. The intricacies and multifaceted nature of CNP present impediment in its therapeutic intervention, thereby posing challenges in effectively addressing this condition despite its serious clinical conditions among a significant number of populations.Our lab has determined that activating TNFR2, with a specific TNFR2 agonist, helps in reducing neuropathology and neuroinflammation in the brain and is therapeutic in several models of chronic neuropathic pain. To elucidate the involvement of TNFR2 signaling in the brain in modulating neuropathic pain, we used cell specific genetic strategies to target TNFR2 signaling in Nex1+/Neurod6 (Nex-Cre^{ERT2}) neurons in the brain and microglia. To induce CNP we implemented chronic constriction injury (CCI) paradigm and subsequently, we administered a specific TNFR2 agonist intraperitoneally on days 7, 10, and 13 post-CCI induction. Using reflexive and cognitive awareness assessment of pain, we have shown that TNFR2 signaling through Nex1+ neurons is crucial (i) in spontaneous recovery and (ii) TNFR2 signaling in these neurons are critical mitigating chronic neuropathic pain both in male and female. Thus, KO the receptor, mice never recover from CNP even after receiving the TNFR2 agonist. We performed RNAseq analysis to identify the TNFR2 signaling mechanism

through neurons where we observed significant changes in different genes which are involved in different pathophysiological functions such as ion channels, immune regulation, stress response, neuronal development, and outgrowth. With respect to neuroinflammation in chronic neuropathic pain, we deleted TNFR2 in microglia by using tamoxifen inducible CX3CR1-Cre^{ERT2}. And our investigation has revealed sexual dimorphism in microglial TNFR2 signaling, highlighting a necessity for TNFR2 signaling via microglia solely in females, but not males, for the resolution of chronic neuropathic pain. Collectively, our findings suggest that localized TNF signaling is crucial in the pathogenesis of CNP, with TNFR2 playing a significant role in its anti-inflammatory and neuroprotective mechanisms.

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Poster

PSTR065: Neuroinflammation: Animal Models

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR065.20/

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: NIH Grant R01NS120960
NIH Grant MH019112
NIH Grant MH014654

Title: Microglia replacement reveals pathologic and therapeutic contributions of brain macrophages to Krabbe disease

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Abstract: Krabbe disease (globoid cell leukodystrophy) stems from loss of function mutations in *GALC*, leading to galactolipid accumulation and the appearance of lipid-laden multinucleated “globoid” macrophages. These pathognomonic macrophages are reduced following bone marrow transplant (BMT), a treatment that replaces the host’s peripheral immune system and results in low levels of donor cell brain engraftment. BMT extends survival suggesting that replacing diseased macrophages is protective. We developed a model to directly test the contribution of therapeutic brain macrophage replacement in Krabbe disease. Using an inducible Cre system, we

depleted *Galc*-deficient microglia from Twitcher mice and replaced them with *Galc*-WT monocytes via direct intracranial transplantation. As a benchmark for assessing the impact of our therapeutic intervention we characterized macrophage transcriptional states across Krabbe disease progression. Pre-symptomatically, the macrophage response is characterized by the expression of interferon stimulated genes. As the disease progresses, multiple macrophage reactive states arise and expand, chiefly characterized by the expression of interferon stimulated genes, lipid response cassettes, or proliferation markers. Harnessing our sequencing data, we used RNA in situ hybridization to identify a transcriptomic signature of globoid cells, which express a combination of lipid-response genes, and ontogeny markers of both monocyte-derived and yolk sac-derived macrophages. Neonatal replacement of *Galc*-Twi microglia with *Galc*-WT monocytes rescued transcriptomic signatures of disease, indicating donor macrophages can remain healthy in the GALC-deficient environment. Furthermore, we observe that transplantation of *Galc*-WT cells reduced gliosis, reduced toxic lipid accumulation, and extended survival in the Twitcher group. We conclude that early microglia replacement reduces Krabbe disease pathology and normalizes macrophage transcriptional states. These findings suggest an avenue towards improved cell therapies for Krabbe disease.

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Poster

PSTR065: Neuroinflammation: Animal Models

Location: MCP Hall A

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Program #/Poster #: PSTR065.21/C80

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: Neural Therapies SL NT-202402
MCIN CPP2020-008855
"NextGenerationEU"/PRTR
MEC DIN2019-010883
MEC DIN2018-010144

Title: Different pre-treatment strategies of AD-MSCs to modulate microglia

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Abstract: The inflammatory response is the body's immune system reaction against injury and infection. In the nervous system, microglia play a critical role in inflammation and understanding the microglial response is crucial for treating neurological disorders, mainly particularly

neurodegenerative diseases or stroke. Recent studies indicate adipose tissue-derived mesenchymal stromal cells (AD-MSCs) or their secretome can effectively modulate microglial activity, presenting promising therapeutic strategies. Here, we report the effects of various pre-treatments on AD-MSCs to understand their immunomodulatory capacity and secretome profile in an *in vitro* model of inflammation induced by lipopolysaccharide (LPS) in an immortalized microglial cell line of mouse (IMG). AD-MSCs were primed with different stimuli including hypoxia, interleukin-4 (IL-4) or LPS, to modulate their secretory profile. Then, IMGs were co-cultured with primed AD-MSCs, secretome or IL-4 (as a control for anti-inflammatory effects) at different times. Experimental assays included analysis of gene and protein expressions of the different phenotypes of microglia. Results demonstrate a significant modulation of pro-inflammatory and anti-inflammatory cytokines compared with LPS and IL-4 treatment alone. This study suggests that the use of AD-MSCs and their secretome offers an effective and promising approach to immunomodulate the inflammatory response in the central nervous system. This study was supported by Neural Therapies SL (Ref NT-202402) and forms part of the project CPP2020-008855, granted by MCIN/AEI/10.13039/501100011033 and the European Union “NextGenerationEU”/PRTR. Amanda Herrero is granted by DIN2019-010883 and Alba Puente Sanz is granted by DIN2018-010144.

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Poster

PSTR065: Neuroinflammation: Animal Models

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR065.22/C81

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: R01 NS5103212
RF1 NS122174

Title: Conditional MHC class I deletion in Tmem119+ microglia attenuates the brain infiltrating virus antigen specific CD8 T cell response

Authors: *M. PEDRA SEADY, M. A. MAYNES, A. HASSANI, J. THELWELL, C. A. OWENS, M. J. HANSEN, F. JIN, A. J. JOHNSON;
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Abstract: Microglia activation is a hallmark feature of the immune response associated with neurological disease. In neuropathological conditions, microglia become fully competent antigen presenting cells and are proposed to perpetuate T cell activation in the brain. Historically, it has been difficult to define the extent microglia enhance CD8 T cell responses in the brain through MHC class I restricted antigen presentation. H-2K^{b} or H-2D^{b} can be deactivated specifically in Tmem119+ cells using a novel single MHC Class I Cre Lox approach developed by our

laboratory. We aimed to determine the role of microglial MHC class I following intracranial (i.c.) administration of Daniel's strain of Theiler's murine encephalomyelitis virus (TMEV) for the Tmem119creER x D^b (Tmem119 D^b cKO) or Daniel's strain of TMEV encoding for the model antigen OVA (TMEV-XhoI-OVA8) for the Tmem119creER x K^b animals (Tmem119 K^b cKO). We observed a marked reduction in CD8 T cells and K:OVA epitope specific CD8 T cells in the brain in Tmem119 K^b cKO mice compared to Cre- controls but not in Tmem119 D^b cKO mice. This data supports a role for microglia during CNS viral infection and reveals expressive differences between the H-2K^b and H-2D^b MHC class I molecules, implicating this process in protective and pathogenic neurologic conditions.

Disclosures: M. Pedra Seady: None. **M.A. Maynes:** None. **A. Hassani:** None. **J. Thelwell:** None. **C.A. Owens:** None. **M.J. Hansen:** None. **F. Jin:** None. **A.J. Johnson:** None.

Poster

PSTR065: Neuroinflammation: Animal Models

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR065.23/C82

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Title: Mouse neuroinflammation models for brain tissue and interstitial fluid measurements

Authors: *M. S. HEINS, S. HATUSUPY, M. F. OLTHUIS;
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Abstract: Neuroinflammatory processes contribute to disease onset and progression in many neurodegenerative disorders. In healthy individuals, the blood-brain-barrier (BBB) ensures the immune privileged state of the brain and protects it from unrequired inflammatory response and signaling from the periphery. It has been demonstrated that peripheral inflammation e.g. by intraperitoneal (i.p.) lipopolysaccharide (LPS) administration can affect the BBB integrity and thereby result in crossover of inflammatory cytokines and cells. This is a significantly different process from neuroinflammation which is driven by activation of the microglia. Importantly, no peripheral response is observed during the initial neuroinflammatory process. A representative model would thus demonstrate local neuroinflammation with no peripheral effects.
Here, we demonstrate experimental designs for a locally, intracerebroventricular (i.c.v.) induced neuroinflammation model in adult male C57Bl/6J mice. Local response and spread of the neuroinflammation was demonstrated by quantitation of pro-inflammatory cytokine levels in defined brain regions and peripheral fluids after administration of LPS +/- BzATP in canulated animals. In addition, further development of this model allowed us to determine levels of pro-inflammatory cytokine levels in interstitial fluid (ISF) over time by push pull microdialysis. Differential distribution and localization of the pro-inflammatory cytokines following the chosen stimuli was also determined for this experimental design.
Results demonstrate that eliciting a neuroinflammatory response in mouse brain tissue, without peripheral effects, is feasible in a reproducible fashion. When combined with microdialysis a

clear neuroinflammatory response with no peripheral side effects can be followed over time. This allows for evaluation of time related effects of anti-neuroinflammatory compounds in the interstitial fluid. Combined results of brain tissue and microdialysate inflammation data present us with guidelines for choosing optimal experimental designs for a variety of neuroinflammatory research questions. In addition, we have gained a better understanding of the timing effects of priming and activation of the neuroinflammatory response and cytokine production. Resulting in improved and defined models for neuroinflammation specific research.

Disclosures: M.S. Heins: None. **S. Hatusupy:** None. **M.F. Olthuis:** None.

Poster

PSTR065: Neuroinflammation: Animal Models

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Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: The Neuroscience Program, the Office of Research and Graduate Studies,the College of Medicine, the John G. Kulhavi Professorship in Neuroscience, and the E. Malcolm Field and Gary Leo Dunbar Chair in Neuroscience at Central Michigan University

Title: Behavioral and Biochemical Characterization of Neuroinflammation in Aged GFAP-IL6 Transgenic Mice

Authors: *M. M. KINNEY[1,2], G. TAVI[1,2], D. DOYLE[1,2,3], O. SMITH[1,2], D. STORY[1,2], B. SRINAGESHWAR[1,2,3], J. ROSSIGNOL[1,2,3], G. L. DUNBAR[1,2,4];
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Abstract: By producing a chronic state of neuroinflammation, the GFAP-IL6 transgenic mouse line is a relevant model for astroglial and microglial activation, involving pathways linked to neurodegeneration, infection, and aging. Within this model, astrocytes overproduce the IL6 cytokine, leading to the subsequent production of potentially harmful inflammatory cytokines, such as TNF-alpha. The aim of this present study is to identify the behavioral and biochemical hallmarks of this strain, under the conditions of natural aging. We evaluated fifteen 19-month-old hemizygous GFAP-IL6 mice and their wildtype counterparts on a battery of behavioral tasks, including acoustic startle response and prepulse inhibition, spontaneous motor activity in an open-field apparatus, and passive avoidance. Brain tissue was collected following these behavioral trials, and Western blotting and immunohistochemistry was used to identify the spatial and quantitative aspects of proteins related to the neuroinflammatory developments within these mice. Our findings indicated that GFAP-IL6 mice had significantly reduced latency to startle compared to wildtype mice ($p = 0.018$). These behavioral profiles correlated to the biochemical profiles of both populations of mice, suggesting that inflammation is related to behavioral responses in GFAP-IL6 mice, such as a decrement in sensorimotor processing.

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Poster

PSTR066: Stroke: Preclinical Studies

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Program #/Poster #: PSTR066.01/C84

Topic: C.09. Stroke

Support: NRF Grant 2022R1A2C1007948
KHIDI Grant RS-2023-00265165

Title: Effect of CO_2 inhalation in a rat model of collagenase-induced acute intracerebral hemorrhage stroke

Authors: C. YOON[1], Y. KIM[1], J. JUNG[1], *H. NAM[1,2];
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Abstract: Timely intervention is vital for all stroke subtypes. Our research explores the feasibility of initiating treatment in the ambulance, even before a definitive diagnosis of ischemic or hemorrhagic stroke is confirmed. While our previous studies have highlighted the neuroprotective effects of CO_2 inhalation in acute focal ischemic stroke, its impact on intracerebral hemorrhage (ICH) remains unclear. Hence, our aim is to elucidate the effect of CO_2 inhalation on ICH in a rat model. We conducted experiments on 20 Male Wistar rats weighing between 270g to 320g, randomly allocated into four groups (n=5 per group): a sham group, sham+CO_2 group, ICH group, and ICH+CO_2 group. ICH was induced by microinjection of bacterial collagenase Type IV (0.23 U) into the left striatum. Thirty minutes after ICH induction, a 20% CO_2 mixed gas was administered for 45 min, comprising with 3 cycles of inhalation for 5 min followed by 10 min recovery in room air. Neurological outcomes were evaluated by blinded behavioral test using Garcia score, Longa score, and modified neurological severity scores (mNSS) at 24 h post-ICH. Hemorrhagic lesion volumes were assessed via morphometric measurement. Our findings revealed that CO_2 treatment significantly ameliorated neurological impairment at 24 h post-ICH, evidenced by lower mNSS in the ICH+CO_2 group compared to the ICH group (ICH, 10.8±1.48 vs. ICH+CO_2, 4.2±1.30; $p<0.0001$). Additionally, Garcia scores in the CO_2-inhaled ICH group were higher than in the non-CO_2 inhalation ICH group (ICH, 9.4±1.14 vs. ICH+CO_2, 12.2±2.49; $p=0.0312$). Furthermore, hemorrhagic lesion volumes were markedly reduced in the CO_2-treated ICH group compared to the untreated ICH group (ICH, 33.48±7.69mm^3 vs. ICH+CO_2, 12.04±3.25mm^3; $p=0.0004$). These findings provide compelling evidence of CO_2 inhalation's potential to mitigate both hemorrhagic lesion volumes and neurological deficits. CO_2 inhalation may be a promising management both hemorrhagic and ischemic stroke in terms of safety and efficacy. However, our preliminary safety data are

encouraging, concerns regarding potential adverse effects of CO_2 in ICH warrant further investigation, particularly in the context of clinical applications.

Disclosures: C. Yoon: None. **Y. Kim:** None. **J. Jung:** None. **H. Nam:** None.

Poster

PSTR066: Stroke: Preclinical Studies

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR066.02/C85

Topic: C.09. Stroke

Support: NINDS Grant R01NS093057

Title: Estrous cycle hormonal influences on optogenetic stimulation after stroke

Authors: *H. KO[1], T. C. CHIANG[1], H. CHEN[1], N. RADIT[1], R. KOPCHOCK, III[1], M. Y. CHENG[1,2], G. K. STEINBERG[1,2];
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Abstract: A damaged stroke area can affect both local and connected brain regions, causing network-wide disruptions in brain functions. There is growing evidence that estrogen, particularly 17β-estradiol, plays a protective role in brain injuries after ischemic stroke. Understanding how hormonal levels impact brain stimulation interventions such as optogenetic stimulation could shed light on varying responses to neuromodulation therapies across different phases of the estrous cycle. Previously we have shown that optogenetic excitatory neuronal stimulations in the ipsilesional primary motor cortex (iM1) enhanced expression of plasticity markers and promoted functional recovery in male mice. In this study, we aim to expand upon these findings by exploring functional recovery and post-stroke neuroplasticity changes in in female mice. Female C57BL6 mice aged 7-9 weeks underwent stereotaxic surgery to express channelrhodopsins-2 (AAV1-ChR2) and implant an optical fiber in iM1. After undergoing a 30-minute middle cerebral artery occlusion (MCAO), optogenetic stimulation was initiated on day 5 post-stroke and continued for 10 days to study its effects on recovery in conjunction with hormonal changes. Estrous cycle changes were assessed through vaginal swabbing and ELISA to analyze interactions between hormonal changes, optogenetic stimulation, and recovery process. Rotating beam tests were performed at pre-stroke, 4, 7, 10, and 14 days after stroke. Histological evaluations focused on the changes of astrocytic activation and microglia/macrophage activation in iM1 region using glial fibrillary acidic protein (GFAP) and CD68 respectively. We observed that after stroke, the phases of diestrus and estrus lasts noticeably longer (>60% of the recorded total estrus cycle days) in majority of mice, and this pattern persisted throughout the optogenetic stimulation period. Furthermore, our results indicate that female mice subjected to optogenetic stimulation exhibit improvements in motor functions, which were associated with changes in CD68 expression in iM1. There were also noticeable differences in post-stroke recovery depending on the estrous cycle stages, with optogenetic stimulation enhancing motor function

during specific phases. These results highlight the importance of considering hormonal cycles in stroke treatment and post-stroke care, and suggest that optogenetic stimulation tailored to specific estrous hormonal phases may optimize recovery outcomes.

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Poster

PSTR066: Stroke: Preclinical Studies

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR066.03/C86

Topic: C.09. Stroke

Title: Improvement of motor function post-stroke: Graphene-Based multichannel electrode array intervention in rat model

Authors: *G. KIM[1], S. YANG[2,3,4], D. KIM[5], E. BAEG[6];
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Abstract: Improvement of motor function post-stroke: Graphene-Based multichannel electrode array intervention in rat model
Gaeun Kim[1*], Donggue Kim[1, 2], Doyoung Lee[1], Junsu Park[1] Eunha Baeg[1], Sungchil Yang[4], Sunggu Yang[1, 2, 31]Department of Nanobioengineering, Incheon National University, Incheon, 22012, Republic of Korea.[2]Center for Brain-Machine Interface, Incheon National University, Incheon, 22012, Republic of Korea.[3]gBrain Inc., Incheon 21984, Republic of Korea.[4]City University of Hong Kong, Hong Kong
Ischemic strokes are a pathological symptom that arises from a brain infarction. The central cause of ischemic strokes is the occlusion of arterial blood vessels. The location of an occluded blood vessel determines a neuropathological symptom associated with the brain area. Currently, ischemic strokes are treated by thrombolytic therapy or stent procedures to achieve reperfusion of blocked blood vessels. Prompt reperfusion can lead to a full recovery; however, delays can result in persistent post-stroke impairments, including motor dysfunction. In this study, we focused on the motor cortex, which plays a significant role in post-stroke motor deficits. We would like improve motor function using graphene-based multichannel electrode array (MEA). MEA can stimulate and record brain waves in the motor cortex. To simulate an infarction in the motor cortex, we induced photothrombotic stroke (PT) in rats and assessed functional outcomes through behavioral tests. After stroke induced, modified neurological severity score is increased and motor function rotarod test and gait test is decreased. Through these results, we confirmed the induction of stroke. We had an implantation of MEA in a stroke-induced rat, stimulated the

motor cortex with 100 Hz theta burst stimulation (TBS), and recorded brain waves. we anticipate motor function improvement through electrical stimulation and stroke diagnosis via brain wave analysis.
Keyword: Stroke, Motor function, Electrical therapy, Brainwave, Wireless technology

Disclosures: G. Kim: None. **S. Yang:** None. **D. Kim:** None. **E. Baeg:** None.

Poster

PSTR066: Stroke: Preclinical Studies

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Topic: C.09. Stroke

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National Research Foundation of Korea Grant 2022R1A2C1091804
National Research Foundation of Korea Grant RS-2023-00278819

Title: Glia-like cells induced from human mesenchymal stem cells exhibit enhanced therapeutic effects for the sequelae of cerebral infarction

Authors: M.-J. LEE[1], E. LEE[2], Y. RYU[2], S.-H. NAM[1], R. KIM[3,4], S. SONG[1,5], K. PARK[3], Y. PARK[3], J.-I. KIM[3,4], S.-H. KOH[2,6], ***M.-S. CHANG**[1,5];
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Abstract: The escalating incidence of stroke, predominantly cerebral infarction, poses a substantial burden, with a considerable proportion of patients experiencing severe neurological aftereffects. However, effective treatments for chronic cerebral infarction are lacking. While stem cell therapy holds theoretical promise for brain regeneration and plasticity, clinical trials, particularly involving mesenchymal stem cells (MSCs), have fallen short of demonstrating significant therapeutic efficacy. Therefore, exploring additional strategies to augment MSC

potential or therapeutic efficacy may yield significant advancements in MSC applications, presenting enhanced clinical opportunities in the future. This study aims to explore the therapeutic potential of glia-like cells induced without genetic modifications from human mesenchymal stem cells (ghMSCs) in alleviating chronic sequelae resulting from cerebral infarction. Transcriptomic analysis revealed the acquisition of neuroprotective astrocytic characteristics by ghMSCs. Both ex vivo simulations using organotypic brain slice cultures and in vivo experiments demonstrated superior neuroregenerative and neuroprotective effects of ghMSCs compared to hMSCs. The dose-dependent efficacy of ghMSCs in restoring neurobehavioral functions and reducing chronic brain infarction were also observed. The observed beneficial effects were attenuated by a CXCR2 antagonist, implicating the involvement of the CXCR2 signaling pathway in mediating these effects. In conclusion, this study suggests the potential of ghMSCs in treating refractory sequelae resulting from chronic cerebral infarction, with CXCR2 playing a crucial role in the underlying therapeutic mechanisms.

Disclosures: M. Lee: None. **E. Lee:** None. **Y. Ryu:** None. **S. Nam:** None. **R. Kim:** None. **S. Song:** None. **K. Park:** None. **Y. Park:** None. **J. Kim:** None. **S. Koh:** None. **M. Chang:** None.

Poster

PSTR066: Stroke: Preclinical Studies

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Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR066.05/C87

Topic: C.09. Stroke

Support: NINDS R01NS093057

Title: Understanding mechanisms of stroke recovery and optogenetic treatment through in vivo Ca^{2+} imaging of behaving mice

Authors: *R. KOPCHOCK III, T. C. CHIANG, H. CHEN, H. KO, M. Y. CHENG, G. K. STEINBERG;
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Abstract: Stroke often results in motor impairments with variable severity and recovery trajectories. The neural circuit mechanisms underlying these impairments and spontaneous recovery remain poorly understood, limiting the development of effective treatments. Building on our lab's previous work showing that optogenetic stimulation enhances post-stroke recovery, this study investigates longitudinal changes in neuronal activity within the ipsilesional primary motor cortex (iM1) using in vivo calcium imaging at cellular resolution, in behaving mice undergoing post-stroke optogenetic stimulation treatment. To monitor neuron calcium activity in the peri-infarct iM1 region, C57Bl6 male mice aged 7-9 weeks underwent stereotaxis surgery for implantation of a miniscope and expression of the calcium indicator GCaMP6f in excitatory neurons. For optogenetic stimulation, Channelrhodopsin (AAV-CaMKIIa-ChR2-EYFP) was expressed in the contralesional cerebellar dentate nucleus (cDN) and targeted with a fiber optic

cannula implant. After 5-6 weeks, strokes were induced via transient Middle Cerebral Artery occlusion (MCAo). Functional recovery post-stroke was assessed using rotating beam tests and locomotor behavior tests. Longitudinal assessments of motor function and neuronal activity were measured over the next 4 weeks to determine neuronal activity dynamics and their relation to stroke-induced deficits and recovery. Following stroke, group analysis shows a decrease in the number of active neurons detected, which then mostly recovers by 2 weeks post-stroke. Of the remaining detectable neurons post stroke, amplitude and frequency of Ca^{2+} transients appear normal, with no overall difference between stroke and sham animals. Analysis of individual animals over time reveals a more detailed representation of how neuron activity dynamics relate to behavior impairment and recovery. We observed differential patterns of neuronal activity profiles between slow and fast-recovered mice, indicating that severity of stroke is linked to neuron activity dynamics and recovery outcomes. Stroke mice receiving optogenetic stimulation show higher rates of coordinated activity among their neurons compared to non-stimulated mice, potentially leading to improved circuit functioning and recovery outcomes. Overall, this work provides a promising foundation for further investigation into the neural mechanisms underlying post-stroke impairments and recovery. By correlating behavior outcomes with changes in neuron activity, we can identify critical neuronal populations that mediate recovery and are viable targets for therapeutic intervention.

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Poster

PSTR066: Stroke: Preclinical Studies

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Topic: C.09. Stroke

Support: NNF Grant 16674
SDC Grant

Title: Insights into remote ischemic conditioning miRNA effects on brain endothelial cells in an oxygen-glucose deprivation stroke model

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Abstract: Acute ischemic stroke (AIS) is one of the leading causes of death and disabilities, and as such, it is of utmost importance to identify novel treatment options. Current acute treatments for AIS are limited to either thrombectomy or thrombolysis, both of which must be initiated

within 4.5-6 hours of symptom onset. Remote ischemic conditioning (RIC) is a promising non-invasive treatment that is thought to activate the body's own protective mechanisms against damaging ischemia through circulating microRNAs (miRNAs). Here, we investigate the transcriptional changes in human brain microvascular endothelial cells (HBMECs) transfected with four selected RIC-upregulated miRNAs (RIC-miRNAs), miR-16-5p, miR-144-3p, miR-182-5p, and miR-451a, under oxygen and glucose deprivation (OGD) - mimicking the initial stages of AIS. Pronounced transcriptional changes were present after RIC-miRNA transfection, with 149 unique downregulated and 212 upregulated differentially expressed genes in HBMECs after OGD and RIC-miRNA transfection compared to all other conditions. These genes were involved in cell cycle regulation, DNA replication, and pathways of energy metabolism. However, we saw no direct effect on cell viability after RIC-miRNA transfection and OGD. In conclusion, we hypothesize that the selected RIC-miRNAs activate pathways that help HBMECs return to normal physiological conditions after exposure to damaging ischemia.

Disclosures: K. Stenz: None. **J. Just:** None. **T.R. Lassen:** None. **K. Vissing:** None. **X. Wang:** None. **K.R. Drasbek:** None.

Poster

PSTR066: Stroke: Preclinical Studies

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR066.07/C89

Topic: C.09. Stroke

Support: AHA 23PRE1018993
T32NS082145
T32GM145432

Title: Sex-based differences in the post-stroke transcriptome after photothrombotic stroke in mice

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Abstract: Background: Stroke induces significant changes in neighboring and distant brain regions. Studies using rodent models have demonstrated that stroke in the primary motor cortex triggers substantial neuroplasticity in the uninjured contralesional motor cortex (cM1) and peri-infarct regions. We previously found that male mice exhibit distinct transcriptional responses in

the cM1 one week after stroke, a critical period characterized by heightened post-stroke plasticity. Given that female mice exhibit differential post-stroke neuroinflammation and diminished plasticity relative to male mice, we investigated how transcriptional responses in the cM1 and peri-infarct region of female mice might differ following stroke. Methods: This study utilized 8-week-old male (n=6) and female (n=9) C57/Bl6 mice that underwent photothrombotic stroke (PT) targeting the primary motor cortex (M1), with a group receiving sham surgery for comparison. One week after surgery, we dissected and processed the peri-infarct and cM1 regions for RNA isolation. Novogene performed quality control, mRNA purification, and paired-end 150 bp Illumina sequencing, followed by analysis using DeSeq2. Results: Differentially expressed genes (DEGs) between stroke and sham groups were more abundant in the peri-infarct region compared to the cM1 in both males and females, enriched for innate immune signaling, leukocyte activation, and viral response pathway activation. Interestingly, there was a higher number of upregulated genes in the female peri-infarct region compared to males (2170 vs. 909). In contrast, the number of DEGs in the cM1 was greater in males than females (288 vs. 49). We identified 626 shared DEGs in the peri-infarct region across both sexes, whereas the cM1 transcriptome exhibited substantial divergence between males and females. Gene ontology analysis revealed similar enriched processes in the peri-infarct region and distinct processes in the cM1, with the female cM1 enriched for inflammatory processes. Conclusions: Sex-based differences in the post-stroke transcriptome were evident in both the peri-infarct region and cM1 one week after stroke. Inflammatory signaling was observed in both sexes within the peri-infarct cortex. However, cM1 gene expression was notably different, primarily due to increased inflammatory signaling in females. These findings support further investigation into the role of sex-specific transcriptional regulation in post-stroke plasticity and recovery.

Disclosures: D. Betz: None. **M. Kenwood:** None. **K. Poinsatte:** None. **S. Lewis:** None. **K.R. Zuurbier:** None. **E.J. Plautz:** None. **P. Rhoton:** None. **P. Douglas:** None. **A.M. Stowe:** None. **M.P. Goldberg:** None.

Poster

PSTR066: Stroke: Preclinical Studies

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR066.08/C90

Topic: C.09. Stroke

Support: NINDS R01NS058784

Title: Neural stem cell transplantation-induced transcriptomic and proteomic changes in the ischemic mouse brain

Authors: *V. GUPTA[1,2], X. LIANG[3], P. HABIB[3], R. T. NORISTANI[3], N. JOHNSTON[3], T. M. BLISS[3], G. K. STEINBERG[1,2];
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Abstract: Neural stem cell transplantation-induced transcriptomic and proteomic changes in the ischemic mouse brain

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Keywords: Stroke; Stem cell; Transcriptomics; Proteomics; Functional recovery
Grant/Other Support: NINDS R01NS058784 (GKS)
Abstract: Transplantation of neural stem cells to augment stroke recovery is a promising therapeutic approach currently in clinical trial. However, there is very little information as to how these cells initiate recovery on a molecular level. To investigate this, we transplanted human embryonic derived neural stem cells (NR1), or vehicle, into the ipsilesional hemisphere of C57BL/6 mice one week after inducing stroke by a 35-minute transient middle cerebral artery occlusion. Mice were trained for rotating beam and pellet reach tests for 3 weeks prior to the stroke. One group of mice were survived for 2 months post-transplantation and tested for functional motor recovery every other week. Another group of mice were sacrificed 7 days after transplantation and brains were harvested. The cerebellum and the two hemispheres were separated and flash frozen. Coronal sections (50um each) were cut and alternate ipsilesional sections were pooled and assigned to transcriptomic or proteomic analysis. In addition, to obtain some broad spatial resolution, sections were separated by brain region into the transplanted frontal region, non-transplanted parietal region, and the cerebellum. Transcriptomic profiling using bulk RNA seq, and proteomics using LC-MS were done to investigate the molecular changes in cell vs vehicle group in different brain regions. Results showed that NR1-transplanted mice showed enhanced motor function recovery compared to vehicle-treated mice. Transcriptomic and proteomic differences between the cell and vehicle groups will be presented. These differences will elucidate the factors and biological processes that initiate stem cell-induced recovery as brains are sampled at a time point prior to observable functional recovery. Furthermore, given the spatial division of our omics samples, we will determine whether the stem cell-induced changes are far reaching or confined to local effects near the transplantation site at this early time point.

Disclosures: V. Gupta: None. **X. Liang:** None. **P. Habib:** None. **R.T. Noristani:** None. **N. Johnston:** None. **T.M. Bliss:** None. **G.K. Steinberg:** None.

Poster

PSTR066: Stroke: Preclinical Studies

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Program #/Poster #: PSTR066.09/C91

Topic: C.09. Stroke

Support: NIH Grant R01HD095187

Title: Intervention induced changes in clinical measures of upper extremity and cortico-cortical connectivity in chronic stroke with moderate to severe impairments

Authors: *K. M. GROSSMAN[1], J. SHAO[2], A. CHANG[2], R. ARCEO[2], C. CARMONA[2], J. DROGOS[2], J. YAO[2];
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Abstract: Introduction: Despite greater impairments and need for motor recovery, moderate to severely impaired stroke survivors are often excluded from interventions that have been designed for the mildly impaired population. With the development of assistive technologies such as functional electronic stimulation (FES) and robotic assistance that combine with AI technologies, recent studies have shown that improved hand function is possible in this chronically and more severely impaired group, although the response rate is relatively low. Currently, the underlying neural mechanisms that determine responsiveness are not well understood, hindering the development of tailored, subject-specific training programs.
Methods: To address the gap in understanding these mechanisms, we conducted clinical tests and EEG measurements from 20 subjects with chronic moderate-to-severe stroke, who underwent an intensive 8-week long device-assisted arm/hand intervention. Clinical measurements, including Box and Blocks Test, Fugl-Meyer, and Action Research Arm Test, were conducted both before and after the intervention. EEG recordings were taken during constrained opening of the paretic hand both before and after the interventions. The EEG recordings were then used to measure the cortico-cortical connectivity among bilateral primary motor areas (M1), premotor areas, and supplementary motor areas.
Results: We found significant changes in the clinical measurements with an overall responsive rate at 59%. Meanwhile, we found a significant reduction in the neural connectivity from the contralesional M1 to the lesional M1 following the intervention. Going forward, we plan to investigate the correlation between changes in neural connectivity and the recovery of hand function.

Disclosures: K.M. Grossman: None. **J. Shao:** None. **A. Chang:** None. **R. Arceo:** None. **C. Carmona:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); ReIn-Hand Technology Company. **J. Drogos:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); ReIn-Hand Technology Company. **J. Yao:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); ReIn-Hand Technology Company.

Poster

PSTR066: Stroke: Preclinical Studies

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR066.10/C92

Topic: C.09. Stroke

Support: United States (U.S.) Department of Veterans Affairs Biomedical Laboratory R&D (BLR&D) Service Merit Review Award 1I01BX006223-01A1
U.S. Department of Veterans Affairs Rehabilitation R&D (RR&D) Service Merit Review Award I01 RX003506
Florida Department of Health 7JK01
Florida Department of Health 21K06

Title: Post-stroke whole body vibration therapy alters transcriptome and reduces cognitive deficits in middle-aged rats.

Authors: *S. H. PATEL[1], H. M. BRAMLETT[2], A. P. RAVAL[1];
[1]Neurol., Leonard M. Miller Sch. of Med., Univ. of Miami, Miami, FL; [2]Neurosurg., Leonard M. Miller Sch. of Med., Univ. of Miami, Miami, FL

Abstract: Stroke is a leading cause of death in the United States, and frailty is linked to increased risk and severity of stroke. Post-stroke physical frailty often accompanies cognitive deficits. Both physical and cognitive deficits in stroke survivors can be reduced by rehabilitative exercise. However, adherence to rehabilitative exercise is often poor due to various factors including preexisting health conditions, motivation, and cost. Effective and affordable rehabilitation interventions are crucial to minimize post-stroke deficits and the overall burden of stroke. Our published studies have demonstrated that an exercise mimetic, low frequency whole body vibration (WBV; 40Hz) therapy, ameliorates both motor and cognitive deficits in a rat model of stroke [1,2]. Our studies have also demonstrated that post-stroke WBV therapy reduces ischemic brain damage, however the underlying mechanisms by which WBV induces ischemic protection and cognitive improvement remain elusive. In the current study, we hypothesize that WBV treatment improves post-stroke outcomes by altering the expression of key genes implicated in stroke recovery. Middle-aged female Sprague-Dawley rats were randomized to sham or transient middle cerebral artery occlusion (tMCAO; 90 min) surgery after which they received no treatment (tMCAO+No-WBV) or WBV (tMCAO + WBV) for 15 minutes twice a day for a week. Following WBV, cortical tissue was collected for analysis of gene expression via RNA sequencing (RNAseq) and gene enrichment analysis via Enrichr. Upon analysis of the RNAseq data, we observed that 89 genes were significantly up regulated, and 180 genes were significantly down regulated ($p<0.0001$) in the tMCAO + WBV group as compared to tMCAO + No-WBV group. The significantly upregulated genes with the greatest increase in fold change include Kif21a, LOC103689968, and AABR07051308. In regard to genes that were reduced in expression, SYNJ1, TLR3, and VPS37C demonstrated the greatest significant decrease in fold change. Enrichment analysis revealed that the genes with greatest decrease in fold change, namely SYNJ1, TLR3, and VPS37C are all involved with neuroinflammation, with the most down regulated gene, VPS37C, being implicated in innate immune system function. The observed WBV induced transcriptional reprogramming may reduce post-stroke inflammation thus improving stroke outcomes, and future confirmatory studies are needed to establish WBV therapy for stroke rehabilitation. References: 1. Kerr, N et al. (2022). Front. aging neurosci, 14, 942717. 2. Raval, A.P. et al. (2018). IJMS, 19(9), 2749. Acknowledgement: The authors thank Ms. Ofelia. Furones-Alonso for surgical assistance.

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Poster

PSTR066: Stroke: Preclinical Studies

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR066.11/C93

Topic: C.09. Stroke

Title: Cross-area Dynamics Underlying Neural Integration: Long-term Monitoring of Transplanted and Host Neurons

Authors: *H. GHUMAN, K. GANGULY;
Neurol., UCSF, San Francisco, CA

Abstract: Loss of nervous system tissue after severe brain injury is a main determinant of poor functional recovery. Neural transplantation is a promising method to restore lost brain tissue and function, yet the intricate neural dynamics behind transplant integration and its interactions with host neurons remains poorly understood. Here we present a comprehensive approach for long-term single neuron monitoring of both the transplanted embryonic cortical neurons, as well as host neurons after cortical injury in adult mice performing a prehension task. We employed dual-color miniscope imaging to investigate the cross-area dynamics of neural integration following transplantation. We observed a progressive alignment of neural activity patterns between transplanted and host neurons with time. Specifically, canonical-correlation analysis (CCA), which finds linear combinations of simultaneous transplant and host activity that are maximally correlated, demonstrated a robust increase in shared variance across both populations. Essentially, this observed increase in shared variance indicates that the neural activity in both populations becomes more synchronized or coordinated with time. Our approach allows greater insight into the underlying neural interactions driving successful network integration and the development of targeted closed-loop interventions aimed at restoring motor functions.

Disclosures: H. Ghuman: None. **K. Ganguly:** None.

Poster

PSTR066: Stroke: Preclinical Studies

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR066.12/C94

Topic: C.09. Stroke

Support: American Heart Association Predoctoral Fellowship (900190)
Undergraduate Research Fellowship (URF)

Title: Forelimb experience-dependent bilateral changes in motor cortical FosB/DeltaFosB after motor cortical infarcts in mice

Authors: *D. SUNDARARAMAN[1], V. NEMCHEK[2], C. HOANG[3], T. A. JONES[2];
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Abstract: The majority of strokes are ischemic, in which a blood clot interrupts blood flow to a part of the brain, and can cause impaired motor function. The region surrounding the infarct, also known as the peri-lesion area, is the site of many endogenous neural repair mechanisms following stroke. Unimanual rehabilitation, which involves training the paretic forelimb after stroke, can improve paretic forelimb function along with the reemergence and reorganization of its corresponding movement representation in the peri-infarct motor cortex. On the other hand, bimanual rehabilitation training involves skillful use of both the paretic and nonparetic forelimbs and is related to bilateral activation of the motor cortex. The role of contralateral regions in post-stroke recovery of function, especially in concert with peri-lesion areas, is unclear. The basic science underlying bimanual rehabilitation is relatively understudied, with little research on the resulting modeling responses.
Our project uses a mouse model of stroke to study the differences in functional and neural changes evoked by various types of post-stroke rehabilitation. After photothrombotic stroke induction, mice were grouped into three post-stroke training experiences, two of which consisted of a skilled reaching task- unimanual, bimanual, and control (no training). The behavioral data collected during the rehabilitation period was used as a measure of motor function. Immunohistochemistry procedures were conducted post-mortem to analyze the relative expression of ΔFosB between hemispheres and across different rehabilitative experiences. ΔFosB serves as a marker of repeated activation of cortex, meaning that regions of the brain repeatedly activated by different rehabilitation techniques will have increased relative Fos expression. We plan to use the staining patterns of this protein in the motor cortices bilaterally as a measure of the patterns of neural activity which underpin post-stroke rehabilitation.
We found that the unimanual group demonstrated the greatest improvements in paretic limb performance. We anticipate differential ΔFosB expression particularly in the contralateral-to-lesion area of the motor cortex between bimanually and unimanually trained mice.

Disclosures: D. Sundararaman: None. **V. Nemchek:** None. **C. Hoang:** None. **T.A. Jones:** None.

Poster

PSTR066: Stroke: Preclinical Studies

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR066.13/C95

Topic: C.09. Stroke

Support: CIHR PJT-183769-2022
Brain Canada Foundation - WBHI
Brain Canada Foundation - Future Leaders

Title: Influence of dopamine on motor recovery after stroke

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Abstract: Loss of motor function is one of the major physical challenges faced by patients recovering from stroke. Motor skills can be learned (or re-learned after a stroke) through practice and repetition. Dopamine, a neurotransmitter typically associated with rewards, pleasure, and addiction, could also play a critical role in motor skill learning and synaptic plasticity in the motor cortex. The motor cortex receives dopaminergic inputs corresponding to motor skill learning from the Ventral Tegmental Area (VTA). During re-learning of motor skills after a stroke, dopamine signals could guide synaptic plasticity and reshape neural circuits in the perilesional area to promote motor recovery. We hypothesize that the DA fibers innervating the motor cortex carry a reinforcement learning signal that guides motor recovery after stroke. In rats, we modeled a stroke to the caudal forelimb area of the motor cortex using Endothelin-1 and then manipulated VTA neurons either using optogenetic or chemogenetic tools daily during a rehabilitation task. We used the Montoya staircase and Cylinder tests to assess forelimb motor deficits before and after the stroke. We used a knob rotation task to assess fine forelimb activity and for motor rehabilitation after stroke. Early results suggest an important role for VTA dopaminergic neurons to guide plasticity and motor recovery after a stroke. Optogenetic VTA stimulation paired with motor rehabilitation increased forelimb motor score at the Montoya and Cylinder tests. These results support the importance of considering reward-related circuits to promote recovery after stroke.

Disclosures: D. Sen: None. **M. Demers:** None. **C. Ethier:** None.

Poster

PSTR066: Stroke: Preclinical Studies

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR066.14/C96

Topic: C.09. Stroke

Support: California Institute of Regenerative Medicine: TRAN1-12891 and DISC2-15137
NIH- NINDS NS103788

Title: cGMP production of hiPSC-Glial enriched progenitors

Authors: *S. AZARAPETIAN[1], E. HATANAKA[3], I. AVILA[4], J. GARCIA[2], S. CARMICHAEL[5], I. L. LLORENTE[6];
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Abstract: Stroke is the leading cause of adult disability and the second leading cause of dementia. White matter stroke (WMS) constitutes up to 30% of all stroke subtypes and is a distinct process from “large artery stroke”. WMS begins as small infarcts in deep penetrating blood vessels in the brain but progresses, accumulates, and expands from preexisting lesions into adjacent white matter to produce hemiparesis with incomplete recovery, gait abnormalities, cognitive decline and difficulties in executive functioning. These lesions accumulate over time to cause vascular dementia (VaD). There is no medical therapy for WMS/VaD. As opposed to “large artery stroke”, WMS does not damage neuronal cell bodies, but damages axonal tracts and glial cells. Therefore, a cell-based therapy that can replace lost glia and induce structural repair in WMS and VaD is of great promise. We have developed a unique allogenic human induced pluripotent stem cell (hiPSC) derived Glial Enriched Progenitor (GEP) cell therapy product for the treatment of WMS/VaD. We have demonstrated that hiPSC-GEPs transplanted into the brain after WMS/VaD promoted motor and cognitive recovery through 3 mechanisms of action: axonal growth, astrocytic modulation, and oligodendrocyte differentiation and remyelination. We have also qualified the entire manufacturing process for the intended therapeutic candidate, hiPSC-GEPs, through safety, identity, purity, activity, and stability qualification assays. To demonstrate the scale-up manufacturing capabilities of the potential therapeutic product, we have developed a new cGMP-compliant manufacturing protocol and produced well above the necessary number of cells for phases 1 and 2 of a future clinical application. This preliminary work could pave the way for a faster route to Pre-IND, FDA approval, and a future clinical application.

Disclosures: S. Azarapetian: None. **J. Garcia:** None. **S. Carmichael:** 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.; Calico. **I.L. Llorente:** None.

Poster

PSTR066: Stroke: Preclinical Studies

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR066.15/C97

Topic: C.09. Stroke

Support: PAPIT IN216221 project
CONACHYT CVU 1084617 scholarship

Title: Noradrenergic changes associated with sensoriomotor recovery in a photothrombotic lesion model

Authors: *I. SAUCEDO[1], A. AVILA[3], A. BUENO-NAVA[4], E. GONZALEZ-GUEVARA[5], F. PEREZ[6], L. RAMOS-LANGUREN[2];
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Abstract: Introduction: Stroke is one of the leading causes of death and disability worldwide. It has been reported that there is a percentage of patients who experience spontaneous recovery following a stroke, and relationships have been proposed between this recovery and changes in neurotransmission systems, such as the noradrenergic system, where a positive correlation with recovery has been observed. Evidence suggests the presence of compensatory mechanisms involving reorganization of contra and ipsilateral structures anatomically linked to the site of injury, implicating neuroplasticity in the recovery process. However, the precise mechanisms underlying noradrenergic-mediated plasticity remain incipient. This study aims to investigate potential alterations in noradrenergic activity associated with stroke recovery in a photothrombotic lesion model. Method: Sixty-nine adult male Wistar rats were randomly assigned to four groups based on sensorimotor evaluation time points (3 and 30 days post-surgery, dps) and sham or lesioned condition. Sham animals recive an intravenous saline, and lesioned animals, a rose bengal photosensitive dye. Both groups undergo light stimulation for 20 minutes at 150 watts over the right primary motor cortex. Subsequent to sensoriomotor assessment 3 or 30 dps, rats were euthanized, and tissue samples from the dentate gyrus, pons and primary motor cortex were processed for analysis of noradrenaline levels via high-performance liquid chromatography (HPLC), and the expression of β-noradrenergic receptors and cAMP response element-binding protein (CREB) via Western Blot. This study has been approved by the Ethics Committee of the National Institute of Rehabilitation, Luis Guillermo Ibarra Ibarra, under protocol number INRLGII/443/2023. Results: At three days post-lesion were observed diminished sensorimotor performance and noradrenaline levels, particularly ipsilateral to the lesion. Conversely, in the group examined 30 days post-lesion, noradrenaline content and sensorimotor performance were restored. These findings suggest a positive correlation between functional recovery following ischemic stroke and alterations within the noradrenergic neurotransmission system. Currently, the analysis of the expression of noradrenergic receptors and CREB is being carried out.

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Poster

PSTR066: Stroke: Preclinical Studies

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR066.16/C98

Topic: I.08. Methods to Modulate Neural Activity

Support: NIH R01 Grant Guanosine

Title: Neurochemical Analysis as a function of ischemic stroke severity

Authors: *K. CALDWELL[1], A. E. ROSS[2];
[1]Univ. of Cincinnati, Cincinnati, OH; [2]Chem., Univ. of Cincinnati, Cincinnati, OH

Abstract: In the brain, glucose and oxygen exchange is imperative for the maintenance of homeostasis. Disruption in this homeostatic exchange can lead to one of the most common forms of brain injury, ischemic stroke. Ischemic stroke results in critical neuronal/tissue damage, loss of motor function, and even death. Some of the major hallmarks of ischemia include excitotoxicity, inflammation, and amplified reactive oxygen species (ROS). Guanosine is a signaling molecule and is an emerging biomarker of interest for neuroprotection. Research has shown the ameliorating effects of exogenous guanosine on the consequences of ischemic stroke, yet the molecular mechanism of how guanosine supports the recovery of stroke events has not been elucidated. Previously, our lab has developed a tunable *ex vivo* oxygen-glucose deprivation (OGD) model (normoxia, mild, and severe). This work cultivated a standard metric for *ex vivo* slice ischemic studies that improves correlation to the varying ischemic severity models that exist for *in vivo* studies. More work from our lab has shown an increase in the rapid release of endogenous guanosine by combining the severe OGD model and fast-scan cyclic voltammetry (FSCV). Interrogation of the brain's response to immediate changes during varying severity of injury will allow for more approachable means of combating ischemia. In this work, we utilized our *ex vivo* slice models to determine the neuroprotective properties provided by exogenous guanosine in various conditions along with altering the production of intracellular guanosine. The major goal of this work is to understand the neuroprotective properties of guanosine in ischemic severity models. ELISAs were used to determine the production of cytokines and changes in hypoxia-inducible factor-1 alpha (HIF-1A). Immunohistochemistry was used to target glial cells (microglia and astrocytes) reactivity in varying conditions and 2,3,5-Triphenyltetrazolium chloride (TTC) was used to assess overall damage in the tissue. Ultimately, this work is set to assess the role of guanosine's function during ischemic severity.

Disclosures: K. Caldwell: None. **A.E. Ross:** None.

Poster

PSTR067: Headache, Migraine, and Trigeminal Circuits

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR067.01/C99

Topic: D.01. Somatosensation – Pain and Itch

Support: Department support

Title: Photophobic effect of light exacerbates migraine-like pain behavior in rats

Authors: *Q. LIN[1], **T. MOVAGHAR**[2];
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Abstract: Migraine affects up to 15% of the population annually contributing to significant disability. Many migraineurs experience extreme and often painful sensitivity to light, a medical symptom of migraine known as photophobia while suffering an episodic attack of headache. Laboratory studies by our and other groups have shown that the administration of nitroglycerin (NTG), a commonly used migraine inducer, evoked light aversion in mice and rats. Clinically, this abnormal light sensitivity is proposed to link to the severity of migraine headaches as more than one-third of patients have cited light as a trigger for their migraine attacks. However, it is still poorly understood whether and how the change in light sensitivity exacerbates migraine-like pain. Using a rat model of migraine by NTG in this study, we initiated to determine whether light stimulation can become aversive during migraine-like pain attacks. von Frey filaments were used to assess the mechanical touch threshold to determine orofacial allodynic pain (a migraine associated symptom) in awake rats after single NTG administration, which was followed by further determining whether such orofacial allodynic pain was exacerbated when these animals experiencing migraine-like pain were exposed to different intensities of light stimulation. Results: In rats that were under background light (80-100 lux) and not administered with NTG, increasing light stimulation with different intensities (500, 1000 and 2000 lux) did not produce significant changes in orofacial mechanical threshold (n=11, P=0.996). In rats that received a single administration of NTG (10 mg/kg, i.p.), orofacial mechanical threshold was decreased (n=8, P=0.004). When these rats were exposed to increasing light stimulation at the time when the effect of NTG reached the peak, their orofacial mechanical threshold was further decreased significantly (n=8, P=0.016). Conclusions: This initial study provides behavioral evidence that light becomes aversive when animals are experiencing an attack of migraine-like pain. Accordingly, light exposure exacerbates the pain evident as severe orofacial allodynia. The data obtained provide the foundation for further studying the underlying mechanisms.

Disclosures: Q. Lin: None. **T. Movaghar:** None.

Poster

PSTR067: Headache, Migraine, and Trigeminal Circuits

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR067.02/C100

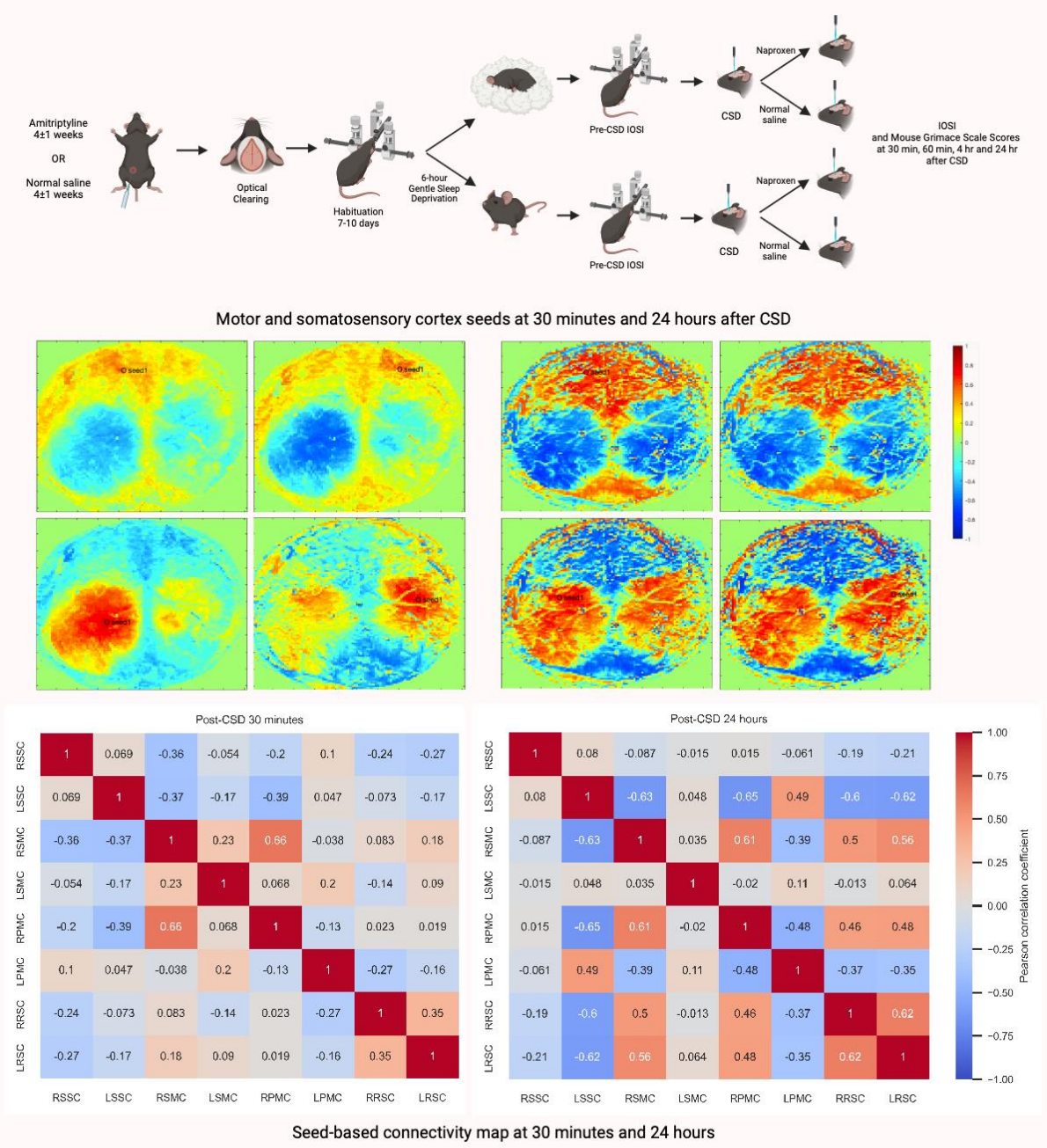
Topic: D.01. Somatosensation – Pain and Itch

Support: Hacettepe University Scientific Research Projects Coordination Unit TDK-2023-20402

Title: Does spreading depression rewire cortical pain networks?

Authors: *B. SOLGUN, B. DONMEZ-DEMIR, H. KARATAS-KURSUN, E. ERDENER; Hacettepe University, Inst. of Neurolog. Sci. and Psychiatry, Ankara, Turkey

Abstract: Resting-state functional imaging is increasingly used to understand how distinct brain networks modulate and respond to pain. As migraine, a common headache disorder, can be experimentally modeled by triggering cortical spreading depolarizations (CSD) in rodents, it is crucial to understand its impact on network connectivity to find imaging markers for experimental evaluation of headache and trigeminovascular activation. We used wide-field intrinsic optical-signal imaging (IOSI) to investigate the impact of CSDs on bihemispheric resting-state functional connectivity. C57BL6-ChR2 mice received i.p. amitriptyline or normal saline for 4±1 weeks, after which they underwent head bar installation and skull optical clearing with 10% EDTA solution. After habituation to the imaging setup, a subset of mice underwent gentle sleep deprivation. We then performed IOSI for 8 minutes under 530nm light to observe changes in total hemoglobin (HbT) concentration in awake mice. Next, CSD was triggered optogenetically using 450nm light and confirmed by laser speckle contrast imaging. A subset of mice received i.p. naproxen after CSD to modulate headache. IOSI was performed at 30 minutes, 60 minutes, 4 hours and 24 hours after CSD. Mouse grimace scale was scored at each time point for behavioral headache documentation. Time traces of HbT were bandpass filtered and regressed. Seeds were placed in primary somatosensory, primary motor, secondary motor, retrosplenial cortices, posterior parietal association and visual areas. We observed time-dependent changes in contralateral somatosensory cortex connectivity after CSD, that may indicate activation of pain processing networks and can serve as a proxy for the headache experience. Extensive evaluation of inter and intra-hemispheric connectivity changes at different frequency bands will be presented. Our work will help identify imaging markers for migraine headache assessment in rodents and will be beneficial for the elucidation of migraine pathophysiology.



Disclosures: B. Solgun: None. **B. Donmez-Demir:** None. **H. Karatas-Kursun:** None. **E. Erdener:** None.

Poster

PSTR067: Headache, Migraine, and Trigeminal Circuits

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR067.03/C101

Topic: D.01. Somatosensation – Pain and Itch

Support: 1R01EY035681-01
KL2TR002002

Title: Comparative analysis of extracellular vesicles from bone marrow and cornea mesenchymal stem cells cultured in 2D and 3D systems and its implications for corneal nerve regeneration

Authors: *H. MASSOUMI[1], D. TEWARI[1], S. WENG[2], S. HOSSEINIBARKOOIE[2], V. H. GUAIQUIL[1], M. I. ROSENBLATT[1], A. DJALILIAN[1], E. JALILIAN[1];
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Abstract: Damage to the corneal nerves, whether due to trauma, surgery, or infection, can result in various vision impairments, including decreased tear production, ocular pain, and even blindness. Existing treatments, such as eye drops, often fall short in moderate to severe cases, emphasizing the urgent need for therapies that can effectively promote rapid regeneration of corneal nerves. This study compared the effects of extracellular vesicles (EVs) derived from bone marrow mesenchymal stem cells (BM-MSCs) and corneal MSCs (Co-MSCs) cultured in 2D and 3D systems and their effect on corneal trigeminal ganglion (TG) nerve regeneration *in vitro* and *in vivo*. Moreover, the molecular cargo of EVs was further explored from both sources and culture conditions utilizing small-RNA sequencing and proteomics. Human BM-MSCs and Co-MSCs were cultured in 2D and 3D systems. EVs were isolated and characterized using ultra-centrifugation, NanoSight, and ExoView. Mouse TGs were treated with EVs to assess neuronal growth over 48 h *in vitro* and *in vivo*, followed by β3 tubulin immunostaining and confocal microscopy. Small RNA sequencing and proteomics were applied to elucidate the gene expression level and enriched proteins. EVs from 3D MSCs showed a substantial increase in concentration and higher levels of exosomal markers (CD63, CD81, CD91) compared to 2D-derived MSC EVs. Both BM-MSCs and Co-MSCs promoted nerve regeneration *in vitro* and *in vivo*. Notably, 3D-derived EVs significantly amplified this effect ($p<0.05$), with a relatively greater enhancement observed in Co-MSCs. EVs proteomic analysis revealed distinct enriched protein profiles for BM-MSCs vs. Co-MSCs and between 2D and 3D culture conditions. Additionally, analysis of small RNA sequencing data revealed distinct expression patterns between BM-MSCs and Co-MSCs, as well as disparities between 2D and 3D culture systems. This underscores the significance of the molecular signature underlying the observed variations in neurite elongation and phenotype. Our study reveals the enhanced regenerative potential of EVs from both BM-MSCs and Co-MSCs cultured in 2D and 3D environments with significantly more regeneration from the 3D culture system for corneal nerve regeneration. Proteomic and small RNA sequencing analyses unveil distinct expression profiles, underscoring the importance of cell source and culture conditions in therapeutic efficacy. These findings offer valuable insights for developing targeted therapies to address corneal nerve damage.

Disclosures: H. Massoumi: None. **D. Tewari:** None. **S. Weng:** None. **S. Hosseinibarkooie:** None. **V.H. Guaiquil:** None. **M.I. Rosenblatt:** None. **A. Djalilian:** None. **E. Jalilian:** None.

Poster

PSTR067: Headache, Migraine, and Trigeminal Circuits

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR067.04/C102

Topic: D.01. Somatosensation – Pain and Itch

Support: NIH Grant U01 EY034680-02

Title: Sex Differences in CGRP Expression in Trigeminal Ganglia Following Corneal Abrasion

Authors: *C. GUNTER[1], C. L. JIANG[1], S. O. ZEIMANTZ[1], D. M. HEGARTY[1], C. W. MORGANS[1], T. M. LARGENT-MILNES[2], S. A. AICHER[1];
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Abstract: Calcitonin gene related peptide (CGRP) is a neuropeptide with diverse functions. CGRP is upregulated in peripheral nerves following injury and is thought to play a role in pain sensitization and wound healing. The mechanisms have not been fully elucidated and are complicated by the fact that some functions of CGRP appear to be sex specific. In this study, we examined the behavioral and molecular response to corneal injury with a focus on sex differences. We used heptanol and debridement to unilaterally abrade corneas of male and female 10-week-old Sprague-Dawley rats (n = 18); control rats did not receive a corneal abrasion (n = 6). Orbital tightening (OT), a behavioral pain indicator of spontaneous pain was assessed at baseline, 24 hrs, 74 hrs, and 1 week after abrasion. Immunohistochemistry was used to determine the proportion of cells in trigeminal ganglia (TG) that contain CGRP or activating transcription factor 3 (ATF3), a nerve injury marker. OT was significantly increased at 24 hrs and 72 hrs following abrasion and there were no sex differences in OT behaviors. The percentage of TG neurons immunolabeled for CGRP (%CGRP) or ATF3 (%ATF3) increased following abrasion and sex differences were seen for both markers. In females, %CGRP was markedly increased at 24 hrs and decreased to below control levels at 72 hrs and 1 week. In males, the %CGRP increase at 24 hrs was more modest, but levels remained high through 1 week. %ATF3 expression in females was greater in magnitude and duration following abrasion and persisted through 1 week, while males returned to control levels by 1 week. Separate groups of female rats were treated with either 1mg/kg Olcegepant, a CGRP receptor antagonist (n=6) or vehicle (n = 6) and underwent corneal abrasion and OT assessment, as described above. Rats treated with Olcegepant had OT responses similar to vehicle treated rats, indicating that CGRP may not directly modulate spontaneous pain. This is consistent with our finding that sex differences were present in CGRP expression in TG neurons, but absent in OT behaviors. Also, we found that CGRP and ATF3 rarely colocalized in TG neurons after abrasion. In abraded rats, only 5% of the ATF3 cells also contained CGRP. Since ATF3 is upregulated in injured cells, this finding indicates that most CGRP immunolabeled neurons seen in TG after abrasion were not directly connected to injured corneal nerves. The fact that ATF3 and CGRP generally do not colocalize suggests that many uninjured TG neurons upregulation CGRP, indicating they may be assisting with healing, perhaps by recruiting glia or immune cells to damaged neurons. Further study is needed to answer these mechanistic questions.

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Poster

PSTR067: Headache, Migraine, and Trigeminal Circuits

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR067.05/C103

Topic: D.01. Somatosensation – Pain and Itch

Support: NIH 75N95019D00026

Title: Comparison of rat models of vascular headache and trigeminal sensitization in male and female rats

Authors: Y. ZHANG[1], T. BERKMAN[1], M. CIKLIC[1], A. DORIA[1], E. DUGAN[1], S. A. WOLLER[2], S. IYENGAR[2], T. HANANIA[1], ***M. URBAN**[1];
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Abstract: In collaboration with the NIH HEAL Initiative Preclinical Screening Platform for Pain (PSPP), we have characterized rat models of vascular headache and trigeminal sensitization and compared the properties and pharmacology of these models in male and female Sprague Dawley rats. Models of vascular headache and trigeminal sensitization involved administration of the nitric oxide donor isosorbide dinitrate (ISDN; 10 mg/kg, i.p.) or dural infusion of inflammatory soup (IS; 2 mM serotonin, histamine, bradykinin, 0.2 mM PGE2), respectively. Facial allodynia was measured by applying calibrated von Frey filaments to the periorbital region of the face and determining facial sensitivity thresholds. Study groups were randomized, the investigators were blinded to treatment, and groups were sufficiently powered to identify statistically significant effects. For the model of vascular headache, single administration of ISDN in male rats produced facial allodynia which was maximal at 2 hours, while administration of ISDN in female rats produced facial allodynia which was more robust compared to male rats and persisted for 3 hours. Pretreatment with the mu opioid agonist morphine sulfate (6 mg/kg) completely prevented the development of facial allodynia in male and female rats, while administration of the 5-HT1B/1D agonist sumatriptan (1 mg/kg), CGRP receptor antagonist olcegepant (1 mg/kg), or delta opioid agonist SNC80 partially inhibited facial allodynia with generally greater efficacy in male rats compared to female rats. For the model of trigeminal sensitization, a single infusion of IS onto the dura produced transient facial allodynia which persisted for 1- and 3-hours in male and female rats, respectively. Additionally, transient facial allodynia following single infusion of IS in female rats was more robust compared to male rats. Repeated infusion of IS (Days 1-5) in female and male rats produced persistent facial allodynia which was apparent by Day 3 and Day 5, respectively, and continued following cessation of dural infusions on Days 6-7. The data demonstrate that facial allodynia produced in rat models of vascular headache and trigeminal sensitization is generally more robust in female rats compared to male rats. Additionally, certain

classes of analgesic compounds, including delta opioid agonists, are more effective in preventing the development of facial allodynia in male rats compared to female rats.

Disclosures: Y. Zhang: None. **T. Berkman:** None. **M. Ciklic:** None. **A. Doria:** None. **E. Dugan:** None. **S.A. Woller:** None. **S. Iyengar:** None. **T. Hanania:** None. **M. Urban:** None.

Poster

PSTR067: Headache, Migraine, and Trigeminal Circuits

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR067.06/C104

Topic: D.01. Somatosensation – Pain and Itch

Support: CONAHCYT N ° CBF2023-2024-3878

Title: Antinociceptive effect of Salvia divinorum and salvinorin A in formalin-evoked trigeminal pain behavior in mouse

Authors: *G. N. QUIÑONEZ-BASTIDAS[1], E. D. TIXTA-RAMIREZ[2], L. E. GRIJALVA CONTRERAS[3], J. BALDERAS LOPEZ, Sr.[4], A. NAVARRETE-CASTRO[5];
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Abstract: Orofacial pain is a disabling condition which affects approximately 13 to 26% of the world's population. The severity of pain and refractoriness to pharmacological treatment are commonly observed in patients who suffer from this condition. Carbamazepine is the first-line option to treat trigeminal pain, however, its clinical efficacy is limited to short period of use due to its adverse effects. Salvinorin A (SA), a potent kappa-opioid receptor agonist, has been showing antinociceptive and antineuropathic effects in several models of pain. However, the antinociceptive effect of SA has not been studied in a trigeminal pain model. Moreover, Kappa opioid receptors are implicated in the process of trigeminal pain. Hence, the aim of this study was to investigate the antinociceptive effect of *Salvia divinorum* (SD) and SA in formalin-evoked trigeminal pain behaviors in mice, as well as the neuropharmacological profile of SA. Pain on male ICR mice (25 to 30 g) was induced by 20 µl of subcutaneous injection of 2.5% formalin into right whisker pad. Trigeminal pain behavior was evaluated as the time that the animal spends rubbing the whisker in blocks of 5 minutes for 45 minutes. Then, animals were submitted to actimeter test to evaluate motor activity, rotarod to evaluate effects on motor coordination, hole board and elevated plus maze to evaluate anxiolytic effect, exploration cylinder to evaluate sedative effect, and forced swim test to evaluate antidepressant effect. All experiments were performed in accordance with the Ethics Committee for the Use of Animals in

Pharmacological and Toxicological Testing and the Guidelines on the Ethical Standards for Investigation of Experimental Pain in Animals. The intraperitoneal administration of SD (3.2-100 mg/kg) and SA (0.1-3.2 mg/kg) produced a significant reduction (*P<0.05) on the formalin-evoked pain trigeminal behavior. Moreover, SA (3.2 mg/kg, i.p.) did not have effects on locomotor activity or anxiolytic of mice. Notwithstanding, SA produced a significant decrease (*P<0.05) on swim and scape behavior in mice submitted to forced swim test, likewise a significant decrease (*P<0.05) on the number of elevations of the animal in the exploratory cylinder test, suggesting depressive and sedative effect. As a conclusion, together results suggested that SD and its bioactive compound, SA, have antinociceptives effects on the formalin-evoked trigeminal pain behavior in mice, as well as central nervous system implications like depressant and sedative effects linked to SA.

Disclosures: G.N. Quiñonez-Bastidas: None. **E.D. Tixta-Ramirez:** None. **L.E. Grijalva Contreras:** None. **J. Balderas lopez:** None. **A. Navarrete-Castro:** None.

Poster

PSTR067: Headache, Migraine, and Trigeminal Circuits

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR067.07/C105

Topic: D.01. Somatosensation – Pain and Itch

Support: Association of Migraine Disorders
DE018661

Title: Characterization of electrophysiological properties of trigeminal ganglion neurons that innervate the maxillary sinus in mice

Authors: *S. GUPTA[1], J. GU[2], F. A. GODLEY[3];
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Abstract: The paranasal sinuses, including the maxillary sinuses, are thought to play the vital roles of lightening the weight of the skull, adding moisturizing and cleansing secretions to the nasal cavities, and suppressing infections. Under pathological conditions, such as viral and bacterial infections, benign and malignant tumors, and dental and orofacial procedures, maxillary sinuses can become a region generating noxious pressure and persistent pain. Furthermore, migraine disease can affect the normal function of the paranasal nervous system and create symptoms that mimic those of a sinus infection. Chronic pain generated from the maxillary sinuses is often poorly treated, partially because of the lack of knowledge on the trigeminal nerves that convey nociceptive signals from the maxillary sinuses. In the present study, we began to fill the knowledge gap by characterizing the electrophysiological properties of the trigeminal ganglion neurons that innervate the maxillary sinus (sinus TG neurons) of mice. We retrograde-labeled the sinus TG neurons by injecting the fluorescent dye DiD into the maxillary sinus. Then,

we performed patch-clamp recordings on the DiD-labeled sinus TG neurons in the *ex-vivo* TG preparation. We performed these experiments using both wide-type and Nav1.8Cre-ChR2/EYFP mice. We showed that the DiD-labeled sinus TG neurons belong to a subpopulation of small-sized TG neurons with a diameter of 20.1 ± 1.9 µm. The DiD-labeled sinus TG neurons were mostly Nav1.8Cre-ChR2/EYFP negative neurons. Most DiD-labeled TG neurons exhibited persistent action potential (AP) firing responding to suprathreshold step current injection, whereas Nav1.8Cre-ChR2/EYFP-positive TG neurons mostly displayed phasic AP firing. The sinus TG neurons had a broad action potential (AP) width and displayed a hump in AP repolarization, a property of nociceptors. All DiD-labeled sinus TGs recorded in the present study were C-afferent neurons. Compared with Nav1.8Cre-ChR2/EYFP-positive C-afferent neurons, the DiD-labeled sinus TG neurons exhibited relatively bigger soma size (21.14 ± 1.29 *vs* 15.75 ± 2.46 µm), larger membrane capacitance (31.45 ± 5.07 *vs* 23.43 ± 4.5 pF), lower input resistance (387.5 ± 119.8 *vs* 773.9 ± 297.0 MΩ), broader AP width (3.7 ± 1.0 *vs* 2.5 ± 0.6 ms), and lower afterhyperpolarization (-19.39 ± 3.758 *vs* -15.01 ± 4.035 mV). To our knowledge, this is the first study to characterize the electrophysiological properties of trigeminal ganglion neurons that innervate the maxillary sinus in mice. Our findings suggest that the sinus TG neurons may be a subpopulation of nociceptors distinct from the Nav1.8-expressing nociceptors in the TGs of mice.

Disclosures: S. Gupta: None. **J. Gu:** None. **F.A. Godley:** None.

Poster

PSTR067: Headache, Migraine, and Trigeminal Circuits

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR067.08/C106

Topic: D.01. Somatosensation – Pain and Itch

Support: Congressionally Directed Medical Research Programs (CDMRP) Award (W81HWH2120457)

Title: Localization of endocannabinoid hydrolyzing enzymes in the trigeminal system and their differential expression following traumatic brain injury.

Authors: *G. NAGARAJAN[1,2], Y. ZHANG[3];
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Abstract: Post-traumatic headache (PTH) is one of the comorbid conditions affecting a third of the TBI clinical population and is facilitated by a trigeminal pain pathway. The two principle endocannabinoids, N-arachidonoylethanolamine (AEA) and 2-arachidonoylglycerol (2AG) are known for their neuroprotective effects, and are rapidly hydrolyzed by fatty acid amide hydrolase (FAAH) and monoacylglycerol lipase (MAGL), respectively. Although endocannabinoids are

differently expressed in different regions of the brain and FAAH and MAGL are widely expressed in the trigeminal system, the cellular localization and functions of these hydrolyzing enzymes involved in trigeminal pain are currently less clear. Here we focused on the gene expression pattern of these endocannabinoid regulating enzymes in the trigeminal sensory ganglion (TG) and trigeminal nucleus caudalis (TNC) of the brainstem that modulate pain following TBI. We hypothesized that FAAH and MAGL have distinct cellular localization and modulate pain response in cell specific manner. Two months old male C57BL/6 mice were subjected to repetitive injury induced by rotational acceleration, once a day for 4 days. Following mild TBI, TG and TNC were obtained from sham and TBI mice (n=4). Tissue processed for in situ hybridization revealed that FAAH and MAGL showed distinct patterns of expression in the TG and the TNC. Within TG, both MAGL and FAAH are expressed in all three branches of the TG, and are mostly present in large and medium sized sensory neurons. Interestingly, only a moderate number of sensory neurons were colabelled with both MAGL and FAAH in the TG. In the brainstem, MAGL expression was found predominantly in the TNC compared to neighboring reticular nucleus and spinal trigeminal tract, whereas, FAAH expression was evenly distributed throughout the brainstem. Seven days following TBI, a moderate increase (10%-20%) in the number of mRNA transcripts was observed within FAAH and MAGL sensory neurons, reflecting a 0.3-0.5 fold change in the quantitative PCR results of the TG. On the other hand, one week post TBI, TNC did not show significant changes in mRNA expression of both FAAH and MAGL. Results from this study suggest that MAGL and FAAH in TG and TNC might have a distinct or have differential effect in modulating pain following TBI.

Disclosures: G. Nagarajan: None. **Y. Zhang:** None.

Poster

PSTR067: Headache, Migraine, and Trigeminal Circuits

Location: MCP Hall A

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Topic: D.01. Somatosensation – Pain and Itch

Support: NIH grant NS128148
NIH grant DA005010
NIH grant UL1TR001881
NIH grant CA196263
NIH grant U54HL119893
NIH grant UG3NS128148

Title: Peripherally acting cannabinoid prevents migraine-like pain and sensitization of dural nociceptors

Authors: Y. KITAOKA[1], K. KOSHIKA[2], Z. LI[1], T. YAMAMOTO[3], Y. MULPURI[4], K. L. WHYLAND[1], F. VAZQUEZ-DOMINGUEZ[1], R. MURALI[1], P. CHABRIA[1], L. P. LE[1], P. AHMADI[1], J. SHAFA[1], L. ANDREASYAN[1], H. SELTZMAN[5], *I. SPIGELMAN[1];

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Abstract: Migraine is a debilitating neurological disorder that affects approximately 15% of the population globally with greater prevalence in females. Cannabinoids acting on Gi/o-coupled cannabinoid 1 and 2 receptors (CB1Rs and CB2Rs) alleviate migraine symptoms in humans and in animal models. However, side effects mediated by CB1Rs in the central nervous system (CNS) limit their widespread use. We developed synthetic peripherally restricted cannabinoid (PRCB) agonists, that do not cross the blood-brain barrier. The prototype compound, 4-{2-[(1E)-1-[(4-propylnaphthalen-1-yl)methylidene]-1H-inden-3-yl]ethyl morpholine (PrNMI) effectively suppressed chronic pain symptoms in preclinical models of cancer, chemotherapy- and traumatic nerve injury-induced neuropathies, all with minimal CNS-mediated side effects or tolerance development. Here, we used non-invasive supradural injection of pH 6.0 saline in 5-week-old female C57BL/6J mice to induce migraine-like pain symptoms of periorbital cutaneous allodynia, which causes priming to normally subthreshold pH 7.0 saline stimulation of the dura (at 3 days) following resolution of the initial pain symptoms (Burgos-Vega, C.C., et al, Cephalgia 1-12, 2018). This model allowed us to address the mechanisms of sensitization of trigeminal dural afferents and the utility of PRCBs in suppressing behavioral symptoms of this sensitization. Supradural co-administration of PrNMI (5 µM) with pH 6.0 saline, but not with pH 7.0 saline, prevented both the initial and latent symptoms of cutaneous allodynia. Co-administration of pH 6.0/PrNMI with the peripherally restricted selective CB1R inverse agonist, 18A (20 µM), or the brain-permeant selective CB2R inverse agonist, SR144528 (20 µM), abolished the preventative effects of PrNMI. Patch clamp recordings from fluorogold-labeled dural afferent trigeminal ganglion neurons (dTGs) acutely isolated 3 days after fluorogold co-injection with pH 7.4 or pH 6.0 saline revealed altered membrane properties and excitability of dTGs from pH 6.0-treated animals. Fluorogold labeled dTGs were small (< 25 µm, n = 96) to medium (25-45 µm diameter, n = 70) size, respectively, with majority (92/74) positive for binding the isolectin B4, which predominantly labels non-peptidergic nociceptors. These data demonstrate altered excitability of dural afferents 3 days after administration of acidic solutions and that PrNMI prevents behavioral symptoms of acid-induced hyperalgesic priming and latent sensitization only if co-administered with the first hyperalgesic stimulus.

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Poster

PSTR067: Headache, Migraine, and Trigeminal Circuits

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Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR067.10/C108

Topic: D.01. Somatosensation – Pain and Itch

Title: Miniscope-based in vivo blood vessel imaging enables a novel assay for testing migraine therapeutic candidates

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Abstract: Vascular dynamics are pivotal in brain health and central nervous system disorders, particularly in conditions such as migraine. However, the specific nature of cerebrovascular reactivity in migraine remains an actively researched topic, with ongoing discussions on whether it acts as the cause or consequence of the disease. The current study delves into the importance of dorsal meningeal arteries and intermediate vessels, whose dilation is frequently linked to the onset of migraine episodes. Within this context, we introduce a novel preclinical tool and associated methods to evaluate vascular changes in vivo by testing vasoactive references such as Levcromakalim and the neuropeptides Pituitary Adenylate Cyclase-Activating Polypeptide (PACAP), to replicate migraine-like conditions and assess their effects on vasodilation. This research strives to enhance our understanding of the relationship between vascular dynamics and migraine pathophysiology. Ongoing efforts include employing these methods to investigate additional potential mechanisms and therapeutic targets implicated in migraine, such as CGRP, VIP or, for instance, assessing whether migraine abortives like Sumatriptan prevents PACAP-induced vasodilation. Our findings may be beneficial for future perspectives on potential migraine therapeutics.

Disclosures: J. Zapata: None. **K. Zitelli:** None. **J.J. Nassi:** None. **B.J. Hall:** None. **P. Botta:** None.

Poster

PSTR067: Headache, Migraine, and Trigeminal Circuits

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR067.11/C109

Topic: D.01. Somatosensation – Pain and Itch

Support: Canada Graduate Scholarship M
UTCSP Pain Scientist Award
OSOTF/Unilever Lipton Graduate Fellowship
IMS Open Fellowship Award

Title: Pain relief following surgery mitigates hippocampal signatures of accelerated brain aging in trigeminal neuralgia

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Abstract: Up to 50% of trigeminal neuralgia (TN) patients eventually require surgery to treat their chronic neuropathic facial pain. However, few biomarkers can reliably predict surgical response. Brain age, a correlate of the brain's biological wellbeing, differs between patients who have pain relief following surgery versus those who do not. Abnormalities in the hippocampus also appear to normalize after pain relief. Given the intrinsic link between the hippocampus and aging, and its ability to recover following surgery, we hypothesize that pain relief may mitigate accelerated brain aging in TN. We created a novel biological clock that primarily uses hippocampal volumes to highlight longitudinal brain age dynamics within TN. Magnetic resonance imaging (MRI) scans of the brains of 522 healthy subjects were obtained from the Cambridge Centre for Ageing and Neuroscience. MRI scans of 123 TN subjects were also collected within 4-months pre- and 8-months post-surgery. T1-weighted MRI scans were segmented into whole-brain and hippocampal subfield volumes using FreeSurfer 7.1. Support vector regression models were trained on the healthy brain volumes and optimized via backwards sequential feature selection, 10-fold cross-validation, hyperparameter tuning, and regression effect correction. The final model was validated on 99 healthy brains from our local database. The chronological age, or brain age, of 105 healthy and 123 TN subjects were predicted and compared. After optimization, healthy brain ages were predicted with very high accuracy (R^2 = 0.95; *MAE* = 3.3 years). TN subjects had a mean brain age 4.5 ± 0.4 years greater than their actual age ($q < 0.001$), indicating accelerated brain aging. This brain age gap significantly decreased in both male (n = 32) and female (n = 66) responders to surgery (both $q < 0.001$) and in subjects with right-sided facial pain (n = 57; q = 0.007), but not in non-responders, nor in left-sided facial pain. In summary, the brains of patients with TN appeared biologically older. We demonstrate for the first time in TN that accelerated brain aging may be mitigated with pain relief. The differing profiles of brain age dynamics between surgical response support brain age as an objective and non-invasive prognostic biomarker for patients with TN. These findings promote a data-driven and inherently personalized approach to aid clinicians in identifying patients that may gain more benefits from surgery, which can ultimately expedite protracted treatment timelines.

Disclosures: J. Li: None. **T.H. Latypov:** None. **P. Srisaikaew:** None. **D. Jorgens:** None. **J. Kim:** None. **M. Hodaie:** None.

Poster

PSTR067: Headache, Migraine, and Trigeminal Circuits

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Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR067.12/C110

Topic: D.01. Somatosensation – Pain and Itch

Support: the National Natural Science Foundation of China 82271295
the National Natural Science Foundation of China 82171264

Title: Knockdown of sodium channel Nax improves neuropathic corneal pain induced by lacrimal gland resection in mice

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Abstract: Background: Neuropathic corneal pain (NCP) induced by dry eye is a heath-threatening condition, impacting quality of life and lacking effective treatment. Nax (encoded by Scn7a) has been identified as an atypical sodium channel which functions as a sodium concentration-sensing channel to maintenance of sodium homeostasis in mammals rather than a voltage-dependent channel. Our previously results of single-nucleus RNA sequencing demonstrated that Scn7a in the TG responds to dry eye induced-NCP in mice. However, whether Nax plays a role in dry disease induced-NCP remains unknown. The aim of this study was to investigate the potential role of Nax (Scn7a) in dry eye induced-NCP and evaluate the analgesic effect of knockdown of Nax (Scn7a). **Methods:** C57bl/6 mice were subjected to dry eye through lacrimal gland resection. Tears volume and the degree of corneal injury were evaluated on d21 after surgery. qRT-PCR was performed to detect Scn7a expression level and immunofluorescence was applied to determine the subcellular localization. From d14 to d18 after surgery, the mice were injected with vehicle or siRNA Scn7a (10 nmol, 1μL) once-daily for 5 consecutive days. Corneal mechanical sensitivity was tested using von Frey filaments (0.008 and 0.02 g) and the chemical sensitivity was measured using one drop (2.5 μL) of 100 μM menthol or 2 μM capsaicin in each eye before and on d14 , d21 and d28 after surgery. The corneal sensitivity was associated with the number of blinks elicited by stimulus. **Results:** Firstly, dry eye mice displayed increased corneal sensitivity with decreased of tear production and increased corneal injury on d21 after surgery. Meanwhile, at a molecular level, upregulated mRNA level of Scn7a was detected in the TG tissue following lacrimal glands removal. At a cellular level, we observed dry eye increased Scn7a-positive neurons in the TG. Furthermore, comparing with the sham group, the corneal mechanical and chemical sensitivity were significantly higher in the lacrimal gland removed-mice on d14 after surgery. However, in vivo knockdown of Nax locally in the TG significantly blocked development of dry eye induced-corneal pain on d21 and d28 after surgery. This analgesic effect was persistent for at least 2 weeks after the intra-TG administration of siRNA Scn7a. **Conclusion:** Our study proves that dry eye can induce corneal hyperalgesia in mice and uncovers the role of Nax (Scn7a) in modulating corneal sensitivity, providing a novel treatment strategy for dry eye induced-NCP.

Disclosures: F. Danyun: None. **Y. Han:** None. **W. Li:** None. **J. Wu:** None. **L. Feng:** None.

Poster

PSTR067: Headache, Migraine, and Trigeminal Circuits

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR067.13/Web Only

Topic: D.01. Somatosensation – Pain and Itch

Support: Scientific and Technological Research Council of Türkiye (TÜBİTAK) 1004 23AG014

Title: Interictal Migraine Reveals Insular Cortex Activation in Response to High- Frequency Stimuli

Authors: *Z. ONLAT[1,2], S. ÜSTÜN[1,2], H. KOLENOGLU[3,2], M. CEREN AKGOR[4], D. VURALLI[4,5], S. ALKAN[4,6], M. ÇIÇEK[1,2], H. BOLAY[4,5];
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Abstract: Migraine, a prevalent neurological disorder marked by recurring headache attacks, is actively being studied in its connection with visual sensory processing and cognition. Understanding migraine's pathophysiology is vital for effective treatment development. This study aims to investigate neural changes linked to visual processing in migraine patients during both ictal and interictal phases.The study utilized a block design to examine differences in sensory sensitivity among migraine patients during interictal and ictal periods, compared to healthy controls. The sample comprised 23 females (6 ictal, 8 interictal, 9 controls), chosen following clinical interviews. During fMRI scanning, participants performed visually demanding shape discrimination and localization tasks designed to measure sensory sensitivity, alongside a control condition. Images were collected using a 3T MRI scanner, and results were analyzed using SPM12.Our main finding suggests increased left insula activation in patients during interictal periods compared to both ictal patients and healthy controls during visual tasks. This increased activation implies heightened sensitivity to visual stimuli during interictal periods. Additionally, the anticipation of pain from high-contrast images may have triggered insula activation. This hypothesis stems from the link between the insula and pain processing, as well as the notion that visually demanding tasks could elicit such a response. Notable differences in neural activation patterns were observed between the control and ictal group during the task. Increased activation in the dorsolateral prefrontal cortex, frontal visual field, and visual cortex in ictal periods suggests challenges in maintaining visual and cognitive attention.

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Poster

PSTR067: Headache, Migraine, and Trigeminal Circuits

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

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Topic: D.01. Somatosensation – Pain and Itch

Support: NIH grant R01CA231396
IASP John. J. Bonica Trainee Fellowship

Title: The role of Oral Cancer Proteases in the Activation and trafficking of PAR_2 in Oral Cancer Pain

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Abstract: Oral cancer pain is one of the most intense among all cancers. High levels of proteases released by the cancer activate the protease-activated receptor 2 (PAR_2, encoded by *F2RL1*) on trigeminal neurons. Our work has shown that the proteases cathepsin S (CTSS) and legumain elicit oral cancer pain and retain PAR_2 at the cell surface. The matrix metalloprotease (*MMP1*) and serine protease 23 (*PRSS23*) redistribute PAR_2 to the cis-Golgi and Rab14 vesicles and matriptase (*ST14*), which cleaves PAR_2 at the same canonical site as trypsin, induces PAR_2 redistribution to endosomes. We hypothesize that the mixture of proteases released in the oral cancer microenvironment activates PAR_2 and promotes its redistribution to multiple intracellular locations, from which PAR_2 elicits oral cancer pain. Understanding PAR_2 spatiotemporal signaling could guide the development of targeted pain relief treatments for oral cancer. We studied PAR_2 trafficking and signaling induced by a mixture of proteases overexpressed in human oral cancers. The mixture included: MMP1, PRSS23, ST14 and CTSS. PAR_2 trafficking was examined by Bioluminescence Resonance Energy Transfer (BRET) assays in HEK293 cells expressing human PAR_2 and resident proteins from the plasma membrane (Kras), endosomes (Rab5 and Rab7), Rab14 vesicles and the Golgi (Giantin and TGN38). PAR_2 signaling was studied by measuring second messengers using the BRET sensor for cAMP (CAMYEL) and FRET sensors for ERK (EKAR), PKA (AKAR) and PKC (CKAR). Intracellular Ca^{2+} was measured using FURA-2 AM. Nociception was assessed *in vivo* by von Frey filaments after injection of the mixture. Our findings show that the mixture of proteases does not display all PAR_2 trafficking and signaling events observed by the individual proteases. The mixture promoted PAR_2 internalization and redistribution to the cis-Golgi and Rab14 vesicles, but not to endosomes. The mixture also elicited differential signaling of PAR_2, promoting Ca^{2+} influx, cAMP and PKA activation. These results suggest that the study of PAR_2 activation by individual proteases *in vitro* may not accurately reflect PAR_2 trafficking in the oral cancer microenvironment. Intraplantar administration of the mixture elicited nociceptive responses assessed with von Frey filaments. Whether oral cancer nociception is mediated by PAR_2 located in the cis-Golgi and Rab14 is yet to be determined. The mixture of proteases allowed us to identify the cis-Golgi and Rab14 vesicles as intracellular locations that could drive PAR_2-mediated oral cancer pain signaling. Nonetheless, further studies are needed to validate whether PAR_2 drives oral cancer pain from a single or multiple cellular locations.

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Poster

PSTR067: Headache, Migraine, and Trigeminal Circuits

Location: MCP Hall A

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Topic: D.01. Somatosensation – Pain and Itch

Support: NIH Grant R01NS102722
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W81XWH1810431

Title: Site-specific variation in TRPV4 functional activity in Schwann cells of squamous cell carcinoma patients: implications for oral cancer pain

Authors: *Y. MULPURI[1], C. SAWICKI[1], B. BENTON[1], D. G. ALBERTSON[2], B. L. SCHMIDT[1];
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Abstract: Oral cancer (squamous cell carcinoma, SCC) patients suffer from debilitating pain while eating and swallowing, actions that result in pressure and stretch at the cancer site. The mechanisms responsible for oral cancer pain are not well understood and the pain is not adequately managed. Schwann cells (SC) are glial cells of the peripheral nervous system that ensheathe axons of sensory neurons; SCs have been implicated as mediators of pain in peripheral neuropathies and chronic migraine. SCs express mechanosensitive ion channels, including TRPV4, a non-selective cation channel activated by mechanical pressure and stretch, suggesting a potential role for SCs in mediating stretch induced pain in oral cancer patients. In support of this hypothesis, we have demonstrated that (1) TRPV4 is functionally expressed on SCs isolated from trigeminal nerve fibers innervating the oral cancer in human patients and (2) TRPV4 on human SCs mediates mechanosensitivity induced by tangential shear stress (Mulpuri et al., SfN Abstr. 544.06, 2023). In the current study, we investigated (1) whether there was an oral cancer site-specific difference in pain reported by patients and (2) whether the functional activity of TRPV4 on SCs varies depending on the anatomical site of the oral cancer. The data on reported pain was collected using the validated UCSF Oral Cancer Pain Questionnaire (UCSFOCPQ). Eight questions on UCSFOCPQ differentiate spontaneous versus function-related pain and determine the quality of pain. Because patients with metastatic cancer report greater pain, we compared the mean pain scores for gingiva (n=8) and tongue (n=17) cancer patients with node-

negative pT1 and pT2 cancers from the cohort of Bhattacharya et al., 2020. Mean pain scores reported by patients with gingival cancers (5.1 ± 2.3) were lower than those of tongue cancer (24.3 ± 5.8) patients ($p=0.04$, two-tailed t-test). Since SCs phenotype varies depending on the peripheral tissues that nerve fibers innervate, we isolated SCs from the nerve fibers innervating the SCC of tongue and maxillary gingiva and palate and evaluated TRPV4 functional activity with patch clamp electrophysiology. In whole-cell patch clamp experiments, the TRPV4 agonist (GSK101, 0.1 μM) induced SC currents (pA/pF) at -90 mV membrane potential for SCs derived from nerve fibers of tongue SCC and hard palate SCC were -22.4 ± 2.4 and -3.1 ± 0.4 (mean ± S.E.M), respectively; the TRPV4 selective antagonist (HC067047, 1 μM) blocked SC currents induced by GSK101 ($p<0.001$, two-way ANOVA, n=2-3 cells/group). These findings are significant because they suggest that SCs may have different responses or involvement in pain depending on the oral cancer site.

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Poster

PSTR067: Headache, Migraine, and Trigeminal Circuits

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR067.16/C113

Topic: D.01. Somatosensation – Pain and Itch

Title: A decrease in perineuronal nets in the mesencephalic reticular formation in mouse models of migraine and opioid induced hyperalgesia.

Authors: *J. AGUILAR[1], W. PAGE[1], S. CUI[1], A. A. PRADHAN[1], A. W. LASEK[2]; [1]Anesthesiol., Washington Univ. in St. Louis, Saint Louis, MO; [2]Pharmacol. and Toxicology, Virginia Commonwealth Univ., Richmond, VA

Abstract: The development of novel therapeutics for migraine has been hindered by the incomplete understanding of the mechanisms that regulate headache disorders. A better understanding of the molecular and cellular contributors to the development of headache could lead to new therapeutic targets. Specialized condensed extracellular matrix structures known as perineuronal nets (PNNs) have recently been implicated in the modulation of inflammatory and neuropathic pain. Our lab has identified a cluster of PNNs surrounding a population of parvalbumin (PV) cells in the mesencephalic reticular formation (MRF), a brain region that innervates regions involved in pain-processing. The present study investigated the effect of two different mouse headache models on PNN integrity: a nitroglycerin (NTG) model of chronic migraine, and a model of opioid-induced hyperalgesia (OIH) or medication overuse headache (MOH). Male and female C57BL6/J mice were tested in these two models, and brains were collected 18-24 h after the final injection in each paradigm, a time at which maximal cephalic allodynia was observed. Immunohistochemistry was performed to visualize PNNs and PV neurons. The number and fluorescence intensities of PNNs and PV+ cells were analyzed in the

somatosensory cortex (SSC), insular cortex, and MRF. PNN and PV numbers did not change following NTG or MOH treatment in any brain region analyzed. In both models, PNN and PV intensity significantly decreased in the MRF in both sexes OIH/MOH also resulted in a significant decrease in PNN intensity in the insula of both sexes with no changes observed in the SSC. We also tested whether these changes would occur after a single NTG treatment, which induces transient cephalic allodynia. PNN and PV intensities in the MRF did not change after acute NTG. These results suggest that changes in PNNs and PV may play a role in pain chronification; future studies will determine the mechanistic role of MRF PNNs in nociceptive and headache pain processing.

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Poster

PSTR067: Headache, Migraine, and Trigeminal Circuits

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR067.17/C114

Topic: D.01. Somatosensation – Pain and Itch

Support: NIH Grant CDM K01NS121195

Title: Exploring the role of TRPV4 in pain induction following mild traumatic brain injury

Authors: *M. L. HERNANDEZ[1], M. FOUANI[2], R. E. CHAPARRO[3], C. D. MOORE[1]; [1]Neurol., Duke Univ., Durham, NC; [2]Duke Univ., Durham, NC, ; [3]Neurosurg., Duke Univ., Durham, NC

Abstract: Headaches are pain sensations that occur somewhere in the head. A frequent complaint after traumatic brain injury (TBI) is post-traumatic headache (PTH), a secondary headache that arises around 7 days following injury or following restoration of sensations. The pathological sequences that induce this phenomenon are not well defined. Transient Receptor Potential Vanilloid 4 (TRPV4), a non-selective cation channel involved in sensing chemical, thermal, osmotic, and mechanical stimuli, has been implicated in various pain syndromes, including headache. We hypothesize that an upregulation of TRPV4 may play a significant role in the development of PTH following mild TBI. This study aims to elucidate the role of TRPV4 in pain induction and the pathological changes following mTBI, using both wildtype and TRPV4 knockout mice models, examining the effects up to 2 weeks following closed head injury, in both male and female adult mice, 12 weeks or older. To assess pain, we used mechanical pain tests including periorbital Von Frey to measure hyperalgesia (up-down method) and allodynia (repeated stimulus). Furthermore, we employed the mouse grimace scale as an additional, non-evoked method to investigate PTH. This approach involved recording the mice and utilizing PainFace Software for the assessment of facial expressions indicative of pain. After the completed timepoint, mice were sacrificed for their trigeminal ganglia and brains, which we

examined for neuronal activity changes and the expression of TRPV4 in key brain regions associated with pain processing: anterior cingulate cortex (ACC), thalamus, periaqueductal grey (PAG), and the trigeminal nucleus. The trigeminal ganglion was also examined and co-labeled via fluorescent immunohistochemistry (IHC) with NeuN and pERK to investigate neuronal activity changes following injury with and without TRPV4. IHC was further used to evaluate the expression markers of gliosis and brain injury, like GFAP and Iba-1. By delineating the contributions of TRPV4 to the development of PTH, we aim to deepen the understanding of the pathological processes post-TBI. This research aims not only to further our knowledge of the molecular underpinnings of pain but also to pave the way for identifying TRPV4 as a promising pharmacological target for the treatment of PTH.

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Poster

PSTR067: Headache, Migraine, and Trigeminal Circuits

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Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

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Topic: D.01. Somatosensation – Pain and Itch

Support: NIH Grant CDM K01NS121195

Title: Deciphering the role of TRPV4 in Mast-cell mediated migraine pathophysiology

Authors: *M. FOUANI, C. WICKWARE, A. CHARLES, S. KUMARI, C. MOORE; Neurol., Duke Univ., Durham, NC

Abstract: Migraine is a complex neurological disorder characterized by recurrent moderate-to-severe headaches along with other symptoms. Transient Receptor Potential Vanilloid 4 (TRPV4), a non-selective cation channel involved in detecting osmotic and mechanical stimuli, has been implicated in various pain syndromes, including migraine. Our study investigates TRPV4 in mast cells (MCs) within the dural meninges. MCs are strategically positioned near sensory neurons, which release neuropeptides that significantly contribute to migraine pathophysiology. We aim to understand TRPV4's role in meningeal neurogenic inflammation and its impact on pain modulation during migraines. To explore the role of TRPV4 in migraine pain, we used 2 migraine models: supradural injections and NTG injection, Pain behavior was assessed using Periorbital von Frey. Primary cultured mouse bone marrow mast cells (BMMCs) were stimulated with Mastoparan 7 (Mas7) and the effects of TRPV4 antagonists on Ca^{2+} influx and degranulation were observed. We conducted hemi-skull preparations to directly stimulate the meninges and monitor MC activity, and we explored the systemic inhibition of MCs using ketotifen to determine its effect on migraine-like pain Our findings demonstrate that TRPV4 activation in the dura led to decreased periorbital cutaneous thresholds, indicating a potential role

for TRPV4 in mediating headache-associated pain. In the NTG model, we observed heightened periorbital allodynia in WT mice, which was attenuated in TRPV4 KO mice. Immunohistochemistry and western blot analysis showed increased TRPV4 immunoreactivity and protein expression in TG from NTG-treated animals. Inhibition or deletion of TRPV4 in BMMCs inhibited Mas 7 induced Ca^{2+} influx and degranulation, supporting TRPV4's crucial role in MC activation. Meningeal MC degranulation was attenuated in TRPV4 KO mice, and systemic inhibition of MC using ketotifen resulted in a pronounced reduction in periorbital allodynia, indicating similar underlying mechanisms between TRPV4 activity and MC stabilization. In summary, our research indicates that TRPV4 is a key player in migraine pathophysiology, affecting pain signaling and MC function. The reduced pain responses in TRPV4 knockout models and the modulation of TRPV4 expression highlight its therapeutic potential. These insights pave the way for new treatments targeting the neurogenic inflammation in migraines.

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Poster

PSTR067: Headache, Migraine, and Trigeminal Circuits

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Topic: D.01. Somatosensation – Pain and Itch

Support: NIH Grant 5U19NS130617-02

Title: Multi-omic and spatial transcriptomic profiling of human trigeminal ganglia

Authors: *E. SEMIZOGLOU[1], P. BHATIA[1], I. LOPEZ[2], J. MOFFITT[3], W. RENTHAL[4]; [1]Brigham and Women's Hosp., Boston, MA; [2]Mass Genreal Brigham, Somerville, MA; [3]Boston Children's Hosp., Boston, MA; [4]Neurol., Brigham and Women's Hosp., Boston, MA

Abstract: Headache disorders, such as migraine, are among the leading causes of morbidity worldwide[1]. They involve activation of peripheral sensory neurons whose cell bodies reside in the trigeminal ganglion (TG)[2], a complex structure comprised of neuronal and non-neuronal cells[3]. Study of the cell types and their genetic profiles in human trigeminal nociceptors, could both help understand the complex genetic mechanisms underlying migraine susceptibility[4] and guide the development of novel headache and facial pain treatments. Recent advances in single-cell transcriptomics have enabled the molecular characterization[5] of human TGs and generation of reference atlases[6]. However, neurons comprise only a small portion of the total human TG cell population, leading most bulk sequencing studies to sequence proportionally more non-neuronal than neuronal cells. Therefore, due to the low number of sequenced neurons it is difficult to decipher the neuronal transcriptomic and epigenetic complexity. Our lab has generated a standard procurement and processing pipeline to enrich for neuronal cells in postmortem human

TG samples and process them for multi-omic sequencing. Cross-species analysis of the data identified evolutionarily conserved epigenomic features that likely contribute to conserved cell-type-specific gene regulatory programs. In addition, our tissue procurement and processing pipeline supports spatial transcriptomic assays, such as multiplexed error-robust fluorescence *in situ* hybridization (MERFISH). We are able to maintain orientation of the trigeminal branches and resolve spatially the location of neuronal and non-neuronal cells based on the expression of G-protein coupled receptors (GPCRs) and ion channels. In conclusion, our lab has standardized a procurement and downstream processing pipeline for postmortem human TGs to support multi-omic and spatial transcriptomic assays. Detection of neuronal epigenomic features as well as the transcriptomic profile and projection-specific location of neuronal clusters will support the identification of novel therapeutic targets for migraine.
[1] Steiner, T J et al. 2020 J Headache Pain[2] Akerman, S et al. 2011 Nature Reviews[3] Goto, T et al. 2016 The journal of physiological sciences[4] Sutherland, HG et al. 2019 Advances in genetics of migraine[5] Yang, L et al. 2022 Neuron6 Bhuiyan, SA et al. 2023 bioRxiv

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Poster

PSTR067: Headache, Migraine, and Trigeminal Circuits

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Topic: D.01. Somatosensation – Pain and Itch

Support: NIH R01-NS126752-01A1

Title: Abhd6 partially reversed medication overuse headache induced allodynia induced by sumatriptan

Authors: *A. M. BURTMAN[1], M. FLOWERS[2], S. A. COUTURE[1], N. STELLA[3], E. LIKTOR-BUSA[4], T. M. LARGENT-MILNES[5];
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Abstract: Title: ABHD6 Partially Reversed Medication Overuse Headache Induced Allodynia Induced by Sumatriptan.
Authors: Anya Burtman*, Matthew Flowers, Manvir Kaur, Simar Singh, Sarah Couture, Sally Young, Nephi Stella, Erika Liktor-Busa, Tally M Largent-Milnes
Background: The pathophysiology of headache disorders such as medication overuse headache(MOH) is poorly understood, making treatment difficult. However, recent evidence has implicated the involvement of endocannabinoid deficiency, specifically in decreased levels of 2-

AG within periaqueductal gray (PAG), in multiple models of headache pain. Our previous research has shown that blockade of 2-AG degradation using a selective ABHD6 inhibitor, KT-182, both prevented and reversed periorbital allodynia in a cortical spreading depression (CSD) headache model. Given our observations that MOH also reduced PAG levels of 2-AG, this study aimed to evaluate the efficacy of inhibiting ABHD6 for MOH headache like pain behaviors. Medication overuse headache (MOH) was induced in female and male Sprague Dawley rats by sustained sumatriptan infusion via subcutaneous osmotic minipumps at a concentration0.6mg/kg/day. On days 4,7, and 10 after minipump implantation, PAG tissue was harvested from male and female rats for analysis of lipids, enzyme activity, and protein levels. In a separate set of rats, intraperitoneal (IP) injections of either an ABHD6 inhibitor (KT-182, 2mg/kg) or vehicle(ethanol-cremophor-saline 1:1:18, v/v/v, 1mL/kg) were dosed. Periorbital allodynia was assessed via von Frey assays and light sensitivity determined at various time points before and after IP injection. Sumatriptan induced MOH in a higher percentage of female as compared to male rats ,though in rats exhibiting allodynic responses, the magnitude was similar in both sexes. In rats with headache like behaviors, those that received the ABHD6 inhibitor had periorbital allodynia thresholds statistically higher than those receiving vehicle, suggesting that targeting ABHD6 for MOH attenuation is a potential strategy. Targeting ABHD6 with the inhibitor KT-182 mitigated periorbital allodynia in sumatriptan induced MOH animals, indicating a potential intervention for the reversal of MOH.
Late-Breaker Justification: Data collection was still underway during the initial timeframe o fabstract submission; therefore, results could not be completed until now.
This study is supported by NIH R01-NS126752-01A1

Disclosures: A.M. Burtman: None. **M. Flowers:** None. **S.A. Couture:** None. **N. Stella:** None. **E. Liktor-Busa:** None. **T.M. Largent-Milnes:** None.

Poster

PSTR067: Headache, Migraine, and Trigeminal Circuits

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR067.21/C118

Topic: D.01. Somatosensation – Pain and Itch

Support: UC2AR082197

Title: Longitudinal calcium imaging to determine the response properties of temporomandibular joint-innervating neurons in the trigeminal ganglion

Authors: *A. X. ROBERTS[1], B. GOOLSBY[2], M. FONSECA[2], E. A. RONAN[4], J. J. EMRICK[5], C. DONNELLY[3];
[1]Anesthesiol., Duke Univ., DURHAM, NC; [3]Dept. of Anesthesiol., [2]Duke Univ., Durham, NC; [4]Mol. and Integrative Physiol., Univ. of Michigan, Ann Arbor, MI; [5]BMSP, Univ. Michigan, Ann Arbor, MI

Abstract: Temporomandibular disorders are the most common form of chronic orofacial pain, affecting >5% of U.S. adults. Despite its prevalence and the high morbidity associated with chronic TMD pain, we lack effective treatments, in part because we have an incomplete understanding of the somatosensory neurons in the trigeminal ganglion (TG) that innervate the component tissues of the temporomandibular joint (TMJ). To obtain a better understanding of somatosensory coding and plasticity of TMJ-innervating TG sensory neurons in health and disease states, we have developed a reliable method which enables us to perform longitudinal calcium imaging to measure the response properties of neurons residing in the V3 portion of the TG. This method relies on the surgical implantation of an intracranial gradient index (GRIN) lens in GCaMP8m-expressing mice. Under anesthesia, a guide needle 1mm in diameter is mounted to a stereotactic holder and slowly advanced until it is directly overlying the V3 region of the TG (approximately -5.7mm z-axis, relative to Bregma). The guide needle is subsequently replaced with a GRIN lens (7mm in length, 0.72mm in diameter, 0.2mm working distance; Inscopix) which is cemented in place. Once implants are stabilized, mice are repeatedly habituated to the presence of a dummy scope and subsequently to the presence of a miniature fluorescent microscope ('miniscope', 1440x1080 resolution; Inscopix) attached to an optical cable fed into a commutator. During habituation sessions, mice are placed in an open field and are permitted to freely move with the miniscope and retractable cable attached. During recording sessions, calcium imaging data are collected at a sampling rate of 30-60 Hz (~1.0 mW/cm2 power). TG neurons innervating the TMJ component tissues are identified using an electric pulse generator. Although we are still working to optimize this method in awake and freely behaving mice, we have successfully used this technique to perform calcium imaging sessions in anesthetized mice, co-registering calcium imaging data with the application of non-noxious and noxious sensory stimuli to identify the response properties of neurons within the receptive. Our ongoing experiments are exploring how the response properties of TMJ-innervating TG neurons are altered in TMD pain models over a longitudinal time course.

Disclosures: A.X. Roberts: None. **B. Goolsby:** None. **M. Fonseca:** None. **E.A. Ronan:** None. **J.J. Emrick:** None. **C. Donnelly:** None.

Poster

PSTR067: Headache, Migraine, and Trigeminal Circuits

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR067.22/C119

Topic: D.01. Somatosensation – Pain and Itch

Title: Comprehensive study of the sex-specific alterations of the brain vascular responsiveness in a preclinical model of migraine, using ultrafast Doppler imaging

Authors: *S. PEZET;
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Abstract: Migraine is one of the most prevalent and disabling neurovascular disorders worldwide. However, despite the increase in awareness and research, the understanding of migraine pathophysiology and treatment options remain limited. For centuries, migraine was considered to be a vascular disorder. In fact, the most successful migraine treatments act on the vasculature and induction of migraine can be accomplished with vasoactive agents. Since, the vascular nature of migraine is still debated, and the emphasis has now shifted to the neural imbalances associated with migraine. Taking advantage of the high sensitivity of ultrafast Doppler imaging to cerebral blood volume (CBV), along with its high spatial and temporal resolutions and its large field of view, this study aimed at studying the changes of cerebral blood volume in a large part of the brain during the development of sensitization in an animal model of migraine (induced by repetitive injections of nitroglycerin), and once sensitized, during inter-ictal periods and during migraine attacks. Existence of a possible dimorphisms was studied through inclusion of two cohorts of male/female rats. The chronic migraine-like model was induced in Sprague-Dawley male rats using repetitive intraperitoneal injections of nitroglycerin (NTG). Facial mechanical threshold sensitivity was monitored using von Frey hair filaments before the model induction and before each imaging session. Ultrafast Doppler imaging sessions were performed in anaesthetized animals through a chronically implanted cranial window before and several hours following the 1st, 4th and 5th injection of NTG. In addition, with the short-term vasodilation induced by NTG, previously reported, our study reveals that the acute injection of NTG in naïve animals induces a long-lasting (2-3 hours) hyperperfusion in groups of brain areas (including the cingulate, retrosplenial and medial visual areas). Once sensitized, female rats display a very strong unilateral hyperperfusion in these same brain regions. In sensitized animals, NTG injection induced an exacerbation over time of the CBV in these areas. In male in contrary, these changes were present, but comparatively modest. Our results show, for the first time in this translational animal model of migraine, clear zones of the cerebral vasculature that are the center of altered vascular tone. The exacerbation observed overtime, its unilateral nature, and its location in mediomedial visual areas are consistent with clinical observations. Our results also point also towards a strong dimorphism in these pathophysiological changes.

Disclosures: S. Pezet: None.

Poster

PSTR067: Headache, Migraine, and Trigeminal Circuits

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR067.23/C120

Topic: D.01. Somatosensation – Pain and Itch

Support: R01NS072497
K01NS124911

Title: Transcriptome-level Identification of Pathways Involved in the Choroid Plexus of Pre-clinical Chronic Migraine Model

Authors: *Y. WOLDEAMANUEL[1], S. DING[2], C. XIA[3], X. ARAKAKI[4];
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Abstract: Motivation: Migraine patients show changes in their choroid plexus (CP), leading to disruptions in the blood-CSF barrier and increased cell adhesion molecules. A comprehensive understanding of transcriptome-level CP changes can unveil regulatory gene pathways involved in migraine. **Methods:** *Chronic migraine model.* The experimental group (3 females, 3 males, Sprague Dawley rats) received nitroglycerin injections every other day for 5 days, while the control group (3 females, 3 males) received saline. All animals were sacrificed 2 hours after the last injection, and the CP of the 4th ventricle was collected for RNAseq. *RNAseq and pathway analysis.* Differentially expressed genes were identified using edgeR ($p < 0.05$, 1.5-fold changes). Enrichment and pathway analyses were conducted using GO, KEGG, and Reactome. **Results:** When comparing the nitroglycerine-induced chronic migraine models to control, the GO enrichment analysis showed biological process changes involving cellular response to peptides, cognitive processes, mononuclear cell differentiation, leukocyte cell-cell adhesion, and regulation of cell adhesion. The cellular component of the GO enrichment analysis revealed changes in the synaptic membrane, extracellular matrix, membrane rafts, and membrane microdomain. Changes in molecular function include potassium ion transmembrane transporter, calcium-dependent protein binding, and P-type Na-K-exchanging transporter. The KEGG pathway analysis (Figure 1) showed MAPK, cAMP, Ras signaling, synaptic vesicle cycle, and cell adhesion molecules as the top altered pathways. The Reactome pathway analysis revealed changes in neutrophil degranulation and regulation of insulin-like growth factors. **Conclusions:** Our findings indicate that chronic migraine is linked to alterations in multiple pathways within the choroid plexus related to pain processing and modulation, signaling, ion transporters, cell adhesion molecules, and leukocyte degranulation.

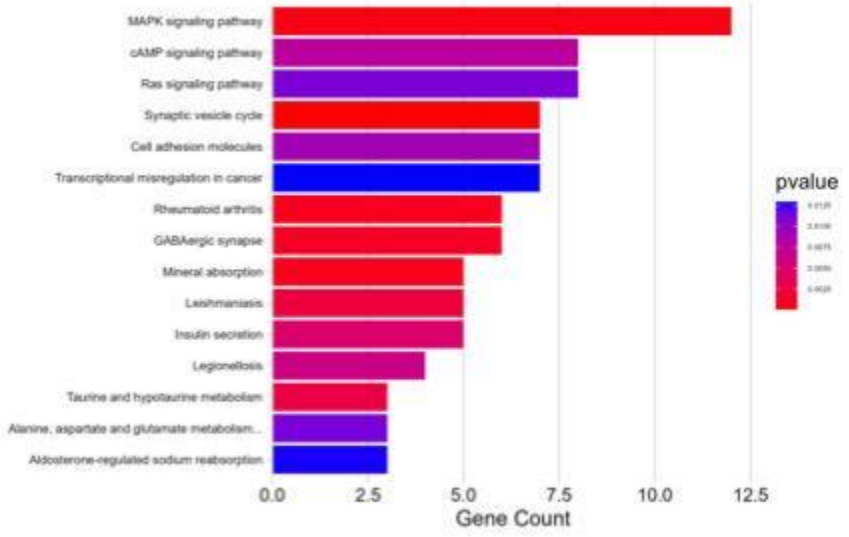

Figure 1. KEGG pathway analysis demonstrates pathways that are dysregulated in NTG-induced migraine model compared to control. Differentially expressed genes were identified using edgeR ($p < 0.05$, 1.5-fold changes).

Disclosures: Y. Woldeamanuel: None. **S. Ding:** None. **C. Xia:** None. **X. Arakaki:** None.

Poster

PSTR067: Headache, Migraine, and Trigeminal Circuits

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR067.24/C121

Topic: D.01. Somatosensation – Pain and Itch

Support: "Sex dimorphism in migraine: thermoTRPs as hormonal and drug targets (GIOCONDA)" Grant number: PID2021-126423OB-C21, Ministerio de Ciencia e Innovación – Agencia Estatal de Investigación co-funded with FEDER funds from EU "Una manera de hacer Europa"
"A pre-clinical human nociceptive in vitro model for investigating sexual dimorphism in chronic migraine and screening drug candidates (HEADaCHE)" Grant: RTI2018-097189_B-C21, Ministerio de Ciencia e Innovación – AEI co-funded with FEDER EU funds

Title: Behavioural roles for TRPM8 in a Mouse Model of Chronic Migraine

Authors: *D. CABAÑERO[1], A. FERNÁNDEZ-CARVAJAL[2], A. V. FERRER-MONTIEL[3]; [1]Univ. Miguel Hernández de Elche, Elche, Spain; [2]Univ. Miguel HernáNdez, Elche, Spain; [3]IDiBE, Universitas Miguel Hernández, Elx/Elche, Spain

Abstract: Migraine is a complex painful disorder marked by emotional manifestations that intensify the pain experience. In some patients, the excessive use of analgesic treatments leads to a co-morbid condition known as Medication Overuse Headache, which has been associated with enhanced impulsivity and alterations in the brain reward system**[1]**. In this study, we aimed to investigate the involvement of TRPM8, a channel clinically associated with chronic migraine**[2]**, in mouse models of anxiety, impulsivity and depression, all symptoms associated with the exacerbation of pain in headache disorders. Female and male mice lacking TRPM8 and wild-type control mice were subjected to a battery of behavioral tasks designed to assess impulsivity, anxiety, and depressive-like phenotypes. Once altered behaviors were identified, these were further examined in a model of chronic migraine induced by repeated administration of nitroglycerine. Mice of both sexes lacking TRPM8 exhibited an enhanced impulsivity in the novelty-suppressed feeding test, which was reflected in a consistent shorter latency to bite a food pellet in a novel environment. While no alterations were observed in further tests evaluating anxiety-like behavior, TRPM8 knockout mice of both sexes showed increased depressive behavior in the forced swimming test, characterized by longer immobility or duration of despair-like behavior. Notably, when animals were exposed to the repeated nitroglycerine treatment, TRPM8 knockouts showed an increase in anxiety-like behavior that was not observed in wild-type mice, highlighting a protective function of TRPM8 in migraine conditions. On the other hand, the depressive-like behavior associated with the lack of TRPM8 was maintained regardless of the treatment with nitroglycerine or vehicle. These findings in genetically-modified mice suggest an involvement of the TRPM8 gene in impulsivity, anxiety- and depressive-like phenotypes. Since single nucleotide polymorphisms affecting TRPM8 are a genetic signature of patients suffering of migraine**[2]**, our study underscores the interest of characterizing behavioral traits involving anxiety, depression and impulsivity in humans carrying TRPM8 variants

associated with migraine. ***References:*** 1- Niddam et al. *An altered reward system characterizes chronic migraine with medication overuse headache*. Cephalalgia. 2023; doi:10.1177/03331024231158088 2-Chasman et al. *Genome-wide association study reveals three susceptibility loci for common migraine in the general population*. Nat Genet. 2011; doi:10.1038/ng.856

Disclosures: D. Cabañero: None. **A. Fernández-Carvajal:** None. **A.V. Ferrer-Montiel:** None.

Poster

PSTR067: Headache, Migraine, and Trigeminal Circuits

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR067.25/C122

Topic: D.01. Somatosensation – Pain and Itch

Support: NIH Grant NS104110
BBS Internal Research Grant from the University of Texas at Dallas

Title: The role of HPA axis and melanocortin signaling in repeated stress-induced migraine-like behaviors in mice

Authors: *Y.-Y. HU[1], R. R. SOUZA[1], A. N. AKOPIAN[2], C. K. MCINTYRE[1], G. O. DUSSOR[1];
[1]Dept. of Neurosci., The Univ. of Texas at Dallas, Richardson, TX; [2]Endodontics, UT Hlth. Sci. Ctr., San Antonio, TX

Abstract: Stress is the most common trigger for migraine attacks, but the mechanisms underlying the influence of stress on migraine attacks remain unknown. The body responds to stressors through the hypothalamic-pituitary-adrenal (HPA) axis activation and the release of glucocorticoids (GCs) to maintain homeostasis. However, migraine may be an adverse consequence of this GC response. We aimed to assess the role of the HPA axis in stress-induced migraines. We previously showed that repeated restraint stress in mice triggers migraine-like behaviors and causes priming to the nitric oxide donor, sodium nitroprusside. In this study, administration of metyrapone, a glucocorticoid synthesis inhibitor, blocked stress-induced hypersensitivity. This implied a strong dependency on corticosterone (CORT) synthesis for these behaviors. However, the effects of metyrapone may be due to either lack of CORT or increased ACTH or both. We found that treatment with ACTH after restraint stress reduced mechanical hypersensitivity and grimace scores in both the post-stress and priming phases in male and females. To identify a potential mediating receptor, we administered THIQ, a melanocortin 4 receptor agonist, after restraint stress. THIQ alleviated stress-induced migraine-like behaviors in males and females. Additionally, we investigated the effect of administering CORT after stress, as ACTH activates the HPA axis to increase CORT levels. Results indicate that while post-stress CORT injection partially reversed acute stress hypersensitivity in females, it had no effect in males. However, there was a reduction in behavioral responses in both male and female mice

during the priming phase. We further examined whether the effect of ACTH in stressed mice was mediated by CORT release. Stressed mice received metyrapone prior to the ACTH injection to prevent CORT synthesis. ACTH blocked stress-induced hypersensitivity in metyrapone-treated male mice, indicating the effects of ACTH are not due to CORT synthesis. In contrast, female stressed mice, under the same conditions, experienced only a partial reduction in hypersensitivity, suggesting a partial role for CORT signaling after ACTH administration. This study increases the understanding of the complex link between stress, the HPA axis, melanocortin signaling, and migraine-like behavior, offering several potential avenues for novel therapeutic interventions in managing stress-induced migraine.

Disclosures: Y. Hu: None. **R.R. Souza:** None. **A.N. Akopian:** None. **C.K. McIntyre:** None. **G.O. Dussor:** None.

Poster

PSTR067: Headache, Migraine, and Trigeminal Circuits

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR067.26/C123

Topic: D.01. Somatosensation – Pain and Itch

Support: NIH Grant NS127637

Title: Inhibition of PAR2 as a potential therapeutic mechanism for migraine

Authors: *H.-R. MEI[1,2], Y.-Y. HU[1,2], K. A. DEFEA[3], J. VAGNER[4], S. BOITANO[4,5,6], T. J. PRICE[1,2], G. O. DUSSOR[1,2];
[1]Univ. of Texas at Dallas, Dept. of Neurosci., RICHARDSON, TX; [2]Center for Advanced Pain Studies, University of Texas at Dallas, Richardson, TX; [3]PARMedics Inc., San Diego, CA; [4]Bio5 Inst., Univ. of Arizona, Tucson, AZ; [5]Asthma and Airway Disease Research Center, University of Arizona Heath Sciences, Tucson, AZ; [6]Department of Physiology, University of Arizona Heath Sciences, Tucson, AZ

Abstract: Migraine is the second most disabling disease worldwide. Despite the availability of various therapeutics, many individuals suffering from migraines do not receive sufficient relief. Previous studies have shown that dural administration of 48/80 (mast cell degranulator) induced periorbital hypersensitivity, and the inhibition of protease-activated receptor-2 (PAR2) with antagonists or genetic knockout PAR2 receptor blocked 48/80-induced periorbital hypersensitivity. This suggests the potential of PAR2 antagonists for migraine treatment. In this study, we assessed the efficacy of a novel PAR2 antagonist (C937) in two different preclinical migraine models. Facial mechanical withdrawal thresholds were measured using von Frey filaments and grimace scores were evaluated by observing mouse facial expressions. We first tested whether C937 blocked 48/80 induced behavioral hypersensitivity. Mice received dural coinjection of C937 (1 µg) with 48/80 (6.5 nmol) one hour prior to dural 48/80 (6.5 nmol). In separate experiments, mice received i.p. or p.o. C937 (10 mg/kg) also at one hour prior to dural

48/80 (6.5 nmol). In each case, C937 significantly reduced the 48/80-induced periorbital hypersensitivity and facial grimace responses, while no effect was observed in the vehicle group. Next, we tested the efficacy of C937 in the repetitive stress migraine model. We have shown previously that repetitive restraint stress (2 hours per day, three consecutive days) induces mechanical hypersensitivity and priming to the nitric oxide donor sodium nitroprusside (SNP). On day two post-stress, i.p. or p.o. (10 mg/kg) C937 did not attenuate stress-induced mechanical hypersensitivity. However, both i.p. or p.o. C937 (10 mg/ kg) one hour prior to SNP (0.1 mg/kg, i.p.) on day 14 post-stress significantly reduced SNP-induced periorbital hypersensitivity. These findings show that block of PAR2 can alleviate migraine-like symptoms triggered by the injection of dural 48/80 or SNP following stress and further support the rationale for development of PAR2 as a novel therapeutic strategy for migraine.

Disclosures: H. Mei: None. **Y. Hu:** None. **K.A. Defea:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); PARMedics. **J. Vagner:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); PARmedics. **S. Boitano:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); PARmedics. **T.J. Price:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); PARmedics. **G.O. Dussor:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); PARMedics.

Poster

PSTR067: Headache, Migraine, and Trigeminal Circuits

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR067.27/C124

Topic: D.01. Somatosensation – Pain and Itch

Support: NIH NIDCR R15 DE025970
NIH NIDCR F31 DE031959

Title: Sex differences in the effects of stress on pain genes in the trigeminal ganglia in a rat model of orofacial inflammatory pain

Authors: *B. ISLAM[1], D. CANTU[1], O. DARWISH[2], D. L. AVERITT[1];
[1]Biol., [2]Texas Woman's Univ., Denton, TX

Abstract: Psychological stress contributes to and amplifies orofacial pain, which is more prevalent in women. We recently reported that exposure to sub-chronic stress exacerbates inflammatory orofacial pain to a greater degree in female than male rats. Neuroanatomical analysis of the trigeminal ganglia (TG) of rats exposed to stress during orofacial pain indicated that stress exposure leads to an increase in GABAergic signaling in the trigeminal sensory

neurons innervating the inflamed orofacial vibrissal pad of male, but not female, rats which may contribute to sex differences in orofacial pain. In support, a decrease in neural excitability in the medullary dorsal horn of male, but not female, rats was observed. To gain insight into neuroplasticity occurring in the sensory ganglia during stress-exacerbated orofacial pain, we performed transcriptomic analysis of the rat TG to identify sex-specific differentially expressed genes (DEGs) relevant to the effect of sub-chronic stress on inflammatory orofacial pain. Adult male and female Sprague-Dawley rats (250-350g) received an injection of complete Freund's adjuvant (CFA) or saline into the right vibrissal pad. All rats were subjected to the forced swim test (FST; sub-chronic stress) or sham paradigm for 3 days. Following day 3 of FST, ipsilateral TG were extracted and flash-frozen in liquid nitrogen. Next-generation RNA sequencing was employed to examine the TG transcriptomic profile of rats exposed to FST (Saline+FST), CFA and FST (CFA+FST), or negative controls (Saline+Sham). Of the DEGs that were found to be significantly upregulated or downregulated, known pain genes were analyzed for sex differences following Saline+FST and/or CFA+FST. We report that genes related to the ECM and GABA neurotransmission were significantly upregulated in male TG (Col3a1, Col9a1, Ltbp1, Slc13a3), while DEGs observed to be upregulated in female TG were related to immune cells (Tmem45b), purinergic receptors (P2rx3), and galanin receptors (Galr2). When the analysis was expanded to compare rats with orofacial inflammation, sexually dimorphic DEGs with higher expression in inflamed males exposed to FST included genes related to the ECM (Col24a1), aldo-keto reductase (Ark1b10), and diazepam binding inhibitor (Dbi). Female-specific upregulated genes were related to ion channels (Atp1a2, Atp1b2) and immune cells (Tmem88b). Together, these data provide evidence that stress alters pain gene expression in the trigeminal sensory ganglia, which is highly sexually dimorphic under pathological conditions related to stress and stress-exacerbated orofacial pain.

Disclosures: B. Islam: None. **D. Cantu:** None. **O. Darwish:** None. **D.L. Averitt:** None.

Poster

PSTR067: Headache, Migraine, and Trigeminal Circuits

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR067.28/C125

Topic: D.01. Somatosensation – Pain and Itch

Support: NIH NIDCR R15 DE025970

Title: Estrogen modulates inflammatory mediator release from macrophages

Authors: *A. BASNET, T. HICKMAN, L. HANSON, D. L. AVERITT;
Biol., Texas Woman's Univ., Denton, TX

Abstract: Orofacial pain is 2-4x more common among women than men and the gonadal hormone estrogen has been evidenced to play a role in sex differences in the greater prevalence of orofacial pain conditions in women. Trigeminal sensory neurons innervate the orofacial

region, relaying pain signals to the central nervous system. Orofacial inflammation has been associated with the infiltration of immune cells, including macrophages, to the sensory neuron cell bodies in the trigeminal ganglia, but their role in trigeminal pain is not clear. We recently reported that 17β-estradiol (E2) and the neurotransmitter serotonin (5HT) interact to modulate inflammatory mediator release from murine macrophage cell lines via estrogen receptor beta (ERβ), G protein coupled estrogen receptor (GPER), and serotonin receptor 2A subtype ($5HT_{2A}$). While estrogen can influence the role of macrophages in inflammatory pain, it is unclear what direct effect this has on trigeminal sensory neurons. We hypothesized that E2 treatment of murine macrophage cell lines increases the release of pro-inflammatory mediators. We quantified cytokines present in the supernatant of IC-21 murine macrophages (intermediate monocyte-macrophage stage of development, AATC) and J774A.1 murine macrophages (mature macrophage phenotype; AATC) following treatment with 50 nM E2 or vehicle as a negative control. The release of cytokines and chemokines was quantified using a Proteome Profiler Cytokine Array Kit (R&D Systems). We found that several key proinflammatory cytokines were increased by E2 in the J774A.1 macrophages, notably the cytokine interleukin-6 (IL-6) and the chemokine C-X3-C motif ligand 1 (CX3CL1; also known as fractalkine). As both IL-6 and fractalkine can regulate the recruitment of macrophages to the trigeminal sensory neurons of the trigeminal ganglia, we postulate that IL-6 and fractalkine may be sufficient to polarize macrophages towards the pro-inflammatory M1 phenotype during orofacial pain in female rats. Estrogen polarization of macrophages at the trigeminal ganglia may amplify orofacial pain signaling at trigeminal sensory neurons to a greater degree in females than males. To follow-up on this possible mechanism, we are currently performing flow cytometry to characterize the immune cell phenotype of the trigeminal ganglia of male and female rats following 1-14 days of masseter muscle inflammation as a rat model of inflammatory orofacial pain. Ultimately, these data will contribute knowledge of immune cell infiltration to the trigeminal sensory ganglia of male and female rats serving as a basis for future hypotheses on sex differences in the neuroimmune interaction in sensory neurons.

Disclosures: A. Basnet: None. **T. Hickman:** None. **L. Hanson:** None. **D.L. Averitt:** None.

Poster

PSTR068: Pain Models With a Focus on Sex Differences, Human and *In Vitro* Approaches

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR068.01/Web Only

Topic: D.01. Somatosensation – Pain and Itch

Support: Beca Conacyt de Doctorado con Número de Apoyo: 824701
"Proyecto apoyado por "CONACYT" en el año 2023." CF-2023-G-289.

Title: Medullary and encephalic nociception in male rats from the prenatal administration of valproic acid model.

Authors: *J. L. ENCARNACIÓN SÁNCHEZ[1], R. DOMÍNGUEZ ORDÓÑEZ[3], A. GALVAN-ROSAS[6], M. GARCIA-JUÁREZ[7], G. MUÑOZ CASTAÑEDA[4], *J. L. ENCARNACIÓN SÁNCHEZ[2], C. E. AGUILAR-PÉREZ, Sr.[8], R. A. LUCIO[9], O. GONZÁLEZ FLORES[5];
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Abstract: Valproic acid (VPA) is a histone deacetylase inhibitor (HDACs) used as an antiepileptic agent. When VPA is administered during pregnancy induces teratogenic effects on the progenies nervous system (NS) (Chomiak y cols., 3013). To explore the previously mentioned effects, a prenatal VPA administration model has been implemented (Rodier y cols., 1997). This model allows the action mechanism study of this drug on the nociception, analgesia, synaptic function, gliogenesis, and neural circuit builds (Schneider and Przewlocki., 2005). The present study evaluates the VPA nociception effects on Sprague-Dawley male rats progenie. For this purpose twenty pregnant Sprague-Dawley rats were divided into two groups for VPA 400mg/kg (n=10) or its vehicle (saline 0.1 ml) (n=10), they received the correspondent injection in the 12.5 pregnancy days. The male offspring were evaluated at 3 months old through nociceptive trials of tail-flick, control group (n=10) and VPA group (n=10) and tail-shock, control group (n=13) and VPA group (n=13). The results were analyzed through a variance analysis (Kruskal-Wallis) and Mann-Whitney U. In the tail-flick trial, we observed a similar threshold to thermic stimuli between the two groups. Interestingly the tail-shock trials show a reduction in the threshold to electric shock in the VPA group compared to the control group. We can observe that in the nociceptive medullary response (tail-flick) there is no difference between the control and VPA groups, while the nociceptive encephalic response is facilitated in the VPA group. These results evidence a VPA effect on neural development only in the somatosensory circuits at encephalic areas.

Disclosures: J.L. Encarnación Sánchez: None. **R. Domínguez Ordóñez:** None. **A. Galvan-Rosas:** None. **M. Garcia-Juárez:** None. **G. Muñoz Castañeda:** None. **J.L. Encarnación Sánchez:** None. **C.E. Aguilar-Pérez:** None. **R.A. Lucio:** None. **O. González Flores:** None.

Poster

PSTR068: Pain Models With a Focus on Sex Differences, Human and *In Vitro* Approaches

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR068.02/C126

Topic: D.01. Somatosensation – Pain and Itch

Support: NIH Grant P20GM103643

Title: Differential endogenous pain inhibition between male and female rats in temporomandibular joint osteoarthritis pain

Authors: J. HOWARD, A. DEL GRECO, *T. KING;
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Abstract: Females develop temporomandibular pain at a much higher rate compared to males. The mechanisms underlying the heightened susceptibility of females to develop temporomandibular pain are not well understood. Sex differences in endogenous pain inhibition have been proposed as a mechanism underlying increased susceptibility of females to develop chronic pain states including temporomandibular pain. We previously demonstrated that females have increased susceptibility to develop non-evoked pain and central sensitization compared to males in a rat model of temporomandibular joint (TMJ) osteoarthritis pain. Using this model, we explored the hypothesis that opioid signaling within the rostral ventromedial medulla (RVM) mediates sex differences in the emergence of pain behaviors in male and female rats. Rats received TMJ injection of monosodium iodoacetate (MIA, 50 µl) at a concentration (16 mg/ml) that produces persistent non-evoked joint pain and central sensitization in females but only localized tactile hypersensitivity in males. We examined whether systemic (3 mg/kg, i.p.) or RVM administration (0.5 µg/0.5 µl) of the opioid receptor antagonist, naloxone, induced conditioned place aversion 14 days following TMJ MIA injection. This time-point was selected based on prior observations of sex differences in behavioral measures of nociception and similar levels of TMJ damage. Systemic naloxone administration induced conditioned place aversion in males with temporomandibular joint MIA, but not saline controls. In addition, systemic naloxone induced FOS expression in the medullary dorsal horn of the males. To explore the hypothesis that this is through opioid signaling in descending pain inhibitory pathways, naloxone was microinjected into the RVM. RVM naloxone produced conditioned place aversion in the TMJ MIA treated males, but not the TMJ saline controls. These observations indicate that blocking endogenous opioids in males increases nociceptive input to the medullary dorsal horn and produces aversive effects sufficient to induce conditioned place avoidance. These observations indicate that blocking opioid signaling in the RVM blocks protective inhibitory signaling within descending pain inhibitory pathways resulting in increased afferent nociceptive input from the TMJ and non-experimenter evoked pain. We propose that this is a mechanism that protects males from developing persistent ongoing pain from ongoing joint pathology. Comparison data in female rats are underway to explore the hypothesis that females lack the protective inhibition from endogenous opioids observed in males.

Disclosures: J. Howard: None. **A. Del Greco:** None. **T. King:** None.

Poster

PSTR068: Pain Models With a Focus on Sex Differences, Human and *In Vitro* Approaches

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR068.03/C127

Topic: D.01. Somatosensation – Pain and Itch

Support: NIGMS Grant P30GM145497

Title: Sex differences in facial nerve injury induced spontaneous pain behaviors

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Abstract: Secondary trigeminal neuralgia (STN) is neuropathic pain that evolves from abnormalities or injury to the cranial region. Trauma to branches of the trigeminal nerve can instigate chronic orofacial pain which develops in 5-10% of facial fractures and 1-5% of impacted tooth removals. Females are more likely to develop trigeminal neuralgia compared to males. Chronic constriction of the infraorbital nerve (CION) is a widely used rodent model of STN. The goal of this study was to evaluate evoked and non-evoked behaviors used to model tactile hypersensitivity and spontaneous pain in male and female rats with CION. Rats underwent surgical protocols that used an intraoral approach permitting the external snout and vibrissae to be undisturbed for tactile testing. Behavioral measures of spontaneous and mechanoceptive behaviors were tested weekly through day 28 using facial swiping (cheek and full head) activity and a modified facial von Frey technique. Male and female CION rats developed tactile hypersensitivity within one-week post-surgery that persisted through day 28. This decrease in tactile thresholds was fully reversed by gabapentin (100mg/kg, IP) on day 15 post-surgery. Male and female CION rats demonstrated increased swiping of the cheek area within 6 days post-surgery that was reversed by gabapentin (100mg/kg, IP) indicating development of spontaneous pain. The total number of full head swipes was not significantly different between CION, sham, or naïve and was unaffected by gabapentin administration, indicating that this behavior can be used as a negative control. Although sex differences were not observed in tactile hypersensitivity to von Frey, sex differences were observed in cheek swipe behaviors. Females had more cheek swipes compared to males. In addition, elevated cheek swipes were observed for a longer period of time in females, persisting through 16 days post-surgery. In contrast on day 16, male rats showed cheek swipe behaviors that were equivalent to sham and naïve rats. This indicates a prolonged period of CION-induced STN in females, an observation consistent with clinical observations that females show higher rates of STN compared to males.

Disclosures: A. Felix: None. **J. Zuke:** None. **D. Giuvelis:** None. **I.D. Meng:** None. **T.E. King:** None.

Poster

PSTR068: Pain Models With a Focus on Sex Differences, Human and *In Vitro* Approaches

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR068.04/C128

Topic: D.01. Somatosensation – Pain and Itch

Support: NIH P20GM103643
NIH R01NS121533

Title: Sex differences in knee joint pain in relation to joint pathology and innervation

Authors: *A. DEL GRECO[1], M. MUETH[2], E. GRLICKOVA-DUZEVIK[3], B. J. HARRISON[1], T. E. KING[4];
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Abstract: Osteoarthritis (OA) pain is a highly prevalent musculoskeletal chronic pain condition worldwide. Females are more commonly diagnosed and report more severe joint pain. OA pain is heterogenous, with two broad categories often described. Mid-stage OA pain is characterized as pain during joint use that abates with rest. Advanced OA pain is characterized as persistent joint pain that does not subside with rest and is often NSAID resistant. These pain profiles have been modeled in a rat model of knee joint OA pain, but not in mice. We established a mouse model of knee joint OA pain that produces reproducible and reliable pain profiles modeling mid-stage and advanced OA pain, and that demonstrates increased susceptibility of females to develop advanced OA pain. We explored the hypothesis that females show increased joint innervation and markers of nerve injury with lower joint damage compared to males. Mice received knee joint injections of monosodium iodoacetate (MIA) . Behavioral assays including weight induced joint pain and persistent ongoing pain were conducted 2 weeks post-injection to establish MIA concentrations that produces mid-stage or advanced OA pain in males and females. Knee joints were then collected to assess joint pathology, changes in innervation, and nerve damage in sensory neurons. Weight asymmetry and conditioned place preference indicated that females develop advanced OA pain at a 5-fold lower MIA concentration compared to the males. Both males and females had increased joint pathology in a concentration-dependent manner, with equivalent levels of joint pathology at the MIA concentration (16 mg/mL) that induced mid-stage OA pain in males but advanced OA pain in females. MIA-induced changes in joint innervation were comparable between males and females treated with 16 mg/mL MIA. In contrast, analysis of a marker of nerve injury, activating transcription factor-3 (ATF3), in sensory neurons showed increased levels in males and females with advanced OA pain (80 mg/mL MIA for males and 16 mg/mL for females). Notably, this marker differed between male and female mice treated with 16 mg/mL, showing a significant increase in females but not males suggesting that nerve injury plays a role in advanced OA pain in both sexes. In summary, our findings show that persistent ongoing knee joint pain emerges in a sex-dependent manner with females demonstrating higher susceptibility to develop advanced OA pain compared to males despite the absence of sex differences in innervation and pathology. Nerve damage, however, may be an important mechanism in the development of advanced OA pain.

Disclosures: A. Del Greco: None. **M. Mueth:** None. **E. Grlickova-Duzevik:** None. **B.J. Harrison:** None. **T.E. King:** None.

Poster

PSTR068: Pain Models With a Focus on Sex Differences, Human and *In Vitro* Approaches

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR068.05/C129

Topic: D.01. Somatosensation – Pain and Itch

Support: NIGMS R35GM138168

Title: Sex differences in development of persistent post-surgical pain in consomic SS-13^{BN} rats

Authors: *R. HORNUNG, C. CAHOON, L. F. FERRARI, N. TAYLOR;
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Abstract: 10% of patients undergoing surgery go on to develop chronic pain at the surgical site despite receiving multimodal pain treatments. The mechanisms responsible for this acute to chronic pain transition are poorly understood. To help separate the potential effects of surgical procedure, sex and genetics on the propensity to develop chronic post-surgical pain, we undertook a series of experiments using consomic SS-13^{BN} rats. Adult male and female SS-13^{BN} rats underwent plantar paw incision surgery on a single hind paw and mechanical nociceptive thresholds were evaluated in the surgical area before and after incision using von Frey filaments. Typically, this procedure only produces acute pain that resolves within 7 days. However, we observed that males developed persistent allodynia up to 139 days post-surgery, while females responded more typically with thresholds returning to baseline within 7 days. To determine if ovarian hormones played a role in this sex dimorphism, female SS-13^{BN} rats were ovariectomized prior to the paw incision. We observed hyperalgesia in the surgical area in the ovariectomized rats until day 69 post-paw incision, suggesting a protective role of ovarian hormones. Then to identify if estrogen was responsible for this effect, we implanted mini-osmotic pumps containing the estrogen receptor antagonist ICI 182,780. During the 14 days post paw incision that ICI 182,780 was delivered, the female rats demonstrated allodynia, which persisted after drug delivery until the 43rd post-surgical day. We then sought to determine the role that descending pain modulating pathways play in the persistent allodynia seen in male SS-13^{BN} rats. Since the rostral ventromedial medulla (RVM) has been implicated in pain chronification, we sought to prevent neural transmission through the RVM by injecting 2% Lidocaine into the RVM once daily. We found that inhibition of RVM neurons in males did not affect the incision-induced pain until the 7th day when lidocaine became increasingly effective in treating the incision-induced allodynia. We concluded that this indicated a recruitment of pain faciliatory RVM neurons led to the acute to chronic pain transition in males. In contrast, when the protocol was repeated in ovariectomized females, inhibition of RVM neurons did not affect the development of allodynia after incision, suggesting sexual differences in the mechanism. We conclude that a gene or set of genes on chromosome 13 produces a propensity to develop persistent post-surgical pain, and that estrogen has a protective effect counteracting these genetic effects. This genetic effect may act by increasing descending pain facilitation in male SS-13^{BN} rats.

Disclosures: R. Hornung: None. **C. Cahoon:** None. **L.F. Ferrari:** None. **N. Taylor:** None.

Poster

PSTR068: Pain Models With a Focus on Sex Differences, Human and *In Vitro* Approaches

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR068.06/C130

Topic: D.01. Somatosensation – Pain and Itch

Support: CONACyT CF-2023-G-1190
INPRF grant NC12165994.0

Title: Systemic quinpirole enhances tramadol analgesia in inflammatory pain, but not in neuropathic pain in male rats

Authors: *F. MERCADO[1], A. ALMANZA-GUTIERREZ[2];
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Abstract: Pain is a morbidity or comorbidity with a high incidence that significantly impacts the well-being of patients. In this study, we evaluated whether systemic administration of tramadol, a weak mu-opioid receptor (MOR) agonist, and quinpirole (a D2-like receptor agonist) by systemic administration produced significant relief of allodynia and hyperalgesia in two pain models. The study was performed in naïve rats of both sexes and male rats with induced inflammatory and neuropathic pain. To measure the antinociceptive effect of the drugs, thermonociceptive and mechanonociceptive stimuli were applied and the emotional aspects of pain were evaluated using conditional place preference (CPP) experiments. In naïve male animals, systemic quinpirole produces antinociception only in the mechanonociceptive test, with no effect in the thermonociceptive test. In female animals, quinpirole produced no effect in either test at the same concentration used in males. Tramadol plus quinpirole reversed the allodynia and hyperalgesia induced by inflammatory and neuropathic insults in male animals, which were not alleviated by either drug alone. CPP experiments revealed that systemic quinpirole plus tramadol treatment was effective in relieving pain only in an inflammatory pain model. To evaluate whether tolerance to the antinociceptive effect was prevented by the combination of the drugs, a repeated administration five-days trial of tramadol plus quinpirole was evaluated under inflammatory pain conditions; however, quinpirole did not prevent tolerance to antinociceptive effect typical of MOR agonists. D2-like agonists are effective adjuvants for the treatment of certain painful conditions in combination with a low dose of MOR agonists, which could lead to the investigation of whether this drug combination might reduce the opioid dose, while it is possible to obtain a higher analgesic effect with fewer side effects from MOR agonists.

Disclosures: F. Mercado: None. **A. Almanza-Gutierrez:** None.

Poster

PSTR068: Pain Models With a Focus on Sex Differences, Human and *In Vitro* Approaches

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR068.07/C131

Topic: D.01. Somatosensation – Pain and Itch

Support: SIP grant A1-S-40015 to VG-S
SIP grant 127 to VG-S

Title: Sex-dependent mechanisms of melatonin in mice with neuropathic pain

Authors: *I. RAMOS RODRÍGUEZ[1], *I. I. RAMOS-RODRÍGUEZ[2], A. M. ISLAS-ESPINOZA[3], M. ESCOTO-ROSALES[3], J. M. PIZAÑA-ENCARNACIÓN[4], E. J. RODRIGUEZ-PALMA[5], C. G. GUZMAN[6], V. GRANADOS-SOTO[4];
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Abstract: Melatonin is a neurohormone that has been shown to have an antinociceptive effect in models of acute and chronic pain. Its effect is mediated by the activation of melatonin MT2 receptors and/or the modulation of opioid receptors. It has been demonstrated that some cellular and molecular mechanisms underlying chronic pain depend on sex. For instance, the effect of melatonin in rats subjected to the forced swim test depends on sex. However, the impact of sex on the mechanisms of action of melatonin in chronic pain are unknown. Therefore, the objective of this work was to evaluate the effect of sex, as well as 17β-estradiol (E2) on the antiallodynic effect induced by melatonin in mice with neuropathic pain. Female and male mice with neuropathic pain induced by L5/L6 spinal nerve ligation nerves were used. Tactile allodynia, thermal hyperalgesia, and spontaneous pain were determined in all animals. Intrathecal administration of melatonin induced a concentration- and sex-dependent antiallodynic effect, being greater in females than males. The MT2 melatonin receptor antagonist 4-PPDOT, but not the MT1 receptor antagonist S26131, partially prevented the antiallodynic effect of melatonin in female and male neuropathic mice. Interestingly, the opioid receptors antagonist naloxone completely blocked the antiallodynic effect of melatonin in male mice, while it partially blocked the effect in female mice. Ovariectomy prevented the antiallodynic effect of melatonin in female mice, while E2 or the estrogen receptor alpha agonist PPT restored the antiallodynic effect of melatonin. In contrast, the estrogen receptor alpha antagonist MPP fully prevented the effect of E2 on the antiallodynic effect of melatonin in female ovariectomized neuropathic mice. Data suggest that melatonin induces a sex-dependent antiallodynic effect. Data also suggest the MT2 receptors partially participate in the antinociceptive effect of melatonin in both female and male neuropathic mice, while the opioid receptors have a greater participation in the antiallodynic effect of melatonin in male than in female neuropathic mice. Finally, the effect of spinal effect of melatonin depends on activation of estrogen receptor alpha in female neuropathic mice.

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Poster

PSTR068: Pain Models With a Focus on Sex Differences, Human and *In Vitro* Approaches

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR068.08/C132

Topic: D.01. Somatosensation – Pain and Itch

Title: Modeling immune-mediated neuropathic pain using an iPSC-derived sensory neuron and macrophage co-culture

Authors: *S. SCHACHTELE, R. FIENE, A. FATHI, K. TWAROSKI, S. HILCOVE, I. SINGEC, C. B. CARLSON;
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Abstract: Between 10-20% of the global adult population experience chronic pain, placing significant financial burdens on health care systems and global economies. However, in the field of pain drug discovery, researchers have been unable to deliver new non-opioid compounds to improve pain management and reduce the personal and societal impacts of chronic pain. Since the onset of chronic and neuropathic pain results from direct and indirect mechanisms following injury, the significance of immune cell-mediated inflammation in neuropathic pain has recently gained increasing interest. When stimulated, macrophages secrete both pro-nociceptive inflammatory cytokines, promoting neuropathic pain, and anti-inflammatory cytokines which can mitigate and resolve pain. Elucidating sensory neuron/macrophage interactions may identify novel targets for pain therapeutics to broaden treatment strategies. Human induced pluripotent stem cell (iPSC)-derived sensory neurons together with human iPSC-derived macrophages provide a biologically relevant co-culture system to recapitulate immune-mediated neuropathic pain *in vitro*. In this study we demonstrate methods for culturing human iPSC-derived sensory neurons with isogenic iPSC-derived macrophages. Human iPSC-derived sensory neurons and iPSC-derived macrophages from the same donor 01279 were from FUJIFILM CDI. Neurons were characterized to identify the expression of nociceptor ion channels and receptors (NaV1.8, TRPV1). Cells were used in functional calcium assays to show neuronal excitability upon treatment with capsaicin (4 uM), ATP (10 uM). Similarly, iPSC-derived macrophages were shown to be functionally naïve and able to respond to pro- or anti-inflammatory stimulation. We next demonstrate that iPSC macrophages can be cultured in sensory neuron medium and retain phagocytic and cytokine function. To model peripheral neuroinflammation we cultured iPSC sensory neurons with unstimulated or LPS-stimulated iPSC macrophages and evaluated the effect of each condition on responses to sensory stimuli using a fluorescent calcium assay. We also investigated differences in sex responses to iPSC macrophages by comparing co-cultures with sensory neurons from male or female donor. These data demonstrate the utility of iPSC-derived sensory neurons and macrophage co-cultures for generating human-relevant, high-throughput approaches to study mechanisms of immune-mediated chronic and neuropathic pain.

Disclosures: S. Schachtele: None. **R. Fiene:** None. **A. Fathi:** None. **K. Twaroski:** None. **S. Hilcove:** None. **I. Singec:** None. **C.B. Carlson:** None.

Poster

PSTR068: Pain Models With a Focus on Sex Differences, Human and *In Vitro* Approaches

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR068.09/C133

Topic: D.01. Somatosensation – Pain and Itch

Title: Developing a Scalable In Vitro Model of Diabetic Peripheral Neuropathy Using hiPSC Derived Sensory Neurons and Schwann Cell Precursors from the Same Donor

Authors: *M. GAVINO[1], G. MCCABE[1], V. TRUONG[2], P. WALSH[1];
[1]Anatomic Inc., Minneapolis, MN; [2]Stem Cell Engin., Anatomic Inc., Minneapolis, MN

Abstract: Diabetes mellitus affects greater than 500 million people worldwide, and the rate of new patients diagnosed each year is projected to continuously rise over the next few decades. Around one half of patients diagnosed with diabetes mellitus develop diabetic peripheral neuropathy (DPN). DPN is characterized by a wide range of symptoms including sensory loss, pain, and tingling sensations within the limbs. Despite the prevalence of this disorder, the development of treatments for DPN is hindered by the lack of translation human models. We have previously shown that human induced pluripotent stem cells (hiPSCs) can be rapidly differentiated into highly pure populations of sensory neurons and Schwann cell precursors (SCPs) using small molecules and growth factors, and that these cell types are transcriptionally similar to analogous primary human tissues via bulk RNA sequencing. To develop a scalable in vitro human model for DPN, we plan to expose co-cultures of these cells to high glucose concentrations and assess apoptosis, cytotoxicity, and sensory neuron function. We will also investigate the effects of Bupropion on this system, a drug previously shown to protect Schwann cell viability and survival under high glucose conditions. Apoptosis will be measured using a lactate dehydrogenase (LDH) assay. Cytotoxicity and morphological changes will be evaluated through SCP-axon alignment using S100B and TUJ1 immunocytochemistry, and myelin formation will be assessed with Sudan Black staining. Additionally, the co-cultures will be plated on the Axion Meastro microelectrode array system and functionally assessed in response to varying concentrations of glucose and Bupropion. These studies aim to determine whether hiPSC-derived sensory neurons and SCPs can serve as a scalable and viable resource for developing an in vitro human model of DPN.

Disclosures: M. Gavino: A. Employment/Salary (full or part-time):; Anatomic Incorporated. **G. McCabe:** A. Employment/Salary (full or part-time):; Anatomic Incorporated. **V. Truong:** A. Employment/Salary (full or part-time):; Anatomic Incorporated. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Anatomic Incorporated. **P. Walsh:** A. Employment/Salary (full or part-time):; Anatomic Incorporated. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Anatomic Incorporated.

Poster

PSTR068: Pain Models With a Focus on Sex Differences, Human and *In Vitro* Approaches

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR068.10/C134

Topic: D.01. Somatosensation – Pain and Itch

Support: NIH Grant 1R43TR004743-01

Title: Pain in a Dish Assay (PIDA): A high-throughput hiPSC-derived screening platform to identify analgesic compounds

Authors: *N. A. SUAREZ[1], C. G. RINES[2], **K. L. GORDON**[3], A. SMITH[4], V. TRUONG[5], P. WALSH[6], J. PRICE[7], P. MCDONOUGH[8];
[1]Vala Sci. Inc., San Diego, CA; [2]Biol., Vala Sci., Inc., San Diego, CA; [3]Biol., Vala Sci. Inc., San Diego, CA; [4]Vala Sci. Inc., San Dieo, CA; [5]Stem Cell Engin., Anatomic Inc., Minneapolis, MN; [6]Anatomic Inc., Minneapolis, MN; [7]Vala Sci., Inc., San Diego, CA; [8]Vala Sci. Inc, San Diego, CA

Abstract: The sense of pain is critical for protecting our bodies. However, over 20 million adults in the US suffer from chronic pain, which disrupts activities of daily living and increases risk for other chronic illnesses. Humans perceive pain when nociceptors, which are specialized sensory neurons in the dorsal root ganglia (DRG), relay signals from peripheral tissues to the brain. Analgesics like opioids can relieve pain by blocking pain signals but carry high risk for addiction and overdose. To identify alternatives to opioids that can treat pain more safely, we are developing a human preclinical Pain in a Dish Assay (PIDA) to enable high-throughput testing of compounds to identify potential analgesics. For PIDA, we culture human induced pluripotent stem cell (hiPSC)-derived nociceptors (RealDRG, Anatomic Inc.) on imaging-quality 96-well plates. After four to six weeks of culture, we assayed RealDRG activity using single-cell high throughput calcium imaging. First, we loaded our cultures with a fluorescent calcium indicator (Calbryte 520, AAT Bioquest). We then pre-treated our cultures with likely antagonists of nociceptor activity or with an inert control. We used Vala Sciences' IC200 Kinetic Image Cytometer (KIC) to acquire baseline RealDRG calcium activity at 4 frames per second. After 1 minute, the IC200 Liquid Handling Module dispensed a pain-causing agonist while the KIC captured any agonist-induced changes in calcium concentration within RealDRG somas and neurites. As a proof of concept, we dispensed the depolarizing agent KCl (10-50 mM final concentration) into RealDRG cultures. We observed an abrupt increase in calcium activity in both the somas and the neurites of individual RealDRGs, as measured by average pixel intensity (API) of the calcium indicator. We also tested an agonist/antagonist pair, the voltage-gated sodium channel agonist veratridine (VTD) and antagonist tetrodotoxin (TTX) in the PIDA workflow. We observed an increase in the calcium activity in RealDRG somas and neurites after dispensing VTD (10-100μM final concentration), and a decrease in activity after dispensing TTX (10nM-1μM final concentration). Pretreatment with TTX blocked the VTD-induced increases in RealDRG calcium activity, suggesting that TTX can inhibit VTD-induced pain responses. We are currently expanding our PIDA workflow to include capsaicin, a known agonist of TRPV1 in nociceptors, and capsazepine, a competitive antagonist of capsaicin. Our work demonstrates

meaningful progress towards the development of a high-throughput hiPSC-based screening system to identify safe and effective analgesic alternatives.

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Poster

PSTR068: Pain Models With a Focus on Sex Differences, Human and *In Vitro* Approaches

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR068.11/C135

Topic: D.01. Somatosensation – Pain and Itch

Title: Scalable iPSC programming strategy in combination with optimised cocktails of neurotrophic factors yields functionally distinct nociceptor sensory neurons

Authors: *M. RAMAN SRIVASTAVA, D. PACITTI, H. SMITH, M. ORTIZ, K. LONG, M. BYRNE, V. YIANNI, A. WILCZYNSKA, S. MILDE, B. NEWMAN, **T. OOSTERVEEN**, W. BERNARD, E. METZAKOPIAN, M. KOTTER;
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Abstract: Nociceptive sensory neurons are a specialised subtype of somatosensory cells residing in the dorsal root ganglia. Nociceptors respond to diverse noxious and pruritic stimuli, and hence are critical for the study of pain mechanisms and neuropathies. Around 20% of adults suffer from chronic pain, but the current analgesics are limited by short duration and adverse events. Unfortunately, the efficacy of analgesics in animal pain are poorly translated to humans as clinical trials for pain therapeutics have only a 2% probability of success. Consequently, drug classes used to treat chronic pain have essentially not evolved over the past 40 years. Thus, there is an unmet need for reliable and scalable human in vitro models to develop new, efficacious, and safe pain therapeutics. However, conventional differentiation methods to generate nociceptors from pluripotent stem cells are complex, inconsistent, and characterised by protracted maturation times. By using our deterministic cell programming technology (opti-ox™), we robustly expressed a combination of transcription factors in iPSCs to generate a homogeneous population of sensory neurons that display critical features of nociceptors. Bulk and single cell RNA-sequencing analysis together with immunocytochemistry showed that within 7 days after the induction of transcription factor expression, the neurons expressed the key sensory markers ISL1, POU4F1 and PRPH. At this early time point, the neurons also expressed the key nociceptor markers such as NTRK1, TRPV1, TRPM8, and SCN9A. Multi-electrode array and calcium assays demonstrated that these sensory neurons are functional displaying asynchronous spontaneous activity and responsiveness to diverse noxious stimuli. Neurotrophic factors play a critical role in sensory neuron subtype specification and, by adapting culture conditions, we were able to enrich for cells expressing key peptidergic nociceptor markers TAC1 as well as ADCYAP1, and substantially increase the responsiveness to specific noxious stimuli. In addition, using an optimised cocktail of neurotrophic factors, and increased culture length,

enhances the percentage of cells responding to TRPM3 and TRPM8 channel agonists in calcium mobilisation assays.
In conclusion, with opti-ox deterministic cell programming, iPSCs are rapidly converted into functional sensory neurons offering a robust and scalable source of human nociceptors that can be used as an in vitro model to study the biology of pain and to develop novel therapies for neuropathies.

Disclosures: M. Raman Srivastava: A. Employment/Salary (full or part-time):; bit.bio. **D. Pacitti:** A. Employment/Salary (full or part-time):; bit.bio. **H. Smith:** A. Employment/Salary (full or part-time):; bit.bio. **M. Ortiz:** A. Employment/Salary (full or part-time):; bit.bio. **K. Long:** A. Employment/Salary (full or part-time):; bit.bio. **M. Byrne:** A. Employment/Salary (full or part-time):; bit.bio. **V. Yianni:** A. Employment/Salary (full or part-time):; bit.bio. **A. Wilczynska:** A. Employment/Salary (full or part-time):; bit.bio. **S. Milde:** A. Employment/Salary (full or part-time):; bit.bio. **B. Newman:** A. Employment/Salary (full or part-time):; bit.bio. **T. Oosterveen:** A. Employment/Salary (full or part-time):; bit.bio. **W. Bernard:** A. Employment/Salary (full or part-time):; bit.bio. **E. Metzakopian:** A. Employment/Salary (full or part-time):; bit.bio. **M. Kotter:** A. Employment/Salary (full or part-time):; bit.bio.

Poster

PSTR068: Pain Models With a Focus on Sex Differences, Human and *In Vitro* Approaches

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR068.12/C136

Topic: D.01. Somatosensation – Pain and Itch

Title: Targeted applications for investigating pain and CIPN using iPSC-derived sensory neurons

Authors: R. FIENE, A. FATHI, C. B. CARLSON, S. SCHACHTELE, S. HILCOVE, *I. SINGEC;
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Abstract: Chronic pain and peripheral neuropathy are pervasive clinical conditions that affect 10-20% of adults globally, resulting in a tremendous impact on individual well-being and financial burdens for health care systems. Discovery of next-generation compounds and therapeutic targets for effective non-opioid pain management can benefit from the use of human-relevant cellular models during preclinical phases of drug discovery pipelines. Advances in human induced pluripotent stem cell (iPSC) technology and protocols for differentiating them into peripheral sensory neurons has enabled the scalable production and increased accessibility of *in vitro* human models of pain and neuropathy. As iPSC models become required for drug discovery programs, it is critical to optimize and standardize the use of iPSC sensory neurons in pain-relevant assays, which will ultimately allow for more efficient drug discovery and cross-platform data interpretation. In this study we employ commercially available iPSC-derived

sensory neurons, from male and female donors, within numerous pain and chemotherapy-induced peripheral neuropathy (CIPN) assays, including classic *in vitro* characterization assays (calcium assays) and advanced assays, such as organ-on-a-chip platforms. We have previously shown that these iPSC-derived sensory neurons have high purity (>80% BRN3A+/UCHL1+) and express hallmark nociceptive channels (i.e. Nav1.7 and Nav1.8) and receptors (i.e. TRPV1 and P2RX). To evaluate the response of these neurons to sensory receptor specific agonists, we established a high-throughput calcium assay using the Hamamatsu FDSS/uCell. We demonstrated that iPSC-derived sensory neurons cultured for ≥ 21 days show consistent responses to capsaicin (TRPV1 agonists) across technical replicates and across manufactured lots of sensory neurons, establishing these cells as robust and reproducible. To improve assay efficiency, we also investigated critical parameters that could affect the calcium assay consistency, including cell density, extracellular matrix, assay media, day of assay, and calcium indicators. Last, we investigated the utility of iPSC-derived sensory neurons in organ-on-a-chip platforms, which offer the ability to compartmentalize compound testing and establish co-cultures, such as sensory neurons and macrophages, to model neuroinflammatory pain. These data further establish the utility of iPSC-derived sensory neurons for high-throughput drug screening and provide methods for pain and CIPN assay standardization.

Disclosures: R. Fiene: None. **A. Fathi:** None. **C.B. Carlson:** None. **S. Schachtele:** None. **S. Hilcove:** None. **I. Singec:** None.

Poster

PSTR068: Pain Models With a Focus on Sex Differences, Human and *In Vitro* Approaches

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR068.13/C137

Topic: D.01. Somatosensation – Pain and Itch

Support: NIH GRANT 1UH3 NS109556
NIH GRANT 1UH3 NS115631

Title: Anterior Insula-based Network Biomarkers of Experimental Pain in Humans

Authors: *Y. HAN, R. B. LERICHE, J. LIN, J. SAAL, E. F. CHANG, P. SHIRVALKAR; Univ. of California San Francisco, San Francisco, CA

Abstract: The neurophysiology of evoked pain experiences involves integration across various brain regions and multiple time scales. The anterior insula is a key component in both ascending and descending brain networks supporting neural responses to pain (Ferraro et al., 2021). In this study, we aimed to understand circ-wide encoding of thermal and mechanical pain stimuli li using stereo-electroencephalography (SEEG) signals from 76 SEEG channels covering 30 brain regions in a male chronic pain patient. We used four sessions of quantitative sensory testing, including two to the left hand and the other to the right; each session contained 30 trials. In each trial, the temperature increased from 30 °C with a speed of 1.5 °C/s and stopped at temperatures

ranging from 36 to 49 °C which remained for four seconds in a trial (i.e., hold periods). In the last second of a holding trial, the patient was asked to report the pain intensity induced by the thermal stimulus with a numerical rating scale (NRS) between 0 (no pain) and 10 (extremely painful). We extracted all hold periods, segmented the data into one-second epochs with 50% overlap, and labeled the epochs with the NRS. To characterize insula relevant brain networks, signals were filtered into five frequency bands (theta: 4-8 Hz; alpha: 8-12 Hz; beta: 12-30 Hz; low gamma: 30-70 Hz; high gamma: 70-200 Hz). Coherences were computed between pairwise channels within each frequency band, which served as the measures of integration between brain regions. Using an XGBoost regressor with leave-one-trial-out evaluation, we predicted NRS based on the top 20 principal components derived from these coherences. The regressor demonstrated very good performance (mean squared error: 0.32, mean accuracy of rounded NRS: 91.00%), and was compared to a null model. By selecting the top 5% important features, this work highlights how coherence between the anterior insula and somatosensory cortex at alpha and high gamma bands contributed the most in predicting pain intensity. We compare these results to pain stimuli in other modalities and discuss the role of ascending vs descending circuits across time in integrating brain responses to evoked pain in humans.

Disclosures: Y. Han: None. **R.B. Leriche:** None. **J. Lin:** None. **J. Saal:** None. **E.F. Chang:** None. **P. Shirvalkar:** 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. C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Medtronic.

Poster

PSTR068: Pain Models With a Focus on Sex Differences, Human and *In Vitro* Approaches

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR068.14/C138

Topic: D.01. Somatosensation – Pain and Itch

Title: Temporal relationship between bodily self-consciousness and acute pain following knee arthroplasty

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Abstract: Introduction: Bodily self-consciousness, such as the sense of body ownership and the sense of agency, influences pain perception. Bodily self-consciousness and pain perception are thought to be influenced not only by bottom-up information but also by top-down processing, suggesting that their relationship is highly individualized. In this study, we focused on pain and bodily self-consciousness following knee arthroplasty to characterize these highly individualized

relationships, particularly their temporal relationships. **Methods**: Participants (n=26) were individuals who had underwent knee arthroplasty. Day-to-day assessments were performed for 21 days after knee arthroplasty to assess resting pain (RP) and walking pain (WP) using an 11-point numerical rating scale (0=no pain, 10=worst pain imaginable). Concurrently, the sense of body ownership (SoO), "My knees seem to be my knees," and sense of agency (SoA), "My knee is moving the way I want it to move," were also assessed daily using a 7-point Likert scale (-3=strongly disagree, +3=strongly agree). Time series data for these variables (RP, WP, SoO, and SoA) were analyzed using a multi-level vector autoregression (VAR) model for the all data (n=26) and a graphical VAR model for individual data (n=1), creating both contemporaneous and temporal (lag-1) network models (NM). **Results**: The contemporaneous NM analyzed from all data showed relationships between RP and WP, SoO and SoA, and between WP and SoA. In the temporal NM, an influence from WP to SoA was observed. The results for individual data in both contemporaneous and temporal NM showed high individual variability. When categorizing based on the temporal relationship (i.e., temporal NM) of the main aim, 50.0% of the groups (n=13) showed bilateral influence between bodily self-consciousness and pain, 3.9% (n=1) showed an influence from bodily self-consciousness to pain, 19.2% (n=5) from pain to bodily self-consciousness, and 26.9% (n=7) showed no influence. **Conclusions**: Regarding temporal relationships, the patterns of NM analyzed from all data showed inconsistencies with the most frequently observed patterns in individual data NM. This discrepancy suggests the need for personalized assessment and treatment decision-making in pain management.

Disclosures: T. Tanaka: None. **S. Morioka:** None.

Poster

PSTR068: Pain Models With a Focus on Sex Differences, Human and *In Vitro* Approaches

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR068.15/C139

Topic: D.01. Somatosensation – Pain and Itch

Title: Correlation of oxidative and antioxidative parameters and anxiety in women with Fibromyalgia Syndrome

Authors: *M. SHARMA;
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Abstract: IntroductionA combination of antioxidative imbalance and oxidative stress are thought to take part in pathogenesis of fibromyalgia syndrome (FMS) as well as its comorbities. The aim of study was two-fold, first to investigate the interplay between oxidative and antioxidative parameters in FMS and severity of its symptoms, second to investigate the sleep abnormalities.MethodsThe indices of Lipid Peroxides-(LPO), nitric oxide-(NO) and Protein carbonyl in plasma,antioxidative parameters catalase, Glutathione peroxidase-(GPx) & Glutathione Reductase-(GR) in 74 female patients (American College of Rheumatology-criteria/FMS) and 62 healthy females. Clinical parameters of FMS were evaluated, Fibromyalgia

Impact Questionnaire Revised-(FIQR) Demographic characters, pain and sleep disturbance by visual analog scale, were gathered.ResultsLPO ($p<0.01$), NO ($p<0.01$) and Protein carbonyl ($p<0.01$) were significantly higher in FMS patients as compared to controls. Catalase ($p<0.01$), GR ($p<0.01$) and GPx ($p<0.01$) were significantly lower in FMS group than in controls. Positive correlation was found between LPO, NO, Protein carbonyl and clinical symptoms of FMS group. FMS group scored significantly worse than the controls with respect to physical role, social functioning and pain. ConclusionIn conclusion, presence of oxidative stress in women with FMS are exposed to depression and sleep abnormalities and which play important role in the etiopathogenesis of the disease. Moreover, our results also show that increased oxidative stress parameters are more in FMS severity score.

Disclosures: M. Sharma: None.

Poster

PSTR069: Non-Opioid Treatments for Persistent Pain

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR069.01/C140

Topic: D.01. Somatosensation – Pain and Itch

Support: FAPESP grant 2021/12712-1
FAPESP grant 2022/05471-0
CAPES grant 88887.619991/2021-00
CNPq grant 309215/2019-6
CNPq grant 306424/2022-3

Title: Fatty acid amide hydrolase inhibition modulates sensory and affective aspects of persistent inflammatory pain in mice depending on mu and delta opioid receptors activity: involvement of heme oxygenase 1 enzyme

Authors: *V. PANSARIM[1], A. A. FERRARESE-TIBALLI[1], O. POL[2], C. R. A. LEITE-PANISSI[1];
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Abstract: The endocannabinoid system regulates many psychological processes related to pain and has potential in the treatment of the affective aspects of chronic pain. Its analgesic effects may depend on the activity of other systems and molecular mechanisms, like the opioid system and the heme oxygenase-1 enzyme (HO-1) activation. Thereby, the objective of the present study was to investigate if fatty acid amide hydrolase (FAAH) inhibition, an enzyme responsible for endocannabinoid depletion, would modulate sensory and affective aspects of persistent inflammatory pain depending on mu (MOR) and delta (DOR) opioid receptors and HO-1 activity. Male BALB/c mice were submitted to seven days of persistent inflammatory pain (CFA injection into the right hind paw; saline as control) and then systemic treated with a FAAH

inhibitor (PF3845), a HO-1 inducer (CoPP) or vehicle (VEHI), combined with a DOR antagonist (naltridole, NTI), a MOR antagonist (CTAP), an HO-1 inhibitor (SnPP) or VEHI (n = 8 per group). Mice were tested for pain sensitivity (mechanical threshold on von Frey test; thermal threshold on hot plate test) and pain aversion (time in light compartment in the place escape/avoidance paradigm, PEAP). Western Blot was conducted to evaluate the HO-1, CB1, FAAH, MOR, and DOR levels in the amygdala, hippocampus, and periaqueductal grey (n = 5-8 per group). ANOVAs were performed to verify treatment effects on pain parameters and protein levels, followed by a Tukey post-hoc test ($p < .05$ to assume effects and differences between groups). Results revealed that the PF3845 and CoPP decreased mechanical threshold and time in the light compared to VEHI in CFA mice, effects that were blocked by NTI, CTAP, and SnPP. NTI alone decreased time in the light compared to VEHI in CFA mice. Only CoPP decreased thermal threshold compared to VEHI, which was reversed by NTI, CTAP, and SnPP. Regarding biochemical results, PF3845 decreased FAAH and increased HO-1 levels compared to VEHI only in the amygdala of CFA mice. In an additional experiment, where CoPP and NTI-treated CFA mice (saline and VEHI as control; n = 5-6 per group) were tested on the elevated plus maze, NTI was able to increase open arms avoidance compared to VEHI in CFA mice. These results indicate that FAAH inhibition can decrease affective and sensory aspects of persistent inflammatory pain depending on MOR, DOR, and HO-1 activity. NTI effect on PEAP may be more related to an anxiety behavior than to a decreased pain aversion. Moreover, the amygdala may play an essential role in the endocannabinoid mechanisms of pain processing and modulation and can be a spot for an interaction among endocannabinoid system, HO-1 and opioid receptors.

Disclosures: V. Pansarim: None. **A.A. Ferrarese-Tiballi:** None. **O. Pol:** None. **C.R.A. Leite-Panissi:** None.

Poster

PSTR069: Non-Opioid Treatments for Persistent Pain

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR069.02/C141

Topic: D.01. Somatosensation – Pain and Itch

Support: CIHR Grant FDN-148413
FWO Vlaaderen Grant 1SB0422N
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CIHR scholarships
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Title: Design, in vitro and preclinical in vivo testing of the potent and safest hybrid opioid/neurotensin ligand for pain management

Authors: *E. BREAULT[1], J. DE NEVE[2], A. RANJBARAN[1], F. LUSSIER[1], R. L. BROUILLETTE[1], M. CHARTIER[1], A. LANOIE[1], I. BROCHU[1], J.-M. LONGPRE[1], L.

L. GENDRON[1], S. BALLET[2], P. SARRET[1];
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Abstract: The ongoing opioid epidemic has highlighted the need to develop safer, more effective pain treatments. In that respect, the neurotensin (NT) system has emerged as an attractive option for pain relief. Indeed, activation of NTS1 and NTS2 receptors by NT ligands induces opioid-independent antinociceptive effects. Moreover, co-administration of opioid and NT agonists produces additive or synergistic effects. Accordingly, various bifunctional compounds, incorporating both NT and opioid moieties, have been shown to inhibit the pain response. Although these hybrid ligands hold great promise, they still induce hypotension via NTS1 activation. Here, we introduced chemical modifications into the previously reported bifunctional peptide (H-Dmt-D-Arg-Aba-βAla-β^3hArg-Arg-Pro-Dmt-Tle-Leu-OH), in particular the substitution of βAla by Gly in position 4 and the introduction of (6-OH)Tic in position 8, thereby altering the binding affinity for NTS1 and producing SBL-OPNT-13 (H-Dmt-D-Arg-Aba-Gly-Arg-Arg-Pro-(6-OH)Tic-Tle-Leu-OH). These modifications shifted the affinity for NTS1 from K_i values of 4 nM to 4002 nM while maintaining good affinity for NTS2 (K_i = 2.62 nM) and opioid receptors (K_i = 0.34 nM and 17 nM for MOP and DOP, respectively). Moreover, SBL-OPNT-13 displayed full agonism at the $G\alpha_i$ pathway but very low efficacy at β-arrestin recruitment (E_{max} = 17%). This favorable signaling profile has been previously reported as a way of improving the analgesic/side-effect ratio. SBL-OPNT-13 was then characterized for its analgesic properties in various pain models. After central (i.t.) or systemic (i.p.) administration, this hybrid showed robust antinociceptive effects in acute and tonic inflammatory pain tests, outperforming at least a 10-fold dose of morphine. Notably, SBL-OPNT-13 exerted its antinociceptive effect for 24 h, while morphine remained effective only for 2 h. Concomitant administration with the opioid antagonist naloxone partially reversed the antinociceptive effects of SBL-OPNT-13, revealing its bimodal mode of action. In more clinically relevant pain models, SBL-OPNT-13 also showed great ability to reverse postoperative and chronic inflammatory pain behaviors. Interestingly, this new hybrid also stands out from its predecessor with regards to NT-related side effects. Whereas previous chimeric compounds led to a significant reduction in mean arterial pressure (40 mmHg), our lead compound was comparable to that of an intravenous bolus of saline. Altogether, this new bifunctional ligand represents a promising avenue towards the development of safer, more effective analgesics with reduced side-effect profiles.

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Poster

PSTR069: Non-Opioid Treatments for Persistent Pain

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR069.03/C142

Topic: D.01. Somatosensation – Pain and Itch

Support: NIH R33NS116203
R21NS137014-01
Dr. Ralph and Marian Falk Medical Research Trust, Bank of America, Private Bank
Advancing a Healthier Wisconsin Endowment Project (5520680 and 5520739)

Title: Preclinical long-lasting efficacy and translational significance of AAV-Ca_V3.2iPA sensory neuron-targetedanalgesia in neuropathic pain

Authors: S. SHIN[1], B. ITSON-ZOSKE[1], F. FAN[2], Q. H. HOGAN[1], *H. YU[1];
[1]Anesthesiol., Med. Col. of Wisconsin, Milwaukee, WI; [2]Physiol., Med. Col. of Georgia at Augusta Univ., Augusta, GA

Abstract: We recently reported that targeting intrinsically disordered regions of calcium channel 3.2 (Ca_V3.2) facilitated the discovery of potent Ca_V3.2 inhibitory peptide aptamers (3.2iPA1 and 2) for AAV-mediated sensory neuron-targeted analgesia in rat chronic pain models. However, the preclinical long-term efficacy of the approach and the translational significance of 3.2iPAs in blocking T-type/Ca_V3.2 in human sensory neurons are not established. In this report, we generated AAV6-encoded concatemeric 3.2iPA that combined 3.2iPA1 and 2 (Co3.2iPA) as a tandem repeat. We extended sensory neuron-targeted T-type/Ca_V3.2 treatment via injection of AAV6-Co3.2iPA into the pathological dorsal root ganglia (DRG) and demonstrated analgesic efficacy in relieving stimulated and spontaneous pain behaviors lasting up to 3.5 months in rat tibial nerve injury (TNI)-induced neuropathic pain. Treatment showed a comparable magnitude and time course of analgesic effects between male and female rats. Immunohistochemistry and quantitative *polymerase chain reaction* of the AAV genome confirmed peripheral nerve-restricted AAV6-Co3.2iPA biodistribution and long-term transgene expression. Inhibition of T-type/Ca_V3.2 channels and suppression of action potential firing by expressing Co3.2iPA is confirmed in the human induced pluripotent stem cells-derived sensory neurons (hiPSC-SNs), suggesting a translational potential of sensory neuron-targeted AAV6-Co3.2iPA treatment for clinical chronic pain conditions that are intractable to the conventional pain therapy.

Disclosures: S. Shin: None. **B. Itson-Zoske:** None. **F. Fan:** None. **Q.H. Hogan:** None. **H. Yu:** None.

Poster

PSTR069: Non-Opioid Treatments for Persistent Pain

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR069.04/C143

Topic: D.01. Somatosensation – Pain and Itch

Support: NIH R33NS116203
R21NS137014-01

Dr. Ralph and Marian Falk Medical Research Trust, Bank of America, Private Bank
Advancing a Healthier Wisconsin Endowment Project (5520680 and 5520739)

Title: Peripherally targeted analgesia via AAV-mediated sensory neuron-specific inhibition of multiple pronociceptive sodium channels

Authors: *S. SHIN[1], B. ITSON-ZOSKE[2], F. FAN[3], Y. XIAO[4], T. R. CUMMINS[5], Q. H. HOGAN[6], H. YU[2];
[1]Med. Col. OF WISCONSIN, Brookfield, WI; [2]Anesthesiol., Med. Col. of Wisconsin, Milwaukee, WI; [3]Physiol., Med. Col. of Georgia at Augusta Univ., Augusta, GA; [4]Dept. of Biol., Indiana University- Purdue Univ. Indianapolis, Indianapolis, IN; [5]Dept Biol. SL306, Indiana University-Purdue Univ. Indianapolis, Indianapolis, IN; [6]Med. Col. of Wisconsin, Milwaukee, WI

Abstract: Peripherally targeted analgesia via AAV-mediated sensory neuron-specific inhibition of multiple pronociceptive sodium channels

Seung Min Shin, Brandon Itson-Zoske, Fan Fan, Yucheng Xiao, Chensheng Qiu, Theodore R. Cummins, Quinn H. Hogan, and Hongwei Yu

Abstract

This study reports that targeting intrinsically disordered regions of $Na_V1.7$ protein facilitates the discovery of sodium channel inhibitory peptide aptamers (Na_ViPA) for adeno-associated virus (AAV)-mediated, sensory neuron-specific analgesia. A multipronged inhibition of $I_{Na1.7}$, $I_{Na1.6}$, $I_{Na1.3,}$ and $I_{Na1.1}$. but not $I_{Na1.5}$ and $I_{Na1.8}$ was found for a prototype, named Na_ViPA1, which was derived from the $Na_V1.7$ intracellular loop 1 and is conserved among the TTXs Na_V subtypes. Na_ViPA1 expression in primary sensory neurons (PSNs) of dorsal root ganglia (DRG) produced significant inhibition of TTXs I_{Na} but not TTXr I_{Na}. DRG injection of AAV6-encoded Na_ViPA1 significantly attenuated evoked and spontaneous pain behaviors in both male and female rats with neuropathic pain induced by tibial nerve injury (TNI). Whole-cell current clamp of the PSNs showed that Na_ViPA1 expression normalized PSN excitability in TNI rats, suggesting that Na_ViPA1 attenuated pain by reversal of injury-induced neuronal hypersensitivity. Immunohistochemistry revealed efficient Na_ViPA1 expression restricted in PSNs and their central and peripheral terminals, indicating PSN-restricted AAV biodistribution. Inhibition of sodium channels by Na_ViPA1 was replicated in the human iPSC-derived sensory neurons. These results summate that Na_ViPA1 is a promising analgesic lead that, combined with AAV-mediated PSN-specific block of multiple TTXs Na_Vs, has potential as peripheral nerve-restricted analgesic therapeutics.

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Poster

PSTR069: Non-Opioid Treatments for Persistent Pain

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR069.05/C144

Topic: D.01. Somatosensation – Pain and Itch

Support: NIH R01AT011517
University of Arizona Institutional Funds

Title: Exploring the Role of GPR63 and GPR153 as Novel Modulators of Opioid-Induced Antinociception in a Mouse Model of Neuropathic Pain Via Glial Cell Modulation

Authors: *A. PENA[1], E. GEVELHOFF[2], J. M. STREICHER[3];
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Abstract: Treatments for chronic pain disorders are currently dominated by opioid drugs which lose efficacy over time and yield various undesirable side effects. Thus, the need for identifying novel targets for modulating pain is critical. In this work, we have identified two potential targets for the development of non-opioid analgesics - the orphan GPCRs GPR63 and GPR153. This was achieved by *in vivo* transfection of targeted CRISPR-Cas9 DNA constructs with a universal promoter in the spinal cords of adult male and female CD-1 mice and evaluating changes in morphine response in a neuropathic pain model. Chemotherapy-induced peripheral neuropathy (CIPN) was induced by 2 mg/kg paclitaxel via intraperitoneal injection resulting in the development of mechanical allodynia. Both models were followed by administration of 3.2 mg/kg morphine SC and a three-hour von Frey time course to evaluate changes in opioid-induced antinociception. Another cohort of animals received a non-targeted universal negative control CRISPR construct. Receptor knockdown ablated the analgesic effect of morphine in this model whereas there was no effect of knockdown on opioid-induced antinociception in an acute tail flick pain model. These findings suggest that these receptors are not involved in direct neurotransmission of pain signals but instead play roles in the neuropathology of chronic pain and/or in altering cellular responses to opioids in chronic pain states. To further investigate this finding, we performed RNAScope *in situ* hybridization in the spinal dorsal horn to localize RNA transcripts of mouse *Gpr63* and *Gpr153* with immunohistochemical markers for microglia (Iba1) or astrocytes (GFAP), cell types believed to contribute to the development and/or maintenance of neuropathic pain. We found that *Gpr63* and *Gpr153* are expressed in ~50-60% of microglia and astrocytes. Lastly, we began exploring the biological mechanism of these receptors and how their knockdown ablates opioid-induced antinociception by repeating the previously described behavioral assay using glial cell-specific receptor knockdown. This was done by replacing the universal promoter of our original CRISPR-Cas9 constructs with the *Aif1* or *Gfap* promoters to restrict expression of the sgRNA to microglia or astroctyes, respectively. Together this work identifies completely novel pain modulators potentially acting through glial cells which could be exploited to develop new pain therapies.

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Poster

PSTR069: Non-Opioid Treatments for Persistent Pain

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR069.06/C145

Topic: D.01. Somatosensation – Pain and Itch

Title: Effect of LP-211 in Combination with Gabapentin on Nerve Conduction Velocity and Nerve Blood Flow in Diabetic Neuropathic Rats.

Authors: *V. GOURA[1], P. JAYARAJAN[1], A. KISHORE[2], R. ABRAHAM[1], R. KALLEPALLI[1], R. NIROGI[1];
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Abstract: Diabetic peripheral neuropathy is a significant complication of diabetes mellitus, which poses challenges in terms of management with current treatments. The major causes of diabetic neuropathy include demyelination, axonal degeneration, and a decrease in nerve blood flow. These factors can result in a decrease in nerve conduction in diabetic rats. In this particular study, the effects of LP-211, a selective 5-HT7 receptor agonist, in combination with gabapentin on nerve conduction velocity and nerve blood flow in diabetic neuropathic rats were investigated. Previous research has shown that the administration of LP-211 can produce antinociception in mouse models of formalin-induced inflammatory pain and chronic constriction injury induced neuropathic pain. To induce diabetes, streptozotocin was administered at a dose of 50 mg/kg, *i.p.* Blood glucose levels were measured after 10 days of streptozotocin administration. Paw withdrawal thresholds were assessed using Von Frey filaments three weeks after streptozotocin administration. Rats with paw withdrawal thresholds below 4 grams were selected for further evaluation of nerve conduction velocity using Power lab. Neuropathic rats were then treated with either vehicle or LP-211 at doses of 1, and 3 mg/kg, in combination with gabapentin 10mg/kg administered intraperitoneally for two weeks, while control rats received vehicle treatment. After two weeks of LP-211 + gabapentin or vehicle administration, the paw withdrawal threshold and nerve conduction velocity were recorded and compared to the control group. Nerve blood flow was also estimated in the control and LP-211 + gabapentin / vehicle-treated diabetic rats using Laser Doppler Flowmetry. The results showed that rats treated with LP-211 at doses of 1 and 3 mg/kg in combination with gabapentin 10 mg/kg exhibited a significant increase in paw withdrawal thresholds, nerve conduction, and blood flow. These findings suggest that LP-211 + gabapentin have an analgesic-like effect in this study. However, further histopathological studies are required to confirm the observed effects and investigate the potential remyelination of the sciatic nerve.

Disclosures: V. Goura: A. Employment/Salary (full or part-time):; SUVEN LIFE SCIENCES LTD. **P. Jayarajan:** A. Employment/Salary (full or part-time):; SUVEN LIFE SCIENCES LTD. **A. Kishore:** A. Employment/Salary (full or part-time):; Manipal Academy of Higher Education. **R. Abraham:** A. Employment/Salary (full or part-time):; SUVEN LIFE SCIENCES LTD. **R. Kallepalli:** A. Employment/Salary (full or part-time):; SUVEN LIFE SCIENCES LTD. **R. Nirogi:** A. Employment/Salary (full or part-time):; SUVEN LIFE SCIENCES LTD.

Poster

PSTR069: Non-Opioid Treatments for Persistent Pain

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR069.07/C146

Topic: D.01. Somatosensation – Pain and Itch

Title: Demonstration of the peripheral analgesic potency of the Nav1.7 channel blocker GNE-3565 using distal electrical threshold tracking of unmyelinated nociceptors in vivo

Authors: *J. ALLARD;
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Abstract: It has been proposed that the analgesic potential of Nav1.7 inhibition might exclusively rely on its role in the initiation of action potential (AP) in nociceptors (Deng et al, Neuron, 2023). To challenge this finding, we designed a threshold tracking method to evaluate the effect of Nav1.7 blockade on the electrical excitability of the distal terminal of unmyelinated nociceptors in anesthetized mice. We also assessed whether the decreased responses of spinal neurons induced by GNE-3565, previously observed in lamina III-V neurons of unknown projection, could be measured at the level of lamina I spinoparabrachial (SPB) neurons. DRG and spinal cord single-unit recordings were performed in ventilated, isoflurane-anesthetized mice, with control of physiological status. Responses to stimulations of the receptive field (electrical, mechanical and thermal) were measured before, during and after the i.v. injection of GNE-3565 or the corresponding vehicle. In nociceptors, AP generated by electrical stimulation displayed increased latency and were eventually abolished following GNE-3565 infusion in most experiments. AP could be transiently restored by increasing the intensity of the electrical stimulation, suggesting that the disappearance initially observed was caused by a generation rather than a conduction failure. Such marked effects were not observed during vehicle injection. GNE-3565 also induced apparent decreases in conduction velocity and electrical excitability in mechanoreceptors, which were fully compensated by the threshold tracking procedure. Responses of nociceptors to noxious mechanical and thermal stimulations were abolished in GNE-3565 treated mice, and noticeably decreased in vehicle-treated mice. The latter result might be related to the tendency of unmyelinated nociceptors to desensitize upon repeated noxious mechanical and thermal stimulations in the present experimental conditions. Responses of mechanoreceptors to light touch were moderately decreased after GNE-3565 infusion, and unchanged after vehicle. The number of lamina I SPB neuron recordings obtained at the time of submission of the present abstract was too limited for analysis. The study is ongoing. The transient recovery of AP in the threshold tracking experiments with nociceptors supports a role for Nav1.7 at the level of their distal terminal. More experiments (e.g. using sciatic nerve electrical stimulations) are required to demonstrate an exclusive role of Nav1.7 at the transduction level. The threshold tracking method used herein could be useful to evaluate the potency of analgesic drug candidates aiming at decreasing the excitability of nociceptors.

Disclosures: J. Allard: None.

Poster

PSTR069: Non-Opioid Treatments for Persistent Pain

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR069.08/C147

Topic: D.01. Somatosensation – Pain and Itch

Support: FDN-148413

Title: A new macrocyclic analog of apelin-13 conjugated to a brain-penetrating peptide effectively relieves pain

Authors: *A. TREMBLAY, K. TRAN, M. CHARTIER, L. THÉROUX, J. COTE, M.-A. BONIN, I. BROCHU, A. MURZA, J.-M. LONGPRE, P.-L. BOUDREAULT, P. SARRET; Univ. of Sherbrooke, Sherbrooke, QC, Canada

Abstract: Apelin (Ape-13) is a peptide hormone acting as one of the endogenous ligands of the class A G protein-coupled receptor, APJ. Tissue expression of APJ includes many brain structures involved in pain transmission and modulation, such as dorsal root ganglia, periaqueductal grey and rostroventral medulla. Consequently, intrathecal (i.t.) administration of Ape-13 induces antinociception suggesting that APJ is a potential drug target for pain management, stimulating the development of ligands acting on APJ. However, Ape-13 exhibits poor brain penetration and low resistance to proteolytic degradation, thus limiting its therapeutic use. We have previously reported a series of linear analogs of Ape-13 with increased plasma stability and potent affinity for APJ. Among them, C-terminal substitution of Phe13 with the unnatural amino acid 2-Nal leads to a more stable analog with antinociceptive properties in a rat model of tonic inflammatory pain. However, due to the presence of the blood-brain barrier (BBB) which tightly regulates the interface between blood and brain, most peptides cannot reach pain-related brain structures. To enhance drug penetration into the brain following systemic administration, we designed and synthesized LT-1019 by conjugating Ape-13(2-Nal) with Angiopep-2 (An2), a brain-penetrant peptide that targets LRP1 receptors expressed on vascular endothelial cells. LT-1019 showed great analgesic potential *in vivo* in rats following intravenous injections in formalin-induced and CFA-induced inflammatory pain models. However, LT-1019 retains a marked hypotensive effect, which restricts its potential clinical use as analgesic. To overcome this undesirable peripheral effect, we decided to conjugate the macrocyclic analog of Ape-13, H2N-c[X-R-L-S-X]-K-G-P-(D-2-Nal), namely KT04-44, to An2. Indeed, KT04-44 retained excellent binding affinity for APJ and high plasma stability, but more importantly exhibited reduced hypotensive action associated with lower β-arrestin 2 recruitment potency and efficacy. Furthermore, KT04-44 was effective in reducing the nociceptive behaviors associated to the tonic (formalin test) and postoperative (Brennan paw incision) pain models following it.t injection. Here, we further report on the *in vitro*/*in vivo* characterization of the An2-conjugated version of KT04-44, covering binding/signaling/plasma stability profiles, ability to induce blood pressure lowering and analgesic effectiveness following systemic delivery. The development of these Ape-13 analogs represents a promising alternative to opioids, for safe and effective pain management.

Disclosures: A. Tremblay: None. **K. Tran:** None. **M. Chartier:** None. **L. Théroux:** None. **J. Cote:** None. **M. Bonin:** None. **I. Brochu:** None. **A. Murza:** None. **J. Longpre:** None. **P. Boudreault:** None. **P. Sarret:** None.

Poster

PSTR069: Non-Opioid Treatments for Persistent Pain

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR069.09/C148

Topic: D.01. Somatosensation – Pain and Itch

Support: FDN-148413

Title: Macrocyclic peptides and small molecules targeting the apelin receptor as promising analgesics

Authors: *M. VILLATTE[1], L. THÉROUX[2], K. TRAN[3], I. BROCHU[4], J. COTE[5], J.-M. LONGPRE[6], P.-L. BOUDREAULT[7], P. SARRET[8];
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Abstract: The opioid crisis along with the individual and societal burden of chronic pain requires the development of new pain treatment options. Apelin-13, the endogenous ligand of the G protein-coupled APJ receptor, has recently been shown to induce antinociceptive effects in different painful conditions. Accordingly, the Ape13/APJ axis has been associated with ascending and descending nociceptive pathways, including primary afferent inputs, spinal cord, and periaqueductal gray. However, Ape13 has a short *in vivo* half-life, and its exogenous administration is linked to peripheral physiological effects, including myocardial contractility and hypotension, thereby limiting its clinical use as analgesic. Although the signaling pathways involved in the antinociceptive effects of Ape13 are still unknown, its hypotensive action is known to be dependent on the recruitment of β-arrestins. Here, we synthesized and characterized different macrocyclic analogs of Ape13 and compared their analgesic properties with those of biased or balanced cyclic APJ agonists (MM07, AMG3054). To this end, we synthesized the smallest active macrocyclic Ape13 analog (KT01-116) truncated at the N- and C-termini with an unnatural amino acid (Nle11) at its C-terminal end. This cyclic peptide binds APJ with high affinity (Ki of 14 nM), but more importantly, displayed an attractive signaling profile, as demonstrated using BRET-based biosensors ($EC_{50}$of β-arrestin2 and $G\alpha_{i1}$: 743 ± 108 nM and 5.4 ± 0.7 nM, respectively). We also used a scaffold-hoping strategy to create new druggable small-molecule ligands starting from the first identified $G\alpha_i$-biased small-molecule ligand at APJ, CMF-019, and studied their functional activity in comparison with other small-molecule agonists

(BMS986224, AMG986). This structure-activity relationship of CMF-019 enabled us to identify small molecules that can bind to APJ with variable affinity (Ki: from 49 to 625 nM). Moreover, we found small molecules with various signaling profiles (β-arrestin2 EC_{50}: from 180 to >10 000 nM, and $G\alpha_{i1}$ EC_{50}: from 2.8 to 309 nM). The best candidates were then tested *in vivo* for their ability to reduce the nociceptive behaviors in acute and tonic pain models and to modulate blood pressure. Interestingly, the macrocyclic analog KT01-116 exerted significant analgesic effects in tail-flick and formalin pain tests without inducing hypotension. The small molecule LT02-20 was also effective in reversing the formalin-induced pain behaviors, while the parent compound CMF-019 had no analgesic effect. Overall, these results highlight the therapeutic potential of biased macrocyclic APJ analogs and small molecules for managing pain.

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Poster

PSTR069: Non-Opioid Treatments for Persistent Pain

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR069.10/C149

Topic: D.01. Somatosensation – Pain and Itch

Support: FDN-148413

Title: Rational Strategy for Designing Cyclic Peptides into Small Molecules: Optimization of the First NTS2-selective Small Molecule Analgesic

Authors: *N. MENEBOO[1], M. DESGAGNÉ[1], M. CHARTIER[2], U. FRÖHLICH[1], C. COMEAU[1], J.-M. LONGPRE[3], P.-L. BOUDREAULT[4], P. SARRET[5];
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Abstract: The peptide neurotensin (NT) and its shorter biologically active fragment NT(8-13) (RRPYIL-OH) exert a variety of physiological effects via recruitment of two G Protein-coupled receptors: NTS1 and NTS2. Activation of NTS1 is associated with analgesia and hypothermia in the central nervous system, as well as hypotension in the periphery while NTS2 is known primarily to produce analgesia. Importantly, NT-induced analgesia is described as opioid-independent. NTS2-selective compounds thus represent a promising avenue for the development of safer analgesics. From a structural standpoint, homology models of the human NTS1 and NTS2 receptors have been built based on the crystal structure of the rat NTS1 receptor and revealed an alignment between the positively charged arginine 212 (R212) of NTS1 and the negatively charged glutamic acid 179 (E179) of NTS2. We observed that the R212 residue of

NTS1 is located close to surrounding negatively charged residues (10 to 14Å) and could form hydrogen bound with them, thus resulting in a possible closed state of NTS1. The NTS2 receptor, on the other hand, would remain in an open state due to the repulsion of negative charges. We therefore hypothesized that the N-terminal arginine residues of NT(8-13) would be required for binding to NTS1, opening the receptor by disrupting the H-bound interactions between R212 and the neighboring negatively charged residues. Here, we describe the design and synthesis of the first series of NTS2-selective small molecules, based on the previously published highly selective macrocyclic derivative MS01-174 (Ki NTS2 = 50 nM, Ki NTS1 > 100 μM). By removing the positively charged N-terminal residues, we synthesized a series of dipeptides based on the hydrophobic C-terminal region of MS01-174 and found that the dipeptide Cha-Cha could bind to NTS2 with an affinity of 2 μM without binding to NTS1. N-terminal expansion of Cha-Cha led to the tripeptide Nle-Cha-Cha (Ki NTS2 = 94 nM, Ki NTS1 > 100 μM) and the tetrapeptide Lys-Nle-Cha-Cha (Ki NTS2 = 44 nM, Ki NTS1 > 100 μM). Interestingly, all three peptides were able to bind with an affinity of 100, 71 and 5 nM, respectively, to the mutated NTS1 receptor, in which R212 has been replaced by an aspartic acid (NTS1-R212E). Moreover, intrathecal injections of Lys-Nle-Cha-Cha (500 to 1000 nmol/kg) produced significant analgesia in different rat pain models, without altering body temperature or blood pressure associated with NTS1 activation. Altogether, these results provide insight into the synthesis of NTS2-selective small molecules, paving the way for a new approach to chronic pain management.

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Poster

PSTR069: Non-Opioid Treatments for Persistent Pain

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR069.11/C150

Topic: D.01. Somatosensation – Pain and Itch

Support: Contract No. 75N95019D00026

Title: In vivo PK, side effect profile, and analgesic efficacy of multiple clinically used compounds in male and female rats

Authors: *E. A. DUGAN[1], D. BUDAC[1], B. STANFIELD[1], M. URBAN[1], V. BRINGS[2], S. A. WOLLER[2], S. IYENGAR[2], M. A. VARNEY[1], T. HANANIA[1];
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Abstract: In collaboration with the NIH HEAL Initiative Preclinical Screening Platform for Pain (PSPP), we evaluated clinically used compounds, including celecoxib, carbamazepine, and a negative control, diazepam, through the tiered approach established to profile potential novel analgesics. First, pharmacokinetic studies were conducted to guide dosing, select the route of

administration, and to determine the time course, supporting subsequent behavioral studies. Next, the modified Irwin (n=4) and rotarod tests (n=10) were conducted to evaluate potential neurologic, physiologic, and fine motor effects that may impact outcome measures in the pain models. Following side effect profile assessment, analgesic efficacy was evaluated in the plantar incision (n=10) and L5/L6 spinal nerve ligation (SNL; n=10) models. The rat plantar incision model is an established model of acute post-operative pain induced by incision of the skin and the plantaris muscle (Brennan et al. 1996). The model is characterized by transient hind paw tactile allodynia and spontaneous guarding behaviors. SNL is a model of peripheral neuropathic pain resulting from chronic nerve compression in which tactile and cold allodynia are produced (Kim and Chung, 1992). All experiments were conducted in a blinded manner. Power analysis was used to determine the group sizes for the various assays. Following pharmacokinetic study recommendations, side effect profile and efficacy studies showed that celecoxib did not produce any significant observable behaviors or impairments on rotarod performance but provided moderate improvements for acute mechanical allodynia and spontaneous guarding behaviors in the plantar incision model. Celecoxib did not show efficacy in the SNL model. In side effect profile studies, carbamazepine showed several observable behaviors in a dose-dependent manner, however carbamazepine administration did not produce any significant impairments on rotarod performance. In efficacy studies, carbamazepine provided improvements on acute mechanical allodynia and spontaneous guarding behaviors in the plantar incision model but mainly in female rats. Carbamazepine did not show efficacy in the SNL model. Diazepam was assessed as a negative control and produced sedative effects and significant impairment on rotarod performance in the side effect profile studies. The results of these studies of clinically used compounds within the PSPP program demonstrate the validation of the models and endpoints described and highlight the goal of providing a robust platform to accelerate the discovery and preclinical development of non-opioid, non-addictive treatments for pain.

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Poster

PSTR069: Non-Opioid Treatments for Persistent Pain

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR069.12/C151

Topic: D.01. Somatosensation – Pain and Itch

Title: In vivo profiling of nalfurafine hydrochloride in rats in the NIH HEAL Initiative Preclinical Screening Platform for Pain (PSPP) program

Authors: V. BRINGS[1], D. KEMPEGOWDA[2], C. CONRAD,[3], S. SHARMA[2], S. A. WOLLER[4], *S. IYENGAR[5];
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Abstract: The Preclinical Screening Platform for Pain (PSPP) program was developed as part of the National Institutes of Health Helping to End Addiction Longterm Initiative, or NIH HEAL Initiative, with the goal of accelerating the discovery and development of non-opioid, non-addictive pain therapeutics. Toward this goal, the PSPP program accepts small molecules, biologics, natural products, and devices from industry, academic, or government asset owners worldwide for preclinical evaluation at no cost to the asset owner. Additionally, the PSPP program aims to disseminate information to enable rigorous preclinical research in the development of potential pain therapeutics. To this end, the PSPP program has developed a public-facing website featuring information about the program, how assets move through the PSPP workflow, and descriptions of optimized and validated methods for assays, models, and endpoints used in the program. The kappa opioid receptor agonist nalfurafine hydrochloride (1-1000 µg/kg, SC) was evaluated in collaboration with PsychoGenics Inc. as part of an effort to evaluate clinically used drugs, negative controls, and CNS active compounds using the PSPP workflow. All in vivo studies used male and female Sprague Dawley rats in fully powered groups and included vehicle and positive control groups. Experimenters were blinded to treatment, pre-determined inclusion criteria were applied for each endpoint, and groups were balanced by specific variables. In a pharmacokinetics (PK) study, nalfurafine (100, 1000 µg/kg) plasma levels were measured to guide the dosing for behavioral assays. The Irwin functional observational battery and rotarod assays showed that 1, 3, 10, and 30 µg/kg nalfurafine were well tolerated with minimal neurological side effects. The plantar incision model of acute post-operative pain and the L5/L6 spinal nerve ligation model of chronic neuropathic pain were assessed with two validated endpoints for each model, including tests of allodynia and spontaneous pain behavior. Dose- and time-dependent analgesic efficacy was demonstrated in both pain models after assessing the effects of 0.3, 1, 3, and 10 µg/kg nalfurafine for all endpoints for both sexes. In addition to evaluating nalfurafine, PSPP has rigorously collected data sets evaluating in vitro assessment of safety and abuse liability and protein binding and in vivo profiling of PK, side effects, efficacy in pain models, and/or abuse liability for over 12 compounds of different classes. The PSPP program and website (https://pspp.ninds.nih.gov/) are resources available to the global community developing potential new, non-opioid, non-addictive pain therapeutics.

Disclosures: V. Brings: A. Employment/Salary (full or part-time):; National Institute of Neurological Disorders and Stroke, NIH. **D. Kempegowda:** None. **C. Conrad,:** A. Employment/Salary (full or part-time):; National Institute of Neurological Disorders and Stroke, NIH. **S. Sharma:** A. Employment/Salary (full or part-time):; National Institute of Neurological Disorders and Stroke, NIH. **S.A. Woller:** A. Employment/Salary (full or part-time):; National Institute of Neurological Disorders and Stroke, NIH. **S. Iyengar:** A. Employment/Salary (full or part-time):; National Institute of Neurological Disorders and Stroke, NIH. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Retiree, Eli Lilly and Company, stockholder.

Poster

PSTR069: Non-Opioid Treatments for Persistent Pain

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR069.13/C152

Topic: D.01. Somatosensation – Pain and Itch

Support: R33 AG075419

Title: Aav-based upregulation of potassium channels as a focal treatment of chronic pain

Authors: *P. I. SENARATNE[1], L. SUN[1], G. CHAHYADINATA[1], B. JOHNSTON[5], J. NAM[7,1], W. DING[8], H. YONG[6], D. M. DUBREUIL[1], A. H. HELD[1], S. ST PIERRE[1], C. BANNERMAN[1], K. R. EBERLIN[2], W. RENTHAL[9], S. SHEN[3], B. WAINGER[1,4,10]; [1]Neurol., [2]Dept. of Surgery Div. of Plastic Surgery, [3]Dept. of Anesthesia, MGH Ctr. for Translational Pain Res., Massachusetts Gen. Hosp., Charlestown, MA; [4]Dept. of Anesthesiology, Critical Care and Pain Med., Massachusetts Gen. Hosp., Boston, MA; [5]Neurosurg., Brigham and Women's Hosp., Boston, MA; [6]Neurol., Brigham and Women's Hosp., Brookline, MA; [7]Physiol., Dongguk Univ. Col. of Med., Gyeongju-si, Korea, Republic of; [8]Dept. of Anesthesia, Critical Care and Pain Med., Mass Gen. Brigham/Harvard Med. Sch., Charlestown, MA; [9]Neurol., Brigham and Women's Hosp., Boston, MA; [10]Broad Inst. of Harvard Univ. and MIT, Cambridge, MA

Abstract: Chronic pain afflicts over 30% of people worldwide, with an approximate annual economic burden of over 500 billion dollars in the United States alone, higher than cardiac disease, diabetes, and cancer. Existing treatments have limited efficacy, particularly for severe pain and substantial side effects. The lack of sufficient pain treatments has fueled the opioid epidemic, with associated life-threatening side effects such as respiratory depression and addiction. Despite the focus on systemic treatment, most chronic pain conditions are focal, and thus systemic side effects may be reduced or avoided through spatially-precise treatments.Strong human genetic evidence supports the strategy of reducing activity of the first-order pain-sensing neurons, nociceptors, as a therapeutic for chronic pain. Homozygous knockouts of the Nav1.7 voltage-gated sodium channel, which is primarily expressed in nociceptors, result in a congenital insensitivity to pain. In contrast, a gain of function mutation can cause severe pain syndromes, including familial erythromelalgia.We have developed a strategy of potassium channel overexpression through the use of a focally directed injection of adeno-associated virus (AAV) vectors. Support for this approach includes studies in which a gain of function of Kv7 mutation exerts disease-modifying effects in patients with familial erythromelalgia. Furthermore, potassium channel haplotypes are associated with reduced labor-associated pain.We have validated the efficacy of this strategy through a series of physiological and behavioral experiments in rodents. Using mice that express channel rhodopsin under the nociceptor promoter TrpV1, we isolate nociceptors, apply a calcium indicator, and measure the light threshold - which we have termed optical rheobase - for calcium flux generation. We showed that in vivo injections of AAV-potassium channels resulted in an increase of optical rheobase, consistent with reduced excitability of the nociceptors. We further validated the reduction of pain in animals receiving AAV-potassium channels compared to control AAV-GFP injections through standard pain behavioural models. Our results validate the overexpression of potassium channels as a promising treatment for severe focal pain.

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Poster

PSTR069: Non-Opioid Treatments for Persistent Pain

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR069.14/C153

Topic: D.01. Somatosensation – Pain and Itch

Support: NIH Grant R01 DE031352

Title: The role of macrophage inhibitory factor (MIF) and receptors CD74 and CXCR4 in human stem cell-induced anti-nociception in a model of orofacial pain

Authors: *K. NIP[1], J. MURILLO[2], S. THAKKAR[3], P. CHANG[3], T. IBRAHIM[4], N. B. RUPAREL[5];
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Abstract: Root canal procedures are effective treatment options for apical periodontitis, a sequela of microbial infection of a tooth. However, post-treatment pain that lasts >6 months occurs in ~2 million patients/year. Prolonged use of existing analgesics leads to significant adverse effects, underscoring the necessity to explore novel, side-effect-free analgesic classes for dental pain. Our preliminary data demonstrate that i.v. injection of human stem cells of apical papilla (hSCAP) reverses orofacial mechanical allodynia in a mouse model of AP. RNA sequencing of hSCAP homed to the infected tooth show a 133-fold increase in the expression of the cytokine, Macrophage Migratory Inhibitory Factor (MIF). A local injection of recombinant MIF reverses AP-induced hypersensitivity while a MIF-Ab eliminates hSCAP-induced anti-nociception. Conditioned media from hSCAP fully reverses capsaicin (Cap)-evoked calcium accumulation $[Ca^{2+}]_I$ in trigeminal ganglia (TG) neurons that is reversed by a MIF-Ab demonstrating a direct inhibitory effect of MIF on TG neurons. However, mechanisms by which MIF inhibits sensory neuronal function is unknown. The objective of our study is to evaluate the role of MIF receptors, CD74 and CXCR4 in mediating hSCAP/MIF-induced anti-nociception in a model of AP. MIF signals via CD74 and CXCR receptors. Using immunohistochemistry, we observed CD74 and CXCR4 (but not CXCR2/7) expression on $TRPV1^+$ TG sensory neurons. Next, we employed $1x10^7$ GC/mouse of adeno-associated viral vectors (AAV), AAV1-GFP-U6-CD74-shRNA and AAV1-GFP-U6-CXCR4-shRNA, to induce intraganglionic functional knockdown of CD74 and CXCR4. Qualitative assessment using immunohistochemistry and

quantitative assessment using western blot demonstrate a knockdown of CD74 and CXCR4. Furthermore, following baseline mechanical thresholds, AAV-shRNA were introduced followed by initiation of AP three weeks after. Mice received weekly injections of hSCAP or saline once a week for three weeks. Our data demonstrate that mice receiving a dual knockdown of CD74 and CXCR4 or a singular knockdown of CXCR4 alone fully reversed hSCAP-induced anti-nociception. These data suggest that CXCR4 serves as the primary receptor for the anti-nociceptive effects of MIF. This was substantiated by electrophysiological experiments that demonstrate complete reversal of hSCAP-induced inhibition of Cap-evoked $[Ca^{2+}]_I$ in presence pertussis toxin (200ng/ml). Data Analysis: 1- or 2-way ANOVA with post-hoc analysis as indicated. Collectively, our studies demonstrate the role MIF-CD74/CXCR4 axis as a direct mechanism in hSCAP-inhibition of trigeminal sensory neuronal function in a model of AP.

Disclosures: K. Nip: None. **J. Murillo:** None. **S. Thakkar:** None. **P. Chang:** None. **T. Ibrahim:** None. **N.B. Ruparel:** None.

Poster

PSTR069: Non-Opioid Treatments for Persistent Pain

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR069.15/C154

Topic: D.01. Somatosensation – Pain and Itch

Support: NIH grant u01 NS113873

Title: Morphological characterization of colonic afferents in thoracolumbar and lumbosacral dorsal root ganglia

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Abstract: Visceral pain associated with irritable bowel syndrome (IBS) show necessitates for novel approaches that are distinct from conventional analgesic treatments. Electrical stimulation of dorsal root ganglia (DRG) holds promise in modulating C-fiber afferents, predominant in extrinsic sensory innervations of the colon and rectum. This study employs sparse labeling with adeno-associated virus (AAV) to conduct a detailed morphological examination of colonic afferents in mouse thoracolumbar and lumbosacral DRG, comparing their stem axon length and orientations with the general afferent population in the DRG. This foundational anatomical data holds the potential to inform the design of DRG neurostimulators aimed at refining the selective modulation of colorectal afferents. We injected Cre-dependent AAV9-ChR2-EYFP into the distal colon wall of VGLUT2-Cre mice to retrograde label colonic DRG neurons (at 3 - 5 sites, ~ 2-4 mm apart, 1μL per site, titer >1 x 10^{13} vg·mL^{-1}). In another group of mice, we conducted intra-thecal (i.c.) injection of AAV9-ChR2-EYFP from the T13 to L1 spinal level to sparsely label DRG neurons (10μL per mouse, titer >1 x 10^{13} vg·mL^{-1}). Five to eight weeks after AAV

injection, both the thoracolumbar (T12 to L2) and lumbosacral (L5 to S1) DRG were harvested and fixed with (4% Paraformaldehyde) for whole-mount immunohistological staining. The DRGs were optically cleared with SeeDB solution (80.2% wt/wt fructose) for 3 hrs, at 37 C°, stained with primary anti-Green Fluorescent Protein (GFP) polyclonal antibody (1:400, 48 hrs at 4 ºC, MBL International Corp, cat #598) and secondary donkey anti-rabbit-488 (1:1200, 48 hrs at 4ºC, Abcam, cat #ab150073). Whole-mount DRG was imaged by a confocal microscopy (Leica SP8) with 63x (HC PL APO, 63x/1.40 Oil CS2) and 40x (HC PL APO, 40x/1.30 Oil CS2) oil-immersion objective lenses with working distances of 0.14 mm, and 0.17 mm, respectively. The afferent neurons are typically sparsely labeled within the DRG, facilitating anatomical tracing from somata to the T-junction, where peripheral and central axons merge with the stem axon. Axonal and soma geometry were quantified and compared between the colonic group (retrograde labeled from the colon wall) and the general group (intrathecally labeled). Thoracolumbar colonic afferents exhibit thicker diameters, longer stem axons, wider angles between the stem and conducting axons, and showed A-fiber afferents than C-fiber afferents. These unique anatomical features suggest that electrical fields parallel to the DRG surface are likely to offer enhanced selective activation of colonic afferents compared to perpendicular orientation.

Disclosures: F. Elshishiny: None. **J. Liu:** None. **L. Chen:** None. **J. Do:** None. **B. Feng:** None.

Poster

PSTR069: Non-Opioid Treatments for Persistent Pain

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR069.16/C155

Topic: D.01. Somatosensation – Pain and Itch

Support: ICTI-PICIR23-058
CIC-UMSNH-18096
CIC-UMSNH-18099
CIC-UMSNH-18146
ICTI/DA/CTI/053/2023

Title: Metformin-melatonin combination prevents sustained pain development

Authors: *L. F. ORTEGA-VARELA[1], J. MARTÍNEZ[2], D. GODINEZ HERNANDEZ[3], C. J. GUTIERREZ-GARCIA[4], C. CERVANTES-DURÁN[5], M. Y. GAUTHEREAU-TORRES[6]; [1]Salud Publica. Univ. Michoacana Sn Nicolas De H ., Morelia, Mexico; [3]Inst. de Investigaciones Quimico Biologicas, [2]Univ. Michoacana, Morelia, Mexico; [4]Ingeniería Química y Bioquímica, TecNM/Campus Morelia, Morelia, Mexico; [5]Escuela Nacional de Estudios Superiores, Unidad Morelia, Univ. Nacional Autónoma de México, Morelia, Mexico; [6]Facultad de Ciencias Medicas y Biologicas Dr Ignacio Chavez, Univ. Michoacana de San Nicolas de Hidalgo, Morelia, Mexico

Abstract: There is growing recognition that pain is a public health problem that has a profound impact on individuals and society, promoting an increase in the demand for pharmacological

therapy to control this condition. The combination of drugs is widely used in pain therapy, in order to improve the analgesic effects and decrease its adverse effects. Drugs with pleiotropic effects such as metformin (antidiabetic) and melatonin (sleep regulator) have analgesic potential for combination. The purpose of this study was to evaluate the interaction between metformin and melatonin orally administered in preclinical models of long-lasting secondary mechanical allodynia and hyperalgesia induced by formalin in rats. Experiments were performed in female Wistar rats (220-350 g), the paw withdrawal responses to von Frey filaments (10 and 250 mN) were used to assess the allodynia and hyperalgesia, respectively. In control rats, formalin (1%), produced secondary mechanical allodynia and hyperalgesia in both paws. ED50 values of metformin, melatonin and their combination (obtained by isobolographic analysis in formalin test), showed a significant decrease in the mean of withdrawal responses compared to control group ($p < 0.05$) in both secondary allodynia and hyperalgesia. The reduction in this long lasting pain related behaviors was observed in both ipsi and contralateral paws, and was higher for the metformin-melatonin combination groups. Together, data suggest that metformin-melatonin combination prevent the onset of sustained pain phenomena and could be useful in pain management.

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Poster

PSTR069: Non-Opioid Treatments for Persistent Pain

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR069.17/C156

Topic: D.01. Somatosensation – Pain and Itch

Title: Targeted Muscle Reinnervation and Regenerative Peripheral Nerve Interfaces to Prevent Neuroma Pain

Authors: *J.-L. SENGER[1], P. HARDY[2], S. W. KEMP[3], B. J. KERR[4], K. CHAN[5], C. A. WEBBER[6];
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Abstract: Background and objectives: Targeted muscle reinnervation (TMR) and regenerative peripheral nerve interface (RPNI) are two surgical interventions used clinically to treat neuroma pain. In both strategies, the nerve is given a motor target to reinnervate either by directly coapting to a motor nerve (TMR) or using a muscle graft (RPNI). It remains unknown how these techniques modulate the pain response, and which is the better treatment strategy. In this study we evaluate the incidence of painful neuromas, and the effects of these two techniques, on

sensory nerves, motor nerves, and mixed sensorimotor nerves. Further, we directly compare the effects of TMR and RPNI surgery using a rodent model to assess the effects of these procedures on neuropathic pain and protein expression at the dorsal root ganglion. **Methods:** The tibial (mixed), sural (sensory), or motor branch to biceps femoris nerve of Fischer rats (36 animals/nerve) was transected and secured to the dermis to promote neuroma formation. Pain was assessed using mechanical stimulation at the neuroma site (direct pain) and von Frey analysis at the footpad (tactile allodynia from collateral innervation). Once painful neuromas were detected, animals were randomized to experimental groups: (a) TMR, where the nerve was coapted to the motor branch to biceps femoris, (b) RPNI, where the nerve was enwrapped with an extensor digitorum longus graft, (c) neuroma excision, and (d) neuroma left in situ. The TMR/RPNIs were harvested to confirm muscle reinnervation, and the sensory ganglia and nerves were harvested to assess markers of regeneration, pain, and inflammation. **Results:** Ten weeks following TMR/RPNI surgery, animals with sensory or sensorimotor nerve neuromas had decreased pain scores compared with controls ($p<0.001$). Animals who formed motor nerve neuromas did not develop painful neuromas. Both TMR and RPNI yielded successful innervation of their targets, evidenced by visualization neuromuscular junction reinnervation. Compared with neuroma controls, immunohistochemistry showed that sensory neuronal cell bodies of TMR and RPNI had a decrease in regeneration markers (pCREB, ATF-3) and pain markers (TRPV1, neuropeptide-Y) ($p<0.05$). The nerve and dorsal root ganglion maintained elevated Iba-1 expression in all cohorts. **Conclusion:** Both TMR and RPNI improved pain scores for animals with sensory or sensorimotor nerve neuromas to a similar extent. This is likely attributable in part to modulating the expression of pain protein expression in the dorsal root ganglia. Motor nerves did not form painful neuromas and likely do not require these surgical interventions.

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Poster

PSTR069: Non-Opioid Treatments for Persistent Pain

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR069.18/C157

Topic: D.01. Somatosensation – Pain and Itch

Support: CAPES (Finance Code 001)
Pronex (Contract 014/2017.; Protocol 46843.484.37488.23052016)

Title: Maresin 2 alleviates nociception and anxious-like behaviors inhibiting IL-1β in spinal and cortical regions from diabetic rats

Authors: *G. GUILHERME[1], M. V. FERREIRA[1], W. A. VERRI[2], J. M. ZANOVELI[3], J. M. CUNHA[4];

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Abstract: The neuropathic pain and anxiety/depression are some of the most prevalent and disabling complications associated with diabetes mellitus (DM). Unfortunately, the therapeutic options for managing these conditions remain limited, often failing to adequately address the pain and anxiety/mood disorders associated with DM. Given that neuroinflammation plays a pivotal role in both the onset and persistence of these complications and Maresin 2 (MaR2), a specialized pro-resolving mediator, has demonstrated antinociceptive effects in inflammatory pain models; in the current study, we aimed to investigate its therapeutic potential in neuropathic pain and anxiety/depression associated to DM. For that, DM was induced in adult male Wistar rats through streptozotocin (STZ; 60mg/kg; i.p.). Subsequent treatment with MaR2 (1, 3, or 10 ng/rat; i.p.) or vehicle (VEH) commenced 14 days post-DM induction and persisted until the fourth week. Mechanical allodynia was evaluated using the electronic Von Frey test (VFT) one day before STZ administration (baseline) and at various intervals following MaR2 treatment. In the fourth week post-STZ induction, behavioral assessments including the open-field test (OFT), elevated plus-maze (EPM), and modified forced swimming test (MFST) were conducted. Additionally, spinal cord (L4-L6), hippocampus, and prefrontal cortex (PFC) samples were processed to assess levels of the pro-inflammatory cytokine IL-1β. All experimental procedures were ethically approved by the institutional Ethics on Animal Experimentation (CEUA-BIO-UFPR #1108). Compared to non-diabetic VEH-treated rats, diabetic VEH-treated animals exhibited: 1) decreased mechanical threshold in the VFT; 2) reduced crossings in the OFT (53%); 3) diminished time and entries on open arms in the EPM test (33% and 25%, respectively); 4) increased immobility time (25%) in the MFST; 5) elevated IL-1β expression in the spinal cord, hippocampus, and PFC by 123%, 229%, and 164%, respectively. Conversely, treatment with MaR2 (1 to 10 ng) in diabetic animals: 1) alleviated mechanical allodynia in the VFT (34%, 40%, 43%) without compromising exploratory behavior in the OFT; 2) exerted an anxiolytic-like effect (3 ng only) by increasing time spent on open arms in the EPM (207%). However, the treatment did not reverse the depressive-like behavior in the MFST but it normalized IL-1β expression in the PFC and spinal cord but not in the hippocampus. These findings demonstrate the protective profile of MaR2 suggesting a therapeutic potential in alleviating mechanical allodynia and anxious-like behavior associated with experimental diabetes.

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Poster

PSTR069: Non-Opioid Treatments for Persistent Pain

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR069.19/C158

Topic: D.01. Somatosensation – Pain and Itch

Support: CAPES FINANCE CODE 001
CNPQ Grant 405545/2023-1

Title: Cannabigerol induces antinociceptive effect in experimental-diabetic rats: a comparative study between sexes

Authors: *M. FERREIRA[1], J. MARIA MIRANDA[2], L. RAUCHBACH OLIVEIRA[2], T. DEMEU[2], J. M. ZANOVELI[3], J. M. CUNHA[4];
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Abstract: Neuropathic pain is the most common complication of diabetes *mellitus* (DM), with women often reporting more severe symptoms. This suggests sexual differences may affect both the presentation as well as treatment responses of the disease. Given the limitations of current pharmacological treatments for diabetic neuropathy, alternative therapies are being considered. In that sense, it has been demonstrated that cannabigerol (CBG), a minor phytocannabinoid known for its broad biological activities, presents potential in pain management. Thus, this study aimed to evaluate the antinociceptive effects of CBG in experimental diabetes model in male and female Wistar rats. For that, experimental DM was induced by a single injection of streptozotocin (STZ; 60mg/kg; i.p) in male and female Wistar rats. The experimental groups were: normoglycemic control rats treated with vehicle (NGL-VEH), diabetic rats treated with VEH (DBT-VEH), male and female (n=10 each) or CBG (1, 3, 10, and 30mg/kg; i.p.; n=10 each) starting 14 days after STZ and lasting until the 28th day. Mechanical allodynia was assessed by the electronic Von Frey test (VF) and was performed one day before STZ injection (baseline) and again on the 7th, 14th, 21st, and 28th days after STZ injection. On the 14th day, VF was assessed before treatment and at 30, 60, 120, and 180 minutes after i.p. treatment with CBG. One hour later, the animals were subjected to the open field test (OFT) for 5 minutes to assess exploratory behavior. All experimental protocols were approved by the Institutional Ethics on Animal Experimentation (CEUA-BIO-UFPR #1584). Compared to NGL-VEH rats, diabetic rats showed a significant decrease in mechanical threshold starting on the 14th day post-STZ administration, persisting until the end of the protocols. In female diabetic rats, this reduction occurred earlier, starting from the 7th day. When compared to the DBT+VEH group, findings include: 1) An acute CBG (all doses) injection in diabetic rats significantly increased mechanical thresholds, with female rats peaking at 120 minutes post-injection and male rats at 60 minutes; 2) Chronic CBG treatment consistently raised mechanical thresholds in both sexes over the weeks, with no sex differences; 3) There was no impairment in locomotion observed in the OFT in CBG-treated rats. Although more studies are needed, our data demonstrate that CBG presents an antinociceptive profile without impairing locomotor activity, suggesting that CBG may be a very promising compound to treat diabetic neuropathic pain. Also, our findings indicate sex differences in the analgesic response after the acute injection of CBG, which may be relevant in the clinic.

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Poster

PSTR069: Non-Opioid Treatments for Persistent Pain

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR069.20/C159

Topic: D.01. Somatosensation – Pain and Itch

Support: CIHR Grant FRN-162434
MS Society of Canada Grant EGID-3761

Title: Targeting CGRP to treat pain specifically in female mice with experimental autoimmune encephalomyelitis (EAE).

Authors: *A. D. MAGUIRE[1], T. N. FRIEDMAN[1], G. TENORIO[2], B. J. KERR[3];
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Abstract: One of the most debilitating and under-managed symptoms of the autoimmune disease Multiple Sclerosis (MS) is neuropathic pain (NP). Not only are women more likely than men to develop MS, but they are also more likely to experience NP when they have the disease. However, clinical pain therapies such as opioids fall short in treating MS patients. Thus, there is an urgent need to find effective treatments that take the sex-linked mechanisms of autoimmune NP into account. Here we have focused on the neuropeptide calcitonin gene-related peptide (CGRP) which is actively studied as a target for migraine treatment in women. We have used a mouse model of MS, experimental autoimmune encephalomyelitis (EAE), which recapitulates many symptoms of MS, including motor impairments and hallmark features of NP such as cold and tactile allodynia. First, we cultured the primary sensory neurons from the dorsal root ganglia (DRGs) of both male and female mice with EAE. We found that only female mice with an established disease phenotype had higher neurite outgrowth compared to non-disease controls. Co-staining with markers of specific neuronal subtypes (NF200, IB4, and CGRP) revealed that only the peptidergic, CGRP-positive pain-sensing neurons accounted for this growth. Next, we histologically examined the CGRP fibers in EAE spinal cord tissue and found increased CGRP immunoreactivity in the deeper laminae of the spinal cords of female mice with established EAE. We also examined DRG tissue from these animals to look for evidence of phenotypic switching (i.e. large diameter mechanosensory neurons expressing CGRP) but did not find any changes. Finally, we tested whether inhibiting CGRP with an anti-CGRP antibody could reverse pain in female EAE mice. We allowed mice to develop the disease normally and found that at the time of symptom onset they had spontaneous pain, as measured by unbiased grimace scoring using PainFace software. We then administered daily anti-CGRP treatment for seven days and found a reversal of pain in these animals compared to vehicle treated EAE animals.Together our results suggest that CGRP-positive primary afferents may be sprouting in the spinal cord of female but not male EAE animals, and that inhibition of this neuropeptide can reverse spontaneous pain in females. Based on these results we propose that anti-CGRP treatment for pain in female MS patients warrants further study.

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Poster

PSTR069: Non-Opioid Treatments for Persistent Pain

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR069.21/C160

Topic: D.01. Somatosensation – Pain and Itch

Title: Development and Clinical Modeling of Kv7 Channel Opener Prodrug for Treatment of Neuropathic Pain

Authors: *P. DANSHINA, S. THRASHER, G. LEE, C. CREAN;
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Abstract: Neuropathic pain is a common public health problem and remains an unmet medical need. The voltage-gated potassium (Kv7) channel openers, such as flupirtine and retigabine (ezogabine), had been used for the management of chronic pain in Europe and evaluated in clinical trials, respectively. However, both are no longer on the market, and the relatively short half-life leading to substantial PK swing and TID dosing of ezogabine limited its potential clinical use due to tolerability AEs. A prodrug of ezogabine is presented here that is effective in a rodent model of neuropathic pain and addresses the PK, and by association the tolerability, with ezogabine. Kv7 channel opener ezogabine was conjugated to a generally recognized as safe (GRAS) promoiety that allows for absorption into systemic circulation through the entire GI tract. The prodrug pharmacokinetics in mice, rats and dogs were determined. The PK data was scaled to human for predictive exposure. Efficacy after PO dosing in the chronic constriction injury (CCI) model was determined in rats to demonstrate bridging between ezogabine literature and prodrug. The prodrug in the CCI model demonstrated an ED_{50} of 2.4 mg/kg 1h post dose after oral administration in the rat. In mice and rats a plateau of ezogabine exposure was present from 1- 24h, suggesting a sustained duration of effect, and in dogs from 4-24h before decreasing up through 72 h. A 1-compartment model was applied to fit the data and allometrically scale for human simulation. A simulated 300 mg single dose of the prodrug provided Tmax, Cmax and half-life of 37 h, 206 ng/mL and 257 h, while a 200 mg dose of ezogabine as a powder in capsule provides a Tmax, Cmax and half-life of 1.5 h, 396 ng/mL and 10.1 h. Following a 400 mg loading dose of the prodrug and 25mg QD maintenance doses a peak to trough swing of 5-6 ng/mL at steady state over a 24 h period was simulated. In summary, a novel Kv7 prodrug of ezogabine has suitable PK/PD allows for a loading dose and small maintenance doses for targeted efficacy with minimal peak to trough swing that may be suitable for QD dosing for treatment of certain neuropathic pain conditions. As a prodrug of ezogabine, it is patent protected and can be developed under the 505(b)(2) regulatory pathway.

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Poster

PSTR069: Non-Opioid Treatments for Persistent Pain

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR069.22/D1

Topic: D.01. Somatosensation – Pain and Itch

Title: Agmatine-based analog reduces tactile hyperalgesia through antagonism of NR2B-containing spinal NMDArs

Authors: *L. D. CAYE[1], B. M. CLEMENTS[2], K. F. KITTO[3], C. A. FAIRBANKS[4], C. PETERSON[3], G. L. WILCOX[5];
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Abstract: NMDA receptor antagonists, such as ketamine, have proven useful in the control of neuropathic pain. We have shown that agmatine (decarboxylated L-arginine) produces antihyperalgesia in chronic pain models, largely mediated by antagonism of NR2B-containing spinal NMDArs. Our laboratory recently developed a strategically substituted analog of agmatine (SSA) with improved biopharmaceutical features relative to agmatine. We sought to characterize SSA in preclinical models of persistent pain as well as determine its molecular mechanism of action by characterizing its efficacy and subunit selectivity in ex vivo spinal cord slices.
Methods: The effects of intrathecally delivered SSA were assessed in models of spared nerve-injury (neuropathic), CFA injection (inflammation), and hindpaw incision (post-operative) pain. Hypersensitivity was assessed by either von Frey monofilament stimulation and open field automated activity monitoring (Blackbox One Machine Learning Behavioral Observation System). To probe the mechanism of action of SSA, we evaluated SSA antagonism of spinal NMDArs as measured by a decrease in the excitatory postsynaptic current (EPSC) amplitude and duration. Male and female NaV1.8-ChR2-expressing mice were used for this experiment to selectively activate NaV1.8-expressing nociceptive afferents. 400uM transverse spinal cord slices were taken from the lumbar spinal cord. Substantia Gelatinosa neurons were optogenetically stimulated with blue light shone on the root entry zone and pharmacological blockers were applied to isolate NMDAr-mediated currents.
Results: SSA prevents the development of morphine analgesic tolerance and produces antihyperalgesia in pre-clinical models of neuropathic, inflammatory and post-operative pain. This was determined by a recovery to baseline levels for weight bearing or von frey stimulation on the affected limb. SSA effectively reduced the amplitude of blue light-evoked NMDA EPSCs in a concentration-dependent manner (EC50 3 mM). SSA also concentration-dependently reduced EPSC duration (EC50 10 mM) as indicated by the decay constant Tau.
Conclusion: The results of this study support the hypothesis that SSA is efficacious across multiple preclinical models of persistent pain, and that SSA shares a mechanism of action with agmatine. The improved biopharmaceutical features of SSA together with this subunit selectivity suggest that SSA may be a therapeutically useful non-opioid analgesic.

Disclosures: L.D. Caye: A. Employment/Salary (full or part-time):; University of Minnesota. C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Goltz Research Professorship in Dermatology. **B.M. Clements:** None. **K.F. Kitto:** None. **C.A. Fairbanks:** None. **C. Peterson:** None. **G.L. Wilcox:** None.

Poster

PSTR069: Non-Opioid Treatments for Persistent Pain

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Topic: D.01. Somatosensation – Pain and Itch

Support: SIP Grant 20240205

Title: The sigma-one receptor antagonist potentiates the opioid receptors: antinociceptive synergism in rats

Authors: *M. DECIGA-CAMPOS[1], L. CHEL GUERRERO[2], E. HERNÁNDEZ NÚÑEZ[3], R. ORTIZ-ANDRADE[2];
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Abstract: Sigma-1 receptors are a type of receptor found in the central nervous system that has been implicated in modulating pain perception. These receptors are unique in that they are not traditional opioid receptors, but they can interact with other neurotransmitter systems involved in pain modulation. Research suggests that activating sigma-1 receptors can produce antinociception. It is believed that these receptors may influence pain sensitivity by affecting the release of certain neurotransmitters and modulating the activity of ion channels involved in pain signaling. This study assesses the synergistic antinociception effect of haloperidol, a sigma-1 antagonist, combined with tramadol in rats with inflammatory pain. The data were interpreted using isobolographic analysis to establish the nature of the interaction. The isobologram was calculated from the effective dose of 50 (ED_{50}) individuals considering a rate of 1:1. The antinociceptive effect was assayed in a formalin test, the systemic administration of haloperidol (ED_{50} =0.25±0.08 mg/kg, i.p.) and tramadol (ED_{50}=2.69±1.32 mg/kg, i.p.) showed a dose-dependent antinociceptive effect. The antinociceptive effects of the combination of haloperidol/tramadol (ED_{50} =0.153±0.02 mg/kg, i.p.) was more potent than the expected value (1.47±0.66 mg/kg, i.p.). This result suggests that combinations with these drugs may have a clinical utility in pain therapy.

Disclosures: M. Deciga-Campos: None. **L. Chel Guerrero:** None. **E. Hernández Núñez:** None. **R. Ortiz-Andrade:** None.

Poster

PSTR069: Non-Opioid Treatments for Persistent Pain

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR069.24/D2

Topic: D.01. Somatosensation – Pain and Itch

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Title: The new mechanism of zinc homeostasis in fracture-induced pain

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Abstract: Fracture-induced acute and chronic pain are important types of perioperative pain. The pain triggered by fractures is divided into acute and chronic phases. The acute phase is associated with fracture- and surgery-induced inflammation, while the later stage is primarily linked to neuropathic pain. Patients with fractures often exhibit reduced serum zinc ion concentrations during the perioperative period, and supplementing serum zinc ions or locally injecting $ZnCl_2$ can alleviate acute and chronic fracture-induced pain. Moreover, our RNA-sequencing database revealed changes in several zinc ion transport-related proteins. Therefore, we suspect zinc homeostasis involving zinc ion transporters participates in fracture-related pain. We aim to explore the mechanism of zinc homeostasis in fracture-induced pain using in vivo animal models and in vitro dorsal root ganglion (DRG) cultures. This will involve pain behavioral analysis, ex vivo DRG calcium and zinc imaging, and C-fiber reflex-related electromyography techniques. Supplementing zinc ions may help alleviate fracture-related pain and enhance the analgesic effects of other pain medications, providing new insights into reducing the use and side effects of opioids and other pain-relieving drugs.

Disclosures: Y. Li: None.

Poster

PSTR069: Non-Opioid Treatments for Persistent Pain

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR069.25/D3

Topic: D.01. Somatosensation – Pain and Itch

Support: GRF Grant 14117122
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Shenzhen Technology Innovation Committee Grant
SGDX20210823103534005
NSFC 82173999

Title: The (2r,6r)-hydroxynorketamine restores postsynaptic localization of ampar in the prelimbic cortex to provide sustained pain relief

Authors: *T. JIN;
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Abstract: (2R,6R)-Hydroxynorketamine restores postsynaptic localization of AMPAR in the prelimbic cortex to provide sustained pain reliefAbstract: Neuropathic pain is a difficult-to-treat pain condition often inadequately managed by conventional analgesics. (2R,6R)-hydroxynorketamine (R-HNK) is a ketamine metabolite without dissociative effects and has been evaluated as an alternative to ketamine in chronic pain management. The mechanism of action remains elusive. In this study, we reported that repeated systemic infusion of R-HNK during the acute stage of nerve injury produced sustained pain relief for at least 14 days in the mouse model of spared nerve injury (SNI). Functional ultrasound imaging (fUSI) revealed that R-HNK administration potently increased cerebral blood flow in the brain regions of pain matrix, including the prelimbic cortex (PrL)and periaqueductal gray (PAG), which exhibited reduced responsiveness to painful stimuli after nerve injury. These results indicate that the brain network comprising these regions is a direct target of R-HNK. This was validated by directly infusing R-HNK into contra-PrL, which replicated the effect of systemic administration. Mechanistically, R-HNK administration countered the decrease in neural activity in response to noxious stimuli and enhanced excitatory postsynaptic currents in the PrL after SNI. Transcriptomic analysis implied that the effects of R-HNK might be due to the inhibition of brain-derived neurotrophic factor (BDNF) signaling, which modulates the activity-regulated cytoskeleton-associated protein (Arc) expression to inhibit the synaptic distribution of AMPAR. R-HNK selectively boosted AMPAR currents without affecting NMDAR currents in lamina V pyramidal neurons in the PrL. This action further strengthened PrL-PAG neurotransmission to mediate pain relief. Upregulating Arc expression by BDNF infusion or forced overexpression abolished the effects of R-HNK on synaptic delivery of AMPAR and pain alleviation. In conclusion, R-HNK recalibrated the Bdnf/Arc/AMPAR axis in the PrL, which restored the connectivity between PrL and PAG and provided sustained alleviation of neuropathic pain.

Disclosures: T. Jin: None.

Poster

PSTR069: Non-Opioid Treatments for Persistent Pain

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR069.26/D4

Topic: D.01. Somatosensation – Pain and Itch

Support: 1133972 CONAHCYT
University of Guadalajara

Title: Evaluation of possible cannabinoid pharmacological treatment in acute osteoarthritis knee model by means of kinematic analysis and pain threshold

Authors: *F. GONZALEZ LUJAN[1], B. DE LA TORRE[1], R. CASTANEDA ARELLANO[2], C. TORO-CASTILLO[1], M. TREVINO VILLEGAS[3], I. G. AGUILAR GARCIA[4], L. P. OSUNA CARRASCO[1];
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Abstract: *Abstract*---- The proposed study proves the option to have a different treatment displayed on quantitative and qualitative parameters of kinematics and pain tests, by experiments with mice groups during walk and mobility analysis with kinematics parameters and pain sensation using Von Frey filaments in acute osteoarthritis knee (AOAK) model. This would allow us to have enough information to recommend or not recommend a new based treatment that can be compared to another successful treatment for osteoarthritis. The study focuses on evaluating a pharmacological treatment not previously used for the treatment of acute osteoarthritis in the knee based on the evaluation of indicators of kinematic movement, angular movement, and pain perception, where the latter is an important factor to consider, which has as main result both the limitation and the facilitation of the mobility of the segment or joint under study. The experimentation is based on working with a mouse model of acute knee osteoarthritis and the evaluation of increase or decrease of the condition by subjecting the subject to a pharmacological treatment, with this, data is obtained and analyzed by characterization of angular movement, kinematics movement of the segment of study and interpretation of pain sensation using Von Frey filament tests. The tentatively ideal drugs to be used for the study are different from those derived from analgesics and nonsteroidal anti-inflammatory drugs, as well as those derived from opiates, seeking to establish a new path for the treatment of symptoms of chronic pain, motor and articular joint difficulty, derived of diseases and degenerative conditions such as arthritis (García-Partida et al., 2021). *Clinical Relevance*---- Therefore, with this study we propose to analyze different compounds of opioids, steroids and non-steroidal anti-inflammatory drugs (NSAIDs) as cannabinoid components, thereby avoiding the pathology of dependence and kidney or hepatic damage in patients treated with any of these types of common treatments, and thus be able to determine its viability in a model in vivo in order to recommend its study in cases closer to a clinical model.

Disclosures: F. Gonzalez Lujan: 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.; Research Grant 1133972 CONAHCYT. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); University of Guadalajara. **B. De la torre:** 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.; SNI member level I of CONAHCYT. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); University of Guadalajara. **R. Castaneda Arellano:** 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.; SNI member level I of CONAHCYT. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); University of Guadalajara. **C. Toro-Castillo:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); University of Guadalajara. **M. Trevino Villegas:** 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.; SNI member level II of CONAHCYT. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); University of Guadalajara. **I.G. Aguilar Garcia:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); University of Guadalajara. **L.P. Osuna Carrasco:** 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.; SNI member level I of CONAHCYT. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); University of Guadalajara.

Poster

PSTR070: Active Vision in Gaze and Locomotion Control

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR070.01/D5

Topic: D.06. Vision

Support: NIH grant EY027361

Title: ON and OFF pathway function in human accommodative eye vergence

Authors: *U. MAHARJAN[1], H. RAHIMI NASRABADI[2], S. POUDEL[1], J. JIN[1], J. M. ALONSO[1];
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Abstract: The human eye is continuously adjusting its accommodation and vergence when exploring the visual environment. Any error in this accommodative system results in blurred vision, which significantly reduces contrast. Here, we investigate the role of ON and OFF visual pathways in generating the contrast signals needed to drive accommodative vergence in humans

with normal vision and myopia (near-sightedness). Eye vergence was measured with Tobii pro glasses 3 (50Hz, TP3Py software) in 24 human subjects (18 females and 6 males, 22-31 years old; 14 myopes with refractions of -0.75 to -9 diopters and eye axial lengths of 24.11 to 27.76 mm; 10 emmetropes with eye axial lengths of 22.53 to 24.23 mm). Light and dark square targets of different luminance (1.5^o/side, 10-800 cd/m^2, 8 contrasts, 160 trials) were presented on mid-grey background (400 cd/m^2) for 5 seconds using a high luminance monitor (FSI XM310K, 60 Hz, ~0-1000 cd/m^2). A tunable lens (Optotune, aperture 16 mm, ± 10 diopters) was used to optically blur the targets seen by one eye (-5 diopters for 2.5 seconds) while the other remained occluded. The optical blur in the open eye made the occluded eye to shift nasally as if the target was approaching the subject, and this shift was used to measure accommodative vergence. Our results demonstrate that the average accommodative vergence is nearly twice as large in myopes than emmetropes (myopes: 11.17^o ± 0.10^o vs emmetropes: 6.91^o ± 0.08^o, $p < 0.0001$, Wilcoxon tests and mean ± standard error reported in the entire abstract), but the vergence change increases with contrast in all subjects (6% vs. 100% change in vergence: 3.17^o ± 0.11^o vs. 4.95^o ± 0.09^o, $p < 0.0001$ in emmetropes; 4.41^o ± 0.13^o vs. 6.04^o ± 0.09^o, $p < 0.0001$ in myopes). We also find that, at low contrasts (3-13%), dark stimuli induce more change in accommodative vergence than light stimuli in both emmetropes and myopes (dark vs. light: 3.76^o ± 0.09^o vs. 3.05^o ± 0.08^o for emmetropes, $p < 0.0001$; 5.18^o ± 0.11^o vs. 4.04^o ± 0.10^o for myopes, $p < 0.0001$). However, at high contrasts (50-100%), the change is independent of stimulus polarity in emmetropes (light vs. dark: 5.05^o ± 0.09^o vs. 4.88^o ± 0.09^o, $p = 0.1895$), but dominated by dark stimuli in myopes (light vs. dark: 5.89^o ± 0.10^o vs. 6.06^o ± 0.10^o, $p = 0.0309$). The light-dark difference across all contrasts is also strongly OFF dominated in myopes but not emmetropes (-0.29^o ± 0.03^o for myopes vs. 0.03^o ± 0.03^o for emmetropes, $p < 0.00001$). We conclude that OFF pathways drive stronger accommodative vergence than ON pathways at low contrasts, but myopia increases OFF dominance at all contrasts, as expected from a myopia deficit in ON pathway function (Poudel et al., 2024).

Disclosures: U. Maharjan: None. **H. Rahimi Nasrabadi:** None. **S. Poudel:** None. **J. Jin:** None. **J.M. Alonso:** None.

Poster

PSTR070: Active Vision in Gaze and Locomotion Control

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR070.02/

Topic: D.06. Vision

Title: Orofacial behaviors, not eye movements, drive movement-related neural activity in mouse V1

Authors: *A. SYEDA[1], L. ZHONG[2], M. PACHITARIU[3], C. STRINGER[4];
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Abstract: Previous studies have found that the mouse primary visual cortex (V1) is correlated to various orofacial movements. However, recent work in primates suggests that monkey V1 is primarily modulated by eye movements, not orofacial movements (Talluri et al 2023). In mice, it remains unclear how much eye movements contribute to the modulation of neural responses in the presence or absence of visual input compared to other orofacial movements. To determine the contribution of eye movements to mouse V1 activity, we recorded the activity of thousands of V1 neurons using two-photon calcium imaging while presenting a visual stimulus or in darkness and monitoring eye movements and orofacial behaviors with a camera. During the recording sessions, mice made saccades around 20 times per minute. We excluded saccade time periods, which ranged from 45 ms to 0.5 s, and binned the remaining time periods by eye position, to divide the recording session into bins of timepoints with the same eye position. In each eye position bin, we fit a separate model that predicts neural activity from orofacial movements. These models performed almost as well as a single model trained from varied eye position locations. Additionally, we found that the eye movements were correlated to other orofacial movements, such as whisking and sniffing and thus may be indirectly correlated to neural activity. These results suggest that mouse orofacial movements drive a majority of the movement-related variability in mouse V1.

Disclosures: A. Syeda: None. **M. Pachitariu:** None. **C. Stringer:** None.

Poster

PSTR070: Active Vision in Gaze and Locomotion Control

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR070.03/D7

Topic: D.06. Vision

Support: NIH EY026924
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NIH EY014800
Research to Prevent Blindness

Title: Behavioral and neuronal characterization of perisaccadic mislocalization

Authors: *G. WENG[1,2], K. CLARK[2], B. NOUDOOST[2], N. NATEGH[2,3];
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Abstract: The brain processes and interprets visual stimuli projected onto the retina to generate a spatial perception of visual scenes, but how this spatial information is represented in neural activity remains unclear. To comprehend how neurons encode spatial information, it's vital to examine changes in neural activity concurrent with changes in visuospatial perception. Saccadic eye movements (saccades) are often accompanied by altered spatial perception, such as

perisaccadic mislocalization, where there's a bias in the perceived location of visual stimuli near the onset of a saccade. This study examines perisaccadic mislocalization in rhesus macaque monkeys through combined behavioral and physiological experiments. We aim to link perisaccadic modulations in extrastriate responses with their behavioral counterparts. We use array and single electrodes to simultaneously record neuronal activity in area V4 and the Frontal Eye Field (FEF) from sites with overlapping receptive fields. Monkeys perform a visually guided saccade task while their eye movements are monitored with a high-resolution eye-tracking system. In each trial, the monkey saccades from a fixation point to a peripheral saccade target. During fixation and saccade execution, a 50-ms visual probe stimulus is presented in one of 9 possible locations in a 3×3 grid placed around the V4 neuron's receptive field. When the probe disappears, the monkey makes another saccade to the perceived location of the stimulus. Mislocalization is measured as the deviation between the perceived location of stimuli presented around the first saccade to those presented during fixation. Our results show that the perceived locations of stimuli presented around the time of saccade execution are altered. We seek to link neural activity in V4 and FEF to localization behavior by examining the spiking activity of individual neurons and the local field potentials in these areas. We will quantify the capacity of these signals in decoding the perceived stimulus location in order to reveal the neural substrate underlying perisaccadic mislocalization, and the role of V4 and FEF neurons in the representation of location information.

Disclosures: G. Weng: None. **K. Clark:** None. **B. Noudoost:** None. **N. Nategh:** None.

Poster

PSTR070: Active Vision in Gaze and Locomotion Control

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR070.04/Web Only

Topic: D.06. Vision

Support: NIH EY026924
NIH NS113073
NIH EY031477
NIH EY014800
Research to Prevent Blindness

Title: A model-based decoding approach for linking perisaccadic sensitivity of extrastriate neurons to transsaccadic perceptual stability

Authors: *A. POURSADEGH[1], G. WENG[2], A. AKBARIAN[3], M. ZEKRI[1], B. NOUDOOST[4], N. NATEGH[5,6];
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Abstract: Three times a second, during saccadic eye movements (saccades), the retinal image changes abruptly, yet our perception of the visual world is continuous and stable, a phenomenon known as transsaccadic stability. Our visual system suppresses the motion signal induced during the eye movement, but the precise neural mechanism underlying transsaccadic integration between the presaccadic and postsaccadic scenes is unclear. This study combines electrophysiological and computational methods to investigate the link between visuospatial information representation in the spiking responses of neurons in the extrastriate cortex and the integrated readout of the visual scene from the perisaccadic sensitivity of visual neurons. To quantitatively characterize the dynamics of perisaccadic visual information encoding, we previously developed a dynamic variant of generalized linear models (GLMs) capable of capturing perisaccadic modulations of neuronal responses with high temporal precision at the level of individual neurons (Niknam et al., PLoS Comp Biol, 2019). Leveraging the decoding aspect of the model, we create an instantaneous readout of the visual scene and track its alterations across a saccade. We record spiking activity from area V4 and middle temporal (MT) area in macaque monkeys using 16-channel linear array electrodes while the animal performs a visually guided saccade task with spatiotemporal visual probe stimulation. By fitting our GLM-based model to the recorded spiking activity, we quantify the sensitivity of each neuron to each location across time relative to the saccade using the model's spatiotemporal kernels, representing the neuron's spatiotemporal receptive field. Using these spatiotemporal kernels obtained for ensembles of neurons, we develop a population-level decoder to predict statistically optimal stimulus location and delay at each point relative to a saccade. Employing this decoder, we construct a dynamic spatiotemporal map of the perceived visual space predicted by the model with high temporal precision and examine its correspondence to the dynamic spatiotemporal sensitivity map of the V4 and MT neuronal population captured by the model's kernels. This integrative experimental and computational approach provides a powerful means for understanding the neural correlates of transsaccadic integration in the extrastriate cortex.

Disclosures: A. Poursadegh: None. **G. Weng:** None. **A. Akbarian:** None. **M. Zekri:** None. **B. Noudoost:** None. **N. Nategh:** None.

Poster

PSTR070: Active Vision in Gaze and Locomotion Control

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR070.05/D8

Topic: D.06. Vision

Support: NIH Grant RF1NS127305
NIH Grant R01NS121919

Title: Active coding of visual input during gaze shifts in the primary visual cortex of freely moving mice

Authors: *J. SHIN[1], E. ABE[2,5], P. R. PARKER[6], D. MARTINS[7,8], E. LEONARD[3], S. SHARP[4], N. CASEY[1], C. M. NIELL[4];
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Abstract: Saccadic eye movements rapidly shift gaze, enabling the brain to gather visual information from various locations in the environment. Coordination of neural activity during saccades has been demonstrated in visual areas and the hippocampus of non-human primates. In rodents lacking a fovea, similar eye movements also have been identified, with recent findings showing coordinated neural dynamics in V1 initiated by gaze shifts. However, it remains unclear whether these responses encode visual information. By using a recently developed method to simultaneously measure visual input, eye position, head movements, and neural activity in freely moving mice, we examined how visual input is coded in V1 during gaze shifts. Mice (n=9) actively foraged in a rectangular arena with diverse visual stimuli, with a multi-shank silicone probe targeting V1. We previously estimated visual receptive fields of freely moving mice using an encoding model, and for this study, we further explored neural responses during gaze shifts to determine whether these coordinated temporal dynamics encode visual information and, if so, what aspects of the visual scene are represented. We first categorized gaze dynamics based on the coordination of eye and head movements into two types: gaze shifts, where eye and head movements moved in the same direction to rapidly sample new locations, and compensatory eye movements, where the eyes moved in the opposite direction of the head to stabilize the current field of view. At the single unit level in V1, visual receptive fields were preserved in the responses following gaze shifts and matched those computed from the head-fixed white noise stimuli. Furthermore, visual receptive fields were more precisely encoded during the gaze shifts than during the compensatory eye movements. Next, to elucidate the visual information represented in V1 at the population level, we trained a decoder using images from head-mounted cameras and neural activity from the recording sessions. Decoding results revealed a rapid representation of visual stimuli ahead of gaze direction, followed by fixation. Additionally, by examining the decoding weights, single units with earlier firing peaks processed low spatial frequencies, while later units processed higher spatial frequencies. In contrast, during compensatory eye movements, only the immediately preceding visual stimulus was represented. Taken together, our preliminary results suggest that visual information is actively encoded in V1 during the gaze shifts, and their coordinated neuronal activity implies a coarse-to-fine processing of newly sampled visual input from a short fixation period followed by each gaze shift.

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Poster

PSTR070: Active Vision in Gaze and Locomotion Control

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR070.06/D9

Topic: D.06. Vision

Title: Self-motion decoding from visual images synthetically explains anisotropic distribution of V1 orientation preferences in striped visual environment

Authors: *H. GOMI;
NTT Communication Sci. Labs, Kanagawa, Japan

Abstract: By visually acquiring information about the external world, human can interact with the environment in an efficient manner. Previous studies revealed that visual processing is developed in the postnatal period. For instance, in the primary visual cortex of kittens raised in a vertical stripes room, many cells maximally responded to stripe close to vertical [Blakemore and Cooper 1970], and restricted vision by goggles with stripes prevent normal development in the visual cortex [Hirsch and Spinelli 1971]. Meanwhile we have shown that, by decoding self-motion with an CNN (convolutional neural network) from first-person perspective views during daily actions, the CNN acquired a spatiotemporal frequency tuning of visual analysis similar to those of the quick manual following response induced by visual motion [Nakamura and Gomi 2023]. This implies that the self-motion estimation important for correcting reaching movements is acquired by interacting with environment. In this study, in order to further explore the acquisition of visual information processing for self-motion estimation, we performed CNN learning to decode self-motion using stripe images transformed with anisotropic image-low-pass-filter from the natural image sequences (30 scenarios), and investigated decoding performance and internal representation of the CNN. Decoding self-motion from the vertical striped image sequences exhibited high performance (r=0.98) in the direction of vertical axis rotation, whereas the performances in the other directions (especially in the three translations) were clearly degraded. Namely, body movements related to the vertical motion components could not be decoded well because of less information in the visual image sequences. In addition, over 90% of the CNN second layer kernels had orientation preference to the static grating pattern within ±45 degrees from the vertical direction. This is contrast to the result that the orientation preferences were isotopically distributed when normal images were used for learning. These changes in decoding performance and anisotropic distribution of kernel orientation preferences are similar to the behavioral deteriorations observed in kittens raised in striped rooms and the anisotropic distribution of orientation preferences of V1 neurons. The results would support an account that the brain function of decoding self-motion from visual information, which is required for dynamic interactions with environment, may be one of important factors causing abnormal visual development in striped visual environments.

Disclosures: H. Gomi: None.

Poster

PSTR070: Active Vision in Gaze and Locomotion Control

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR070.07/D10

Topic: D.06. Vision

Support: R21 EY033071

Title: Receptive fields in cat visual cortex during natural locomotion

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Abstract: Understanding how visual information is processed during natural behavior is a fundamental problem of neuroscience. Despite recent insights from research in alert head-fixed subjects, it remains largely unknown how visual processing is affected by active behavior: self-motion and active selection of visual targets for serving on-going behavior. We established a unique experimental paradigm of active vision in freely moving cats during natural locomotion. We tested a hypothesis that visual input and visual processing are shaped by the needs of on-going behavior, specifically, by different demands on accuracy of steps during locomotion. Cats either walked on a flat surface, which imposed no demands on the accuracy of steps, or stepped on elevated rungs of a horizontally placed ladder, which imposed high demand on the accuracy of steps. Using this robust and repetitive natural behavior we measured (i) visual input, (ii) neuronal activity, and (iii) behavioral output. To measure visual input, we took footage from a head-fixed camera, recorded movement of eyes using an eye-coil system with head-mounted magnetic field emitter (Rivers et al., 2014), and reconstructed gaze trajectory. Using video footage from the head-fixed camera and eye movement signals, we calculated visual input in retinotopic coordinates. As behavioral output, we measured parameters of cat's steps using a sensor attached to the right forepaw. We recorded activity of neurons in area 18 of the primary visual cortex, and used reverse correlation of spiking activity with retinotopic visual input to reconstruct receptive fields of neurons while the cat walked on a flat surface, stepped on rungs of the horizontal ladder, and, for comparison with prior data, while sitting with the head fixed and watching visual stimuli presented on a computer screen. We found that neuronal responses in visual cortex are stronger during walking along the horizontal ladder than on the flat surface. Respectively, receptive field profiles have higher peak, however, no difference in the receptive field area (measured at 50% of the peak) was found between two locomotion conditions. We discuss possible confounds due to difference in visual statistics between two walking environments, feasible controls, and possible implications of obtained results for understanding visual processing during natural visually-guided locomotion.

Disclosures: I.N. Beloozerova: None. **V. Serdyukov:** None. **M.A. Volgushev:** None.

Poster

PSTR070: Active Vision in Gaze and Locomotion Control

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR070.08/D11

Topic: D.06. Vision

Support: RF1NS121919

Title: Visually guided obstacle avoidance in freely moving mice

Authors: *M. SIDIKPRAMANA[1], C. M. NIELL[1], D. MARTINS[2];
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Abstract: Navigating through dynamic environments is a vital aspect of visual behavior. The integration of visual and self-motion cues is known to guide such locomotion, but the neural circuits that integrate these signals are poorly understood. Mice provide a powerful model system to study neural circuits of visual processing during navigation, but there is a lack of visually guided locomotor tasks as most visual physiology in mice is done while head-fixed. To address this we developed a novel ethological visuomotor task, based on a similar human paradigm, in which freely moving mice must avoid unexpected obstacles while traversing to a goal. Our initial analysis indicates that mice efficiently steer around an obstacle before tactile information can be sampled. This suggests that mice use vision in this task to estimate the location of obstacles. To further explore how mice utilize vision to steer around obstacles we compared the behavior of mice in this task in light and dark contexts. In the absence of visual information, mice spend more time closer to the obstacle and perform spatially inefficient trajectories when compared to performance in the light. When visual information is available, mice perform edge directed movements to steer around the obstacle beginning at a distance approximately at 10 cm. In the dark mice continue on their initial heading at the start of each trial, often resulting in obstacle collision. Subsequently we demonstrate that these edge directed movements are refined and become more stereotyped over experience and are dependent on the availability of visual information. This suggests mice are potentially integrating spatial memory with sensory information to execute stereotyped trajectories based on the estimated position of the obstacle. This task serves as a new paradigm to study naturalistic visual behavior in mice and a basis for future physiological experiments to determine how ethologically relevant visual information is encoded during natural behavior.

Disclosures: M. Sidikpramana: None. **C.M. Niell:** None. **D. Martins:** None.

Poster

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Program #/Poster #: PSTR070.09/D12

Topic: D.06. Vision

Support: NIH 1F30EY035930-01
SCGB 542999

Title: Effects of behavioral state on inter-areal communication in the mouse visual system

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Abstract: A central question in systems neuroscience is how brain states modulate sensory processing. Because sensory processing is accomplished by a distributed network of areas, how brain states modulate sensory processing might depend heavily on how they influence the relaying of sensory signals between brain areas. Various behavioral states, including locomotion, arousal, and face movements, have been shown to alter neuronal activity in the mouse visual system. However, how these states affect the relaying of signals between visual areas is poorly understood. We presented head-fixed, but otherwise freely behaving mice, with visual stimuli whilst recording simultaneously from retinotopically-aligned portions of the dLGN, V1 and LM using high density laminar probes. Consistent with prior work, we found modulation of single neuron activity in each area by multiple behavioral states. To understand how this modulation affects inter-areal signaling, we employed Group Factor Analysis (GFA), a dimensionality reduction method. GFA decomposes the measured population activity in each area into a linear combination of latent, population activity patterns. GFA revealed dimensions of population activity that were private to each area, other dimensions that were shared between each pairing of visual areas (pairwise patterns), as well as activity patterns shared between all recorded areas (termed global activity patterns). Global activity patterns explained more shared variance than within-area and pairwise activity patterns. To assess how behavioral state modulates inter-areal interactions, we projected population activity on each trial onto the different types of activity patterns and attempted to predict those projections using our measurements of locomotion, pupil diameter, and face movement. Models predicting fluctuations in global activity projections performed better than those predicting projections onto pairwise or local activity patterns. We also tested whether GFA models fit to trials involving one behavioral state generalized to data from another state. Models tested across behavioral conditions performed slightly less well than those tested on data from the same behavioral state. This performance loss appeared to involve differences in both inter-areal and within-area activity patterns across states. Our results suggest that behavioral states modulate both activity patterns within each area as well as those shared across areas.

Disclosures: E. Kim: None. **A. Kohn:** None.

Poster

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Topic: D.06. Vision

Support: U19NS118246

Title: Perceiving object motion and depth during self-motion: a macaque paradigm for studying causal inference

Authors: *V. LERNER, G. C. DEANGELIS;
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Abstract: How the brain transforms sensory information into internal representations and subsequently performs cognitive functions is a key question for understanding brain function and reducing cognition to its mechanisms. We focus on the process of transforming retinal motion and binocular disparity into perceived depth and motion of objects. When the observer is stationary and an object's image moves on the retina, it is clear to the observer that the object is moving in the world. However, when the observer is moving, retinal motion can be attributed either to self-motion or object motion, and retinal motion is not sufficient to decide whether the object is moving or not in the world. To make such a decision, an observer needs additional information about depth and self-motion. The same logic can be applied to decisions about object depth, which can depend on object motion and self-motion. Preliminary results from human psychophysical experiments, combined with Bayesian modeling, indicate that causal inference is a likely mechanism underlying joint inference of object motion and depth. We train macaque monkeys to discriminate depth sign (nearer or farther than the fixation point) and motion (stationary or moving in the world) of an object during self-motion in a virtual environment, using a four-choice task (moving+near, moving+far, stationary+near, stationary+far). We simulate passive self-motion by presenting optic flow in ground and ceiling planes. The animals successfully perform the dual-report task and, importantly, they report motion of the object in the world rather than the motion of its image on the retina. This behavior establishes a framework to study neural mechanisms underlying joint inference of object motion and depth during self-motion. Furthermore, we develop a system for using long Neuropixels probes to access large neuronal populations in three brain areas known for their contributions to perception of motion and depth: middle temporal area (MT), medial superior temporal cortex (MST), and parietal area 7a. This will allow us to assess whether neural representations of depth and self-motion are modulated by the animal's belief about object motion. We will test the prediction that causal inference, rather than feedforward gating by flow parsing, is the neural mechanism underlying joint inference of depth and object motion in complex dynamic environments.

Disclosures: V. Lerner: None. **G.C. DeAngelis:** None.

Poster

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Topic: D.06. Vision

Support: ANR-21-CE37-0023

Title: A glimpse into self-motion : cortical specializations for optic flow processing across primate brain

Authors: *S. MARCHAND, M. BRACONNIER, N. VAYSSIERE, B. R. COTTEREAU, A. SÉVERAC CAUQUIL, J.-B. DURAND;
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Abstract: Controlling our motion in the environment requires the collaborative work of several sensory modalities to recover parameters such as the direction and speed of self-motion. In addition to muscular proprioceptive and vestibular modalities, the visual system plays a key role in this mechanism, through the optic flow generated by our self-motion. Previous studies in humans and monkeys revealed a large cortical network involved in the processing of optic flow. Recently, we have explored further the specialization of these regions by providing humans with vestibular and optic flow stimuli characterizing distinct directions of self-motion during MRI acquisition. Our results revealed that areas VIP and V6 process more specifically self-motion signals along the anterior-posterior axis, with V6 being even more tuned for the forward direction.With a view to determine the relevance of the macaque monkey, an arboreal and quadrupedal species, as a model for studying the cortical control of self-motion and spatial orientation in our terrestrial and bipedal human species, we now wish to elucidate whether the areas involved in processing self-motion signals in macaques show similar preferences for self-motion directions specified visually through optic flow patterns.Three female rhesus macaques are included in this study. They were exposed to visual stimuli consisting of optic flow patterns of moving random dots mimicking forward, backward, left-translational or right-translational self-motion, as well as a control condition with brownian motion of the random dots pattern.Results for the first macaque individuals indicate that the activation maps between the 4 optic flow and the control conditions highlight a network consistent with previous reports, including notably the MST, VIP and FEF regions. Interestingly, the contrast between the forward and backward optic flow conditions reveals the prominent forward preference of area V6, among other areas. These results will be strengthened by ongoing acquisitions in the two remaining macaque individuals and a parallel study on humans will assess the relevance of the monkey model. Given that primates use forward movement most naturally, it is likely that this specialization has an ecological explanation. At the same time, by highlighting a new functional homology with humans, this study would confirm the relevance of the macaque monkey model for studying the cortical regions involved in the control and perception of self-motion.

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Poster

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Support: NSF Grant 2309589

Title: Optokinetic response maintained for long durations in Zebrafish larvae through direction switching of rotating visual stimulation

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Abstract: The optokinetic response (OKR) is a gaze stabilization reflex for environmental motion and has been studied in Zebrafish larvae (Danio Rerio) extensively for behavioral screening and visual acuity. However, minor work has been done to study the relationship of sustained duration OKR and visual attention. We developed a system that elicits OKR in Zebrafish larvae for long duration trials to elucidate visual attention patterns. Elicitation of OKR is done via displaying an animation of rotating black and white arc gratings under the larva's ventral side through an LCD screen. Simultaneously, the system tracks the larva's eye movements through a microscope camera which is processed through software utilizing the open computer vision (OpenCV) library. Our system keeps a larva's body constrained via an agarose mold holder while allowing eye rotation and vision of the stimuli. Preliminary trials displayed that Zebrafish larvae presenting positive OKR adapt to rotational visual stimuli of a constant direction and speed over time with reduced OKR gain. Furthermore, OKR gain was found to be restored to a certain degree after this adaptation through directional switching of the visual stimuli. Additional trials confirmed this effect by including dynamic direction switching of the rotating visual stimuli at constant speed and displayed a maintained elicitation of positive OKR for durations >30min in 5dpf+ wild type larvae. This work explores a novel method for sustained duration OKR in Zebrafish larvae and its potential for new studies in attention and adaptation.

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Poster

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Title: Neural dynamics of gaze shift responses in mouse superior colliculus

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Abstract: Vision is an active process that involves sampling of the visual scene, and exploring the environment through eye, head, and body movements. Our lab has implemented methods to

study the impact of gaze shifts on visual processing in primary visual cortex (V1) and superior colliculus (SC) in freely moving mice, using chronically implanted high density electrodes combined with head-mounted cameras to measure both eye movements and the visual scene from the animal's point of view. Recently we examined how V1 visual responses are modulated by head/eye movements, demonstrating a dynamic temporal sequence following gaze shifts that is driven by the onset of new visual input. Here we extend these studies to explore gaze shift response dynamics in superior colliculus. We find that neurons in superficial SC (sSC) have two primary response types: a rapid positive response or more sustained negative response. Additionally, sSC gaze shift responsive cells are visually dependent and have temporal frequency preferences that are consistent with coarse-to-fine visual processing. Our results show that sSC neurons have distinct gaze shift dynamics as compared to V1 but are similarly visually responsive and tuned for spatial frequency. On the other hand, recordings in deep SC (dSC) reveal responses that are tuned to direction of the gaze shift and persist in the dark, consistent with motor signals. These initial results provide insight into how neurons across mouse SC encode gaze shift information during free movement.

Disclosures: S.L. Sharp: None. **J. Shin:** None. **D.M. Martins:** None. **C.M. Niell:** None.

Poster

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Title: Effects of a psychedelic seroton-2a receptor agonist on visual response dynamics following gaze shifting eye movements in freely moving mice

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Abstract: Psychedelic compounds act upon the serotonergic pathway to generate altered states of consciousness and profound perceptual disturbances, such as visual hallucinations. While psychedelics have recently gained attention for their cognitive and therapeutic effects, how these compounds alter sensory processing to generate altered visual perception is not as well characterized. Previously, we investigated the effects of the psychedelic serotonin-2A receptor agonist DOI (2,5-dimethoxy-4-iodoamphetamine) on visual responses in head-fixed mice and found that DOI significantly and specifically attenuated the early, transient portion of visual responses in the mouse visual cortex. In separate studies examining the neural basis of active vision, we found that after mice shift their gaze during free movement, there is a ripple of visual

activity throughout the visual cortex which carries patterned information about the visual scene. The early portion of this response carries coarse, low spatial frequency, information about the visual scene while the late portion of this response carries finer, high spatial frequency, information. Collectively, these findings suggest that psychedelics, like DOI, may disrupt the coarse-to-fine visual processing that occurs during free movement following gaze shifts. Here we combined head and eye movement measurements with neural recordings from the visual cortex of freely moving mice before and after administration of DOI to investigate whether psychedelics alter the coarse-to-fine processing of visual inputs. Our initial results suggest that DOI attenuates visual responses during free movement and disrupts the coarse-to-fine temporal dynamics that occurs following gaze shifts. Interestingly these neurophysiological effects occur despite DOI simultaneously increasing locomotor activity as well as the number of gaze shifts. These preliminary findings suggest psychedelics may alter the temporal pattern of visual processing that occurs during natural behavior leading to altered perception including visual hallucinations.

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Poster

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Topic: H.09. Spatial Navigation

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Title: A role for the mouse nucleus prepositus hypoglossi in relaying eye movement information during gaze

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Abstract: Animals rely on visual and nonvisual cues to form a spatial representation of their environment, essential for successful navigation. Monitoring spatial cues allows for rapid updating of an animal's orientation by estimating the linear and angular displacement of the head. Head direction (HD) cells are one type of spatially selective cell that fire as a function of the animal's directional heading. The nucleus prepositus hypoglossi (NPH), located within the brainstem, is said to relay vestibular information in the form of angular head velocity to the head direction (HD) network, a ring-attractor network that has coordinated firing based on the direction of the head-in-space. However, the NPH is a known oculomotor integrator essential for voluntary (saccades) and involuntary (reflexive) eye movements. This has been established across various species including primates (McFarland & Fuchs, 1992, Cullen et al. 1993).

Though seminal work on HD network activity has been performed in rodents, it remains unknown if NPH activity in rodents is a component of coordinated eye movements, thereby relaying gaze information to the HD network. To address this question, we recorded the activity from the NPH while tracking head and eye position during behavioral paradigms that elicited either combined eye-head motion or movement of the eye alone. A small camera system tracked horizontal pupil position and a potentiometer measured head rotation. Adult mice (n=5) underwent reflexive evocations of eye movement while head-fixed, undergoing whole body rotations to elicit activity of the vestibulo-ocular reflex (VOR), and whole world rotations while stationary to elicit optokinetic nystagmus (OKN). These assessments were performed while recording from NPH using Neuropixel probes. Results identify a dynamic eye movement-based model that corelates with neuronal responses in the absence of head motion. We expand on these findings by recording from mouse NPH (n=3) while performing an active head movement task that requires the mouse to voluntarily orient between two waterspouts for reward. We use the real-time feedback of our experimental setup along with Neuropixel recordings to establish how the head and eye components of active gaze redirection are successfully encoded and integrated. Our results provide evidence that mouse NPH encodes eye-related movements, similar to its function in primates, and suggests that eye motion information is relayed to the HD network in mice. Future work will expand on our understanding of the head-eye motion relay to the head direction network in mice, furthering our knowledge of gaze interpretation in the rodent brain.

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Poster

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Title: Functional connectivity of oculomotor cortical network supports implicit motor sequence learning

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Abstract: Background. Given the visual nature of learning new motor learning tasks ("look-and-reach"), we hypothesized that brain regions supporting oculomotor control are implicated in motor learning. However, it is currently not known if, or how, oculomotor control is implicated in learning of novel movement sequences. Thus, the current study examined whether changes in

arm movement behaviour resulting from implicit motor sequence learning were related to brain resting-state functional connectivity (rsFC) of oculomotor and oculomotor-motor learning regions. **Methods.** Twenty participants (14 female, mean age=28+/-5) underwent structural and functional (rest and task) MRI scans before and after practice of an implicit motor sequence learning task, which was performed on a KINARM robot. Practice occurred over 3 consecutive days (640 trials, 15 min per day). A 24-hour retention test assessed learning. Magnitude of learning was defined as the difference in reaction time (RT) between reaches for sequence and random trials; more negative values represent faster RT of the repeated sequence and demonstrates more change associated with learning the repeated sequence. Oculomotor control [frontal eye fields (FEF), parietal eye fields (PEF), supplementary eye fields (SEF)] regions of interest (ROI) derived from group-level task functional MRI results were used in a rsFC analysis. Mean timeseries from each ROI for each rest functional MRI scan (pre and post) were extracted. The analyses also included two brain regions implicated in implicit motor sequence learning [supplementary motor area (SMA) and striatum]. Timeseries for ROI-ROI pairs were correlated to derive rsFC correlation coefficients, for each participant and time point. Brain-behaviour, Pearson's correlations were performed to examine the relationship between rsFC (baseline, post minus pre change) and magnitude of learning. **Results.** Higher baseline rsFC of frontal-parietal oculomotor regions (right FEF - right PEF: r = -0.44, p = 0.048; left FEF - left PEF: r = -0.46, p = 0.037) and decreased rsFC change of oculomotor-motor learning regions (right FEF - right Striatum: r = 0.51, p = 0.021) correlated with greater behavioural change associated with learning. **Conclusions.** Implicit motor sequence learning modulates rsFC of oculomotor cortical network and oculomotor-motor learning brain regions. Uniquely, baseline rsFC from the oculomotor network could index capacity for implicit motor sequence learning.

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Poster

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Title: The medial temporal lobe guides eye movements: causal evidence revealed through human deep brain stimulation

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Abstract: Classic models of visual search do not consider the medial temporal lobe (MTL) as central to oculomotor guidance. Although a growing literature has implicated the MTL in visual processing, there is less evidence for its causal role in guiding eye movements. Here, we report a re-analysis of behavioral and eye tracking data from 13 epilepsy patients, who received MTL deep brain stimulation (DBS) while performing a naturalistic visual search task during episodic memory encoding (Katz et al., 2024). In the visual search task, participants looked for four cartoon targets, which were imbedded within images of indoor and outdoor scenes. Targets were placed in camouflaged locations, using the structural similarity index (SSIM) to encourage active exploration. On a given trial, participants viewed each scene image for 4 seconds while their gaze was recorded, after which they indicated the number of targets they found. Concurrently, participants received closed-loop DBS (10 ms burst: five 0.1ms biphasic pulses separated by 2ms) that was time-locked to either the peak or trough of the MTL saccade initiation ERP. To evaluate the effect of stimulation timing on visual search, performance was compared to randomly timed stimulation and sham stimulation conditions. Preliminary analyses of sham corrected behavioral responses revealed effects of stimulation time and location: posterior MTL stimulation led to more targets found than anterior MTL stimulation, and later post-saccadic stimulation times led to fewer targets being found. To evaluate the influence of MTL stimulation on oculomotor guidance, we analyzed the number of saccades for which a target was within the range of central vision (fovea and parafovea; here, ~3 degrees of visual angle). Stimulating at the peak of the MTL ERP lead to an increase in the number of saccades that placed targets within central vision. For participants whose stimulation timing was customized, posterior MTL stimulation led or more saccades that subsequently returned to targets (within central vision). These findings may suggest that MTL processing enables efficient visual search by improving memory for prior gaze locations. Lastly, the number of these return eye movements that placed targets within central vision predicted the reported number of targets found, suggesting a breadth-first visual search strategy. Collectively, our visual search findings are consistent with the purported role of posterior hippocampus in spatial processing and provide causal evidence for the MTL in the cognitive control of oculomotor behaviour.

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Poster

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Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq)

Title: Effects of cue probability on presaccadic perceptual enhancement

Authors: E. CARLOS-LIMA[1], M. RODRIGUES GUIMARÃES[1], L. Z. BORTOLUZZI[1], ***G. ROHENKOHL**[1,2,3];
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Abstract: Visual perception is enhanced at the locations of planned saccades prior to execution of the eye movements. This perceptual facilitation strongly resembles the classical findings of covert attention orienting studies. One well-known factor that modulates covert orienting is the probability associated with a central spatial cue to accurately indicate a target location - also known as cue validity. In this study, we investigated if the probability of target occurrence at the saccade location modulates presaccadic perceptual enhancement. A total of 19 participants performed a visual orientation discrimination task in which a central cue indicated the location of a target stimulus with four different probabilities (88, 40, 22, and 10%) in a blocked design. These were presented either in presaccadic or covert (endogenous) attention sessions. In the presaccadic sessions, the participants were instructed to make a saccade to the location indicated by the cue, and a visual target was presented before saccade onset. In the covert attention sessions, participants were required to maintain fixation throughout the whole trial. In both conditions, participants were presented with an array of four stimuli - one in each quadrant of the visual field - that contained one visual target (clockwise or counterclockwise tilted Gabors), and three other distractors (vertical Gabors) presented in the remaining quadrants. A response cue was used to indicate the target location after the array offset. Participants were required to report the orientation of the stimulus presented at the location indicated by the response cue. Saccades reaction times and accuracy values were equivalent across the four different probability conditions. As expected, our results showed that during covert orienting, attentional modulation increased linearly with cue probability, and target discrimination was only higher at the cued location associated with higher probabilities (88 and 40%). In the presaccadic condition, however, target discrimination was improved in all probability conditions, even when the probability of a target occurring at the saccade location was very low (i.e. 10%). Interestingly, the magnitude of the presaccadic perceptual enhancement also seemed to increase linearly with spatial probability. Together, our findings suggest that presaccadic perceptual enhancement might rely on two distinct processes. One modulated by top-down attentional goals, likely voluntary, and similar to covert attention orienting. The other seems automatic, always coupled with the saccade goal, and is possibly associated with oculomotor programming.

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Poster

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P30EY000331

Title: Utilizing an emerging visual behavioral assay to assess visual function in advanced retinal degeneration

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Abstract: Rodent cricket hunting has recently been developed as an assay to understand how mice visually track and pursue objects in their environment. Cricket hunting has the advantage of being a relatively high throughput assay that requires the dynamic utilization of visual signals and necessitates minimal training. These features make cricket hunting a potentially useful assay for tracking the behavioral consequences of retinal degeneration, rescue, and manipulations to the retinal circuit's development and function. Here we examine the utility of cricket hunting in assaying retinal degeneration and present a semi-automated workflow for data acquisition and analysis. We developed a cricket hunting arena that video records mice and crickets from 5 perspectives using a single camera and 4 mirrors. The system allows for precise control of the ambient light level and tracking of animals in two or three dimensions. We also showcase the development of a habituation protocol, a processing pipeline for markerless tracking of cricket and mouse body parts, and a custom algorithm to extract potential behavioral features of interest (FOI). These FOIs include vectored approaches (VAs: times when the mouse orients its gaze towards and rapidly approaches the cricket) and extended immobilizations (EIs: times when the mouse captures and holds the cricket for an extended period of time). We also developed a graphical user interface that allows for the efficient, manual classification of FOIs. We use this system to track progressive vision loss in a mouse model of retinitis pigmentosa (Pde6b, rd10), a retinal degenerative condition characterized by the death of rod photoreceptors followed by cone photoreceptors. We assayed control (C57BL/6J) (n=16) and rd10 mice (n=16) through the pipeline and measured hunting performance under cone isolating (photopic) conditions. C57BL/6J mice were also tested in darkness to provide a comparison for blind mice. While differences in median performance, consistency, and approach behavior arise early, we find that performance between the two groups is strikingly similar well into advanced degeneration. Eventually, rd10 performance was indistinguishable from C57BL6J performance in total darkness. These results indicate that cricket hunting is a useful task for behaviorally assaying the consequences of retinal degeneration and rescue.

Disclosures: A.M. Tarakji: A. Employment/Salary (full or part-time):; UCLA David Geffen School of Medicine. **S. Proctor:** A. Employment/Salary (full or part-time):; UCLA David Geffen School of Medicine. **R. Joshi:** None. **Z. Djenidi:** None. **P. Okani:** None. **C. Tran:** None. **B. Cruz:** A. Employment/Salary (full or part-time):; UCLA David Geffen School of Medicine. **M. Scalabrino:** A. Employment/Salary (full or part-time):; Medical College of Wisconsin. **T. Dunn:** A. Employment/Salary (full or part-time):; Duke University. **M.R.**

Tadross: A. Employment/Salary (full or part-time):; Duke University. **G.D. Field:** A. Employment/Salary (full or part-time):; UCLA David Geffen School of Medicine.

Poster

PSTR070: Active Vision in Gaze and Locomotion Control

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR070.20/D23

Topic: E.04. Voluntary Movements

Support: NIH U01NS126055
DoD Vannevar Bush Faculty Fellowship
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Title: Robotic two-photon imaging and optogenetic manipulations of neural activity across multiple brain regions of mice performing a visually guided motor task

Authors: *Y. SHIKANO[1], T. H. KIM[1,2], Y. ZHANG[1,2], O. P. JAIDAR[1], J. J. LI[1], M. J. SCHNITZER[2,3];
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Abstract: Goal-directed, complex motor behaviors involve coordinated neural activity patterns across the brain's motor areas, each of which may support one or more functional capacities, such as action selection, movement preparation, or kinematic control. To date, however, it has often been challenging to monitor and manipulate the dynamics of identified neuron-types in multiple brain areas concurrently, owing to a lack of suitable technologies. To address this challenge, we recently developed a microscopy platform, termed the Octopus microscope, that has multiple robotically controlled optical arms, each with a miniaturized objective lens for two-photon imaging over a 400-μm-wide field-of-view. Here, we present an updated Octopus microscope that allows concurrent two-photon Ca^{2+} imaging and widefield optogenetic manipulations of neural activity in each robotic arm. Using multiple robotic arms, we can now examine how optogenetic manipulations in one or more brain areas impacts animal behavior and neural dynamics across all the brain areas under observation. With this enhanced version of the Octopus, we are investigating how different motor areas of the brain contribute to complex movements. These studies also use a novel chronic imaging preparation for mice that affords optical access to the motor cortex, dorsolateral striatum, cerebellar cortex and retrosplenial cortex—all in an individual mouse. We are examining the role of each brain area as mice perform a visually guided motor task[1], in which mice control a cursor on a video monitor by turning a physical steering wheel. On each trial, the cursor appears either on the left or right side of the monitor; to receive a reward, the mouse steers the cursor to the center of the monitor. This task design helps us to distinguish signals related to action selection (*i.e.*, leftward *vs.* rightward cursor displacements) from those related to kinematics (*e.g.*, forepaw movements to steer the wheel). During optogenetic inactivation of neurons in motor cortex or striatum, mice made

kinematically normal paw movements but had impaired task performance owing to errors in action selection. By comparing optogenetic manipulations in the brain's left versus right hemispheres, during and outside the visuomotor task, we found that neural activity in dorsolateral striatum seems more consistently related to action selection than that in motor cortex. In ongoing experiments, we are studying how optogenetic manipulations of cerebellar or retrosplenial activity may affect motor behavior, and how multi-area neural Ca^{2+} dynamics are affected by the regional activity manipulations.
[1] Burgess, *et al.* Cell Rep. (2017).

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Poster

PSTR070: Active Vision in Gaze and Locomotion Control

Location: MCP Hall A

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Program #/Poster #: PSTR070.21/D24

Topic: E.04. Voluntary Movements

Support: NS094754

Title: An effector-independent map of target location in the superior colliculus

Authors: *K. BAKHURIN[1], G. LEE[2], M. ROSHCHINA[3], B. LU[1], H. H. YIN[3];
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Abstract: Freely moving animals must coordinate not only the head, but a variety of other body parts to successfully orient to targets in egocentric space. Furthermore, certain conditions may require the prioritization of one effector over the other to accomplish the same goal. The superior colliculus is known to play a critical role in orienting numerous parts of the body with respect to points in space, but the circuit mechanisms that allow the SC to organize and select from a variety of effectors to obtain the same spatial target are not well understood. We used optogenetic stimulation to map the functional contributions of VGlut2+ projection neurons in the intermediate layer of the SC in VGlut2-Cre mice. We used high resolution video analysis of freely moving mice receiving unilateral stimulation of the SC and characterized the relative movements of the head, torso, and limbs during orienting movements. Stimulation elicited three distinct contraversive targeting behaviors: forward-oriented movement of the forelimbs and neck, a redirection of only the head to points near the body, and large circling movements of the posterior parts of the body to orient to the space behind the animal. By varying the location of stimulation, we revealed a topographic organization of spatial targeting behaviors: Forward-orienting movements were located in anterior SC, peripersonal targeting movements were evoked in the anterolateral region of the SC, and large movements orienting to the space behind the body was evoked in the posterior SC. Whereas freely moving mice moved their head, body,

and limbs, head-restrained mice receiving unilateral stimulation in the anterolateral regions of this map produced robust contraversive licking. Within the same animal, the angular deviation of licking while restrained was correlated with turning angle while freely moving. To better understand the relationship between head movements and licking, we also measured force exertion in head-fixed mice. Force exertion during stimulation was contraversive and the direction of this vector was consistent with their orienting movements in the open field. Licking evoked by SC stimulation occurred after force initiation and only began once animals' force exertion began to decelerate. Together these results show that the SC contains a representation of egocentric space rather than specific effectors. It can flexibly recruit a variety of effectors to target distinct points in space.

Disclosures: K. Bakhurin: None. **G. Lee:** None. **M. Roshchina:** None. **B. Lu:** None. **H.H. Yin:** None.

Poster

PSTR070: Active Vision in Gaze and Locomotion Control

Location: MCP Hall A

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Program #/Poster #: PSTR070.22/D25

Topic: E.04. Voluntary Movements

Support: NIH U19 NS107466

Title: Active sensing through neuronal coordination of head, vibrissa, eye, and tongue movements

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Abstract: Across the animal kingdom, dynamic movements of sensory organs enable different creatures to actively explore their environment and gather sensory information, a phenomenon referred to as active sensing. For instance, rats employ coordinated movements of their vibrissae, head, eyes, and snout to collect information. In terms of vision, swift repositioning of the eyes is followed by synchronized movements of the head towards visual targets. Likewise, in the vibrissa touch system, movement of the vibrissae coordinated with head and body movements, facilitates tactile exploration of nearby objects.
To understand how the nervous system orchestrates orofacial coordination in active sensing, we developed a finely-controlled behavioral apparatus in which rats employed coordinated movements of their head and vibrissae to locate a reward delivery spout and orient toward the spout. This transitions into the use of the tongue toward the end of movements to ascertain the location of the reward delivery tube and acquire the reward. Toward this goal, the animal produces precise head, eye, and vibrissa movement that is highly reproducible within and between animals. Remarkably, the trajectory and timing of head and vibrissa movements were

specific to the spatial location of the reward spout.
To investigate the neural circuitry that underlies coordinated orofacial movements, we targeted deep layers of the superior colliculus. Unilateral inactivation of the superior colliculus resulted in a deficit in motor coordination across the head, vibrissa, and tongue. Animals exhibited a predominant orientation bias towards the ipsilateral side of the inactivation and displayed a steering bias for both contralateral and ipsilateral orientation. Moreover, temporal synchrony between vibrissae on each side of the snout and head was disrupted, causing the animals to miss the target.
Multi-site electrophysiological measurements are currently underway to capture the activity of a large population of neurons in the deep layers of the superior colliculus. The resultant data should lead to a model in which midbrain and medullary nuclei coordinate their output to orchestrate the timing of head, vibrissa, eye, and tongue movements in active sensing.

Disclosures: A. Fassihi: None. **J. Duckworth:** None. **D. Kleinfeld:** None.

Poster

PSTR071: Sensorimotor Transformation: Neuroprocessing

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR071.01/D26

Topic: D.07. Visual Sensory-Motor Processing

Support: STI2030-Major Projects (2021ZD0203700/2021ZD0203703)
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Title: Distinct roles of pv- and foxp2-expressing external globus pallidus neurons in perceptual decision behavior

Authors: *X. PU[1,2], J. REN[1,2], L. DECHEN[1], H. YAO[1];
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Abstract: *Rationale and objective*: The external globus pallidus (GPe), a hub nucleus connecting with the direct, indirect, and hyper-direct pathways in the basal ganglia (BG), plays an important role in both motor control and cognitive function. GPe neurons exhibit heterogeneity in projection patterns, molecular markers, and electrophysiological properties. Specifically, PV-expressing GPe neurons project to the thalamus and downstream targets of the BG, while FoxP2-expressing GPe neurons project to the striatum. Here we investigate the roles of PV and FoxP2 GPe neurons in processing sensorimotor signals during perceptual decision behavior. *Methods:* PV-Cre and FoxP2-Cre mice (2-6 months old) were used in the study. To manipulate neuronal activity, we injected AAV-DIO-NpHR-EYFP (or AAV-FLEX-EGFP as a control) in GPe. For optogenetic tagging, we injected AAV-DIO-ChrimsonR-mCherry in GPe. Task-related signals of GPe neurons were analyzed using a generalized linear model (GLM) to fit the responses. *Results*:

Inactivating PV GPe neurons impaired behavioral performance by increasing the false alarm (FA) rate (NpHR vs control ΔFA rate: $p = 1.75\times10^{-4}$, n = 9 vs 7 mice, Wilcoxon rank sum test), and the effect was not attributed to a direct influence on licking movement. By contrast, inactivating FoxP2 GPe neurons did not affect behavioral performance. We next recorded from GPe, using optogenetic tagging to identify PV and FoxP2 neurons. Based on the GLM coefficients, GPe neurons were categorized into two clusters, with cluster one displaying stronger stimulus- and outcome-related activity and cluster two exhibiting stronger lick-related activity. Compared to FoxP2 neurons (n = 30), PV neurons (n = 47) showed a higher proportion in cluster one and a lower proportion in cluster two. Furthermore, recording from the substantia nigra pars reticulata (SNr) revealed that inactivating PV GPe neurons induced changes in the stimulus- and outcome-related signals of SNr neurons. *Discussion*: These results demonstrate the distinct roles of PV and FoxP2 GPe neurons in perceptual decision behavior and the encoding of sensorimotor signals. Further experiments will explore the whole-brain inputs to PV and FoxP2 GPe neurons.

Keywords: external globus pallidus; basal ganglia; sensorimotor signals; mouse

Disclosures: X. Pu: None. **J. Ren:** None. **L. Dechen:** None. **H. Yao:** None.

Poster

PSTR071: Sensorimotor Transformation: Neuroprocessing

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR071.02/D27

Topic: D.07. Visual Sensory-Motor Processing

Title: Sensorimotor synchronization accuracy during treadmill walking with rhythmic auditory stimulation (RAS)

Authors: *H. KIM;
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Abstract: Synchronizing walking with an external rhythm seems effortless yet remarkable. Humans exhibit an innate ability to synchronize movement with auditory cues across various activities such as music, dancing, speaking, and sports. The locomotor system for walking integrates central and peripheral inputs from multiple brain regions and sensory modalities, including the cerebellum, motor cortex, basal ganglia, proprioceptors, and visual and vestibular sensors. Neurophysiological studies have demonstrated biomechanical and neuromuscular adjustments during movement, revealing the interaction between auditory and motor systems through entrainment. However, the neural mechanisms underlying sensorimotor synchronization during treadmill walking remain incompletely understood. This study aimed to investigate the temporal accuracy of treadmill walking associated with auditory-motor synchronization. We hypothesized that non-preferred speeds or rhythmic auditory stimulation (RAS) conditions would require an attentional demand, potentially disrupting the spatial and temporal integration. Forty participants (20 healthy young adults and 20 typically developing children) were recruited. After

the baseline trial of preferred RAS at the preferred speed, participants were randomly assigned to either auditory or motor manipulation conditions: slow and fast speed conditions, and slow and fast RAS conditions. Kinematic data were recorded using a VICON motion capture system. The error percentage in temporal accuracy was calculated by difference between calculated cadence and expected cadence. A series of two-way mixed ANOVA with repeated measures (2 Group * 3 Condition) was conducted for statistical analysis. No significant group effect was observed. Error percentages were lowest at slower speeds and RAS frequencies and increased with increasing speed ($F_{2, 76} = 47.83$, $p < .001$) and RAS frequency ($F_{2, 74} = 90.33$, $p < .001$) for both children and adults. Post hoc analysis with Bonferroni adjustment revealed significant differences between every condition ($p < .001$), regardless of treadmill speed and RAS frequency. Consistent with previous research, participants were most inaccurate at the fast speed and fast RAS frequency, highlighting the challenge posed by diverse constraints. Future studies focusing on temporal accuracy could provide the maximized benefits of sensorimotor synchronization by identifying optimal training conditions, particularly beneficial for clinical populations with gait impairments. Such investigations offer valuable insights into the mechanisms by which the locomotor control system sustains temporal accuracy.

Disclosures: H. Kim: A. Employment/Salary (full or part-time):; University of Wisconsin-La Crosse.

Poster

PSTR071: Sensorimotor Transformation: Neuroprocessing

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR071.03/D28

Topic: D.07. Visual Sensory-Motor Processing

Support: Canadian Institutes for Health Research (CIHR)
Canada First Research Excellence Fund (CFREF)

Title: Regular- and fast-spiking frontal eye field neurons provide complementary visuomotor codes for gaze control

Authors: *S. SEO[1], V. BHARMAURIA[2], X. YAN[1], H. WANG[1], J. CRAWFORD[1];
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Abstract: In neural circuits, various cell types make different contributions to perception, cognition, and behaviours. However, it is not clear how regular-spiking (RS - linked to pyramidal neurons) and fast-spiking (FS - linked to inhibitory neurons) cells differentially contribute to short-term spatial memory and transformations in motor systems. To answer this question, in a memory-guided saccade task, we recorded frontal eye field (FEF) neural activity from head-unrestrained monkeys' shifted gaze (G, final gaze endpoint) toward remembered visual targets (T). We then analyzed the activity in relation to target onset, gaze onset, and in

between these epochs. This task also included a visual landmark that was surreptitiously shifted during the memory delay. Previously, we showed that FEF implements a progressive T-G transformation either with (Bharmauria et al. 2020) or without (Sajad et al. 2015) landmarks. Here, we dissociated FEF neurons into 62 RS and 51 FS units, and the plotted the progression of their response fields through time. Fitting these data against spatial codes along a 10-step T-G continuum, we found that: (1) RS cells' visual response fields primarily coded T whereas the motor response fields showed a bimodal distribution for T and G. On the other hand, FS cells' visual and motor response fields showed bimodal coding for T and G. (2) At the population level, both types showed a spatiotemporal progression from T toward G. Notably, these cell types showed a complementary response to the landmark shift: FS cells showed a sudden (and stronger) coding shift toward G, whereas RS cells showed a more gradual, meandering progression. The findings suggest that RS cells encode separate aspects of visual and motor information, whereas FS cells exhibit a more integrated coding scheme, with bimodal representations of both visual and motor information. These data suggest a dynamic interaction between excitatory and inhibitory circuits in shaping neural representations of spatial memory and motor transformations.

Bharmauria et al. (2020). Integration of Eye-Centered and Landmark-Centered Codes in Frontal Eye Field Gaze Responses. *Cerebral Cortex 30* (9), 4995-5013
Sajad et al. (2015). Visual-motor transformations within frontal eye fields during head-unrestrained gaze shifts in the monkey. *Cerebral Cortex 25* (10), 3932-3952

Disclosures: S. Seo: None. **V. Bharmauria:** None. **X. Yan:** None. **H. Wang:** None. **J. Crawford:** None.

Poster

PSTR071: Sensorimotor Transformation: Neuroprocessing

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Program #/Poster #: PSTR071.04/D29

Topic: D.07. Visual Sensory-Motor Processing

Support: NIH Grant UH3NS107714

Title: Context Dependent Encoding of Sequences in the Sensorimotor Cortex

Authors: *Y. WON, M. RYBAR, J. E. DOWNEY, N. G. HATSOPOULOS;
Dept. of Organismal Biol. and Anat., The Univ. of Chicago, Chicago, IL

Abstract: Previous studies have established that internally and externally generated sequences are encoded differently in supplementary and lateral premotor cortices. We analyzed sensorimotor cortex activity in a human clinical brain-computer interface participant with residual upper-limb movement function. Here, we show that the sensorimotor cortex exhibits different encoding patterns under different sequential movement contexts during native limb performance of a reach-grasp-transport task: 1) visually guided, externally generated sequences,

2) visually guided elements of a sequence, and 3) memory-guided internally generated sequences. Our results demonstrate that the three contexts yield distinct neural encoding patterns at the single neuron level as well as at the population level using dimensionality reduction techniques to analyze the behavior of neural trajectories in a low-dimensional state space. Our results indicate that visually guided sequences induce consistent and robust neural representations, whereas internally guided sequences manifest more diverse and dispersed firing patterns, reflective of the increased cognitive demands associated with self-generated movement planning. At the population level, we observed differential neural trajectories in motor and sensory cortical areas which were paralleled by distinct patterns modulated by the task context. Subspace analysis further revealed a substantial divergence between contexts, particularly for internally versus externally guided movements, highlighting the potential for distinct neural mechanisms underpinning these processes.

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Poster

PSTR071: Sensorimotor Transformation: Neuroprocessing

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR071.05/D30

Topic: D.07. Visual Sensory-Motor Processing

Support: Canadian Institutes of Health Research (CIHR)
Natural Sciences and Engineering Research Council (NSERC)
The Connected Minds Program

Title: Landmark-centered reaching increases dorsal-ventral integration in human visual cortex

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Abstract: Introduction: The dorsal and ventral streams of visual cortex are associated with egocentric (EGO) allocentric (ALLO) coding, respectively, but the network dynamics of this system during landmark-centered reaching have not been investigated. We hypothesized that landmark-centered reaching would involve increased sharing of information between the dorsal and ventral streams and tested if this communication is mediated by overall trends in cortical

activation. **Methods:** Here, we performed a secondary analysis of the event-related fMRI task from Chen et al. (2014), to distinguish human brain networks involved in egocentric versus allocentric spatial representation of reach targets. The paradigm consisted of three tasks with identical stimulus display but different instructions: egocentric reach (remember absolute target location), allocentric reach (remember target location relative to a visual landmark), and a nonspatial control, color report (report color of target). We performed a graph theoretical analysis on time series data recorded during the memory delay period, contrasting egocentric and allocentric data versus baseline and detrending the timeseries. Network hubs, clustering coefficient, and efficiency of the networks were found. The community organization of the network into modules was determined as well as dynamical measures of network connectivity. **Results:** Both tasks showed three significant network modules spanning dorsal parietofrontal cortex, inferior parietal / lateral prefrontal cortex, and occipital-temporal-frontal cortex, but the ALLO network showed more functional integration than EGO. Specifically, the dorsal parietofrontal recruited additional ventral occipital areas in the ALLO task. However, removing the linear trend in these data (the general rise in BOLD), reduced this dorsoventral interaction. ALLO hubs that facilitated within-module interactions were found ventrally. **Conclusion:** Our results demonstrate cortical modularity and increased dorsoventral interaction in human visual cortex during landmark-centered pointing. This interaction is facilitated by the linear trend in the timeseries, suggesting the trend is a signature of network integration.

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Poster

PSTR071: Sensorimotor Transformation: Neuroprocessing

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR071.06/D31

Topic: D.07. Visual Sensory-Motor Processing

Support: HHMI

Title: Neural Circuits Underlying Distance Estimation

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[1]Harvard Med. Sch., Boston, MA; [2]Neurobio., Harvard Med. Sch., Cambridge, MA; [3]Neurobio., Harvard Univ., Boston, MA

Abstract: Perception of distance from a visual object is constructed from multiple visual cues including size, binocular disparity, motion parallax, contrast and elevation. Integrating multiple cues is useful when there is limited time to make a decision, but multiple cues can also be conflicting. It is unknown how these cues are being integrated. Drosophila melanogaster is a good model for studying sensory processing due to its well-characterized neural circuitry, and genetic tools that allow targeting of specific neurons for optogenetics, calcium imaging and electrophysiology. Past studies using freely moving flies have shown that courting males will

chase a female, and they will speed up when females are moving farther away. In addition, recent work suggests that visual cues contribute to a male's estimate of his distance from a female during courtship chasing. In this study, we propose courtship chasing as a behavioral paradigm for understanding mechanisms of cue integration for distance perception. We developed a virtual reality environment that displays visual objects that elicits chasing to head-fixed male flies placed on a spherical treadmill that allowed them to run forward, backward, sideways and rotate. In addition, we activated P1 neurons optogenetically to put these animals in an aroused state that facilitates chasing. This head-fixed virtual reality approach is compatible with electrophysiological recordings and allows us to easily dissociate the different visual cues that contribute to distance estimation. The first visual cue we focused on is object size, which we varied parametrically while measuring the male's forward running speed. On average, when the object was small, the male fly speeded up. Conversely, when the object was big, the fly slowed down. This result suggests males use object size to estimate distance, and it supports the feasibility of using head-fixed flies to study distance perception. However, not all male flies showed this behavioral response, which could mean that other cues are also used to estimate the object's distance. Therefore, we are now beginning to explore other cues separately and together, both congruent and conflicting. Ultimately, we want to investigate how the brain is integrating this information by identifying relevant neurons and their interactions, using calcium imaging, electrophysiology, and connectome analysis. A mechanistic understanding of how the brain estimates distance to a visual object by combining multiple cues would provide insight into the general problem of evidence integration in sensory perception.

Disclosures: F. Medeiros Contini: None. **D.A. Pacheco pinedo:** None. **R.I. Wilson:** None.

Poster

PSTR071: Sensorimotor Transformation: Neuroprocessing

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Topic: D.07. Visual Sensory-Motor Processing

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NIH-NINDS R01 NS121535
Sloan Foundation
Whitehall Foundation

Title: Task-relevant information is enriched in mouse PPC but not selectively propagated to M1

Authors: *P. RAVISHANKAR[1,2], H. A. GRIER[3], D. A. SABATINI[4], M. T. KAUFMAN[5]; [1]Univ. OF CHICAGO, CHICAGO, IL; [2]Committee on Computational Neuroscience, University of Chicago, Chicago, IL; [3]Committee on Computat. Neurosci., Univ. of Chicago, Chicago, IL; [4]The Univ. of Chicago, Chicago, IL; [5]Organismal Biol. and Anat., Univ. of Chicago, Chicago, IL

Abstract: To understand how visual information is transformed into action, we must determine how task-relevant information propagates forward while task-irrelevant information is discarded. Some cortical projections are known to preferentially carry general classes of information that are more relevant to the downstream area. However, it is unclear whether selective routing can develop when information-relevance is particular to a learned task. We developed a novel, closed-loop, visuomotor 2D-joystick task that included relevant and irrelevant visual motion information in the stimulus to study how task-relevant information is routed. We focused on the mouse Posterior Parietal Cortex (PPC), an area that preferentially engages in vision-to-movement tasks and exhibits complex task-feature selectivity. First, we determined PPC's role in expert mice by optogenetically inducing inhibition during behavior. Choice accuracy decreased but joystick movements were unaffected, arguing that inactivating PPC reduced the animal's ability to translate visual information into movement. Next, we determined whether PPC can selectively route task-relevant information to M1. We performed two-photon calcium imaging of L2/3 pyramidal cells in contralateral PPC of expert mice (>14,000 neurons, 5 mice, 2-3 months experience), with PPC-M1 projection neurons identified via retrograde-tracing (>500 neurons). We identified what task features modulated each neuron's activity using linear encoding models. PPC neurons were, on average, most strongly modulated by joystick movement. Most visually-responsive neurons were more strongly modulated by task-relevant than by task-irrelevant visual drift (61%). These results argue that PPC more strongly encodes task-relevant information. Surprisingly, however, encoding in labeled PPC-M1 neurons was indistinguishable from unlabeled neurons. Both groups of neurons exhibited similarly random mixed selectivity, and crucially, PPC-M1 neurons were not more biased toward task-relevant information than unlabeled cells were. This argues that the full representation present in PPC is sent downstream to M1 and, at least for this pathway, half a lifetime of training is insufficient to induce selective information routing.

Disclosures: P. Ravishankar: None. **H.A. Grier:** None. **D.A. Sabatini:** None. **M.T. Kaufman:** None.

Poster

PSTR071: Sensorimotor Transformation: Neuroprocessing

Location: MCP Hall A

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Program #/Poster #: PSTR071.08/D33

Topic: D.07. Visual Sensory-Motor Processing

Title: Spatial and non-spatial abstract choice-related signals in extrastriate visual cortex

Authors: *N. ZHANG[1], Y. GU[2];
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Abstract: Choice-related signals have been frequently observed in sensory areas during perceptual decision making tasks. However, the source of these signals largely remains unclear and under debate. One pitfall in most of the studies is that the choice targets are typically

allocated at alternative locations around the fixation point with fixed choice and location association rule, making it a confound to know whether the choice-related signals really reflect an abstract decision about the sensory input, or arise from a spatial effect, for example, eye movement to a target at the left or right side of the visual space. To disentangle the two types of signals, here we trained macaques to perform a random dot direction discrimination task in which the animals made saccadic choice to corresponding color targets that could varied in their spatial locations. For example, the leftward moving dots correspond to a red choice target that could be at either left or right side of the fixation point, and vice versa for the rightward motion stimuli. Single-unit recordings in the extrastriate visual cortex, including the medial superior temporal area (MST) and the middle temporal area (MT) revealed a strong spatial effect in the choice-related signals that were quantified by choice probability (CP). In particular, the sign of CP was reversed for trials when the choice target (e.g. red) was at one side of the fixation point versus the other side. A relatively smaller proportion of neurons on contrary, exhibited choice target-space independent effect by remaining their CP sign. This pattern holds and is even clearer in the ventral intraparietal area (VIP), and the lateral intraparietal area (LIP). Based on the response delay, it is likely that the strong spatial choice signals in MST and MT originated from VIP and LIP, thus consistent with a top down origin. In summary, our study revealed a large part of spatial effect on choice related signals in the sensory areas.

Disclosures: N. Zhang: None. **Y. Gu:** None.

Poster

PSTR071: Sensorimotor Transformation: Neuroprocessing

Location: MCP Hall A

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Topic: D.07. Visual Sensory-Motor Processing

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Title: Horizontal information flow in the primary motor cortex at the β-frequency ranges in neural responses to visual instruction cue in a visuomotor task.

Authors: *H. WATANABE[1], K. TAKAHASHI[2], N. G. HATSOPOULOS[3], H. MUSHIAKE[1]; [1]Tohoku Univ., Sendai, Japan; [2]Ruten Inc., Chicago, IL; [3]Univ. of Chicago, Chicago, IL

Abstract: The cerebral cortical areas in the mammalian brain are functionally identified as performing specific information processing functions, while neural activities in each cortical area contribute to process sensory stimuli heterogeneously. It has been reported that phase of the β oscillations in the primary motor cortex (M1) is locked by a visual cue and propagate to horizontal direction. This indicates that visual information in the β oscillation spreads horizontally in the M1, but it is unknown depth profile of cortical neural dynamics for processing the behaviorally relevant visual information. Here, we examine the existence of network dynamics for visual processing in the monkey motor cortex by identified depth profile functional connectivity in the β frequency band. The monkey was trained to control a cursor on a screen by using the upper limb to perform two-dimensional reaching in the horizontal plane. The monkey kept the cursor at an initial resting target for 3.4 seconds while a second target appeared in one of three random positions. The color of the resting target changed and served as a visual cue during the resting state. A 96-channel electrode array (Matrix Array, NeuroNexus) was implanted in the M1 forelimb region. Sixteen electrode sites were positioned linearly on each shank and an array of six shanks was inserted perpendicular to the M1. Cortical network dynamics were evaluated by the phase-locking (PL) scores of the β oscillation across the trials. To identify functional connectivity in the β oscillation coupled with the visual cue (i.e. color change in the resting target), phase transfer entropy (PTE) analysis was performed across recording sites. A task-relevant signal was identified by detection of significant differences of amplitude at β and high-γ frequency bands in between the resting and the action state (p<0.05, U-test). The task-relevant signals appeared in over 40% of recording sites. There was no systematic depth dependence in the spatial distribution of the task-relevant signals. The visual cues significantly facilitated the PL scores in the task-relevant signals (24/39 channels, p<0.05, U-test). PTE analysis described intracortical horizontal information flow across the same cortical depths and vertical information flow across various cortical depths in the β-frequency band during visual cues. The β-frequency signals carried rich information across horizontal directions compared to vertical direction. These suggested the M1 processes information using a horizontal cortical network at the β-frequency band in response to sensory stimuli and give insights into how such information flow optimizes cross-functional processing.

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Poster

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Program #/Poster #: PSTR071.10/D35

Topic: D.07. Visual Sensory-Motor Processing

Title: Leg spinal excitability changes according to different jump heights simulated by virtual reality

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Abstract: Virtual Reality (VR) is a computer simulation of a three-dimensional environment. While specific brain activations in premotor, motor, and sensorimotor regions were noted during virtually simulated actions, little is known regarding a potential influence on spinal networks. The present experiment aimed at investigating spinal excitability of leg muscles during a VR simulation of different jumping tasks. Twelve healthy young participants (24.8 ± 5 years old) were enrolled in a single-session experiment. They were equipped with a VR headset that displayed simulated drop jumps in a first-person perspective at different heights: 90 cm (VRlow) and 250 cm (VRhigh). These conditions were compared to two control conditions, standing at rest on the ground in a VR neutral environment (VRrest) or standing at rest on the ground without VR (noVR). Participants were standing, equipped with electromyographic sensors on right soleus, gastrocnemii, and tibialis muscles, as well as motion sensors (accelerometers and gyro) on leg, hip, and head. For each condition, spinal excitability of calf muscles was assessed through the recording of H-reflexes, elicited by stimulating the posterior tibial nerve transcutaneously, normalized by maximal muscle action potential, i.e. maximal M-wave or Mmax. While there were no differences in body oscillations, nor in background muscles' activities, spinal excitability, expressed as the ratio H/Mmax, was significantly (P=0.02, one-way repeated measure ANOVA, Bonferroni post-hoc) lower during VRhigh (0.31 ± 0.17, a.u.) as compared to baseline (noVR: 0.40 ± 0.27) and VRrest (0.37 ± 0.28). VRlow H/Mmax (0.35 ± 0.22, a.u.) was significantly (P= 0.03) lower than VRrest and noVR. The present study raised that spinal excitability modulation by virtual jumps seems to mimic the behavior observed during real conditions. Indeed, during the aerial phase of real drop jumps, spinal excitability of locomotor muscles was usually reported to decrease. During real drops, cutaneous afferents of the feet and vestibular discharges may explain this downward modulation. However, during VR, participants are standing with foot contact on the ground and no sufficient body oscillation to suggest a direct intervention of the vestibular system. The modulation of spinal excitability generated by jumps simulated through VR may then suggest a strong influence of visual cues on spinal network, overpassing the other sensorial information that do not suggest that the body is actually falling. Overall, the present study provides promising results regarding a potential role of the spinal cord into motor neural system plasticity observed after a VR intervention.

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Poster

PSTR071: Sensorimotor Transformation: Neuroprocessing

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Topic: D.07. Visual Sensory-Motor Processing

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Title: Morphology and synapse topography optimize linear encoding of synapse numbers in Drosophila looming responsive descending neurons

Authors: *A. MORENO-SANCHEZ[1], A. N. VASSERMAN[1], H. JANG[2], B. W. HINA[2], C. R. VON REYN[2,3], J. AUSBORN[1];
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Abstract: Synapses are often precisely organized on dendritic arbors and their topographic organization is thought to critically influence single neuron computations. While some functional implications of synaptic topography and its role in neural computations have been explored, difficulties in simultaneously localizing synaptic inputs and effectively activating individual or groups of synapses have posed challenges. Using electron microscopy (EM) connectomics, we explore synaptic topography within the looming detection circuits of *Drosophila melanogaster*, which drive motor responses to objects approaching on a direct collision course. These circuits contain retinotopically tuned visual projection neurons (VPNs) that encode distinct features of the looming stimulus (such as angular velocity or size) and establish synaptic connections with descending neurons (DNs). Synapses of a given VPN type project to non-overlapping regions on DN dendrites. We find that within these spatially constrained clusters, synapses are not retinotopically organized, but instead adopt near random distributions. However, at the local scale, we find that any two neighboring synapses are more likely to belong to the same presynaptic VPN, suggesting a potential influence on synaptic integration. To explore how this organization affects DN integration, we have developed biophysical multicompartment models of DNs using precise EM morphologies, synapse locations, experimental electrophysiology and spike initiation zone labeling data. Our models suggest that the dendritic morphologies of DNs provide a normalization of postsynaptic potentials of individual synaptic inputs at the spike initiation zone, regardless of location on the dendrite. We have discovered that this near-random distribution of synapses enables a linear encoding of synapse numbers from individual VPNs by minimizing shunting of their synaptic inputs. These findings shed light on how synaptic topography impacts dendritic integration, suggesting that linear encoding of synapse numbers could be an inherent strategy established through connectivity and passive neuron properties. This passive normalization and linear encoding of synapse numbers provides a foundation to which active properties and plasticity can be tuned as needed.

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Poster

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Topic: D.07. Visual Sensory-Motor Processing

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Title: The timing of LIP remapping is consistent with a cortical wave rather than a jump in RF

Authors: *Y. ALKAN, A. MORRIS, J. W. BISLEY;
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Abstract: Maintaining stable perception amidst dynamic visual input driven by eye movements is are markable feat of the brain. One proposed mechanism underlying this phenomenon is response field (RF) remapping in the lateral intraparietal area (LIP), in which neurons pre-saccadically update their RFs to compensate for eye movements. A current mechanistic model of remapping hypothesizes that remapping occurs as a cortical wave, based on the finding that a small response can be seen in neurons with RFs between the pre- and post-saccadic stimulus location. To test this hypothesis, and to compare it to the alternative, in which remapping occurs as a single jump, we investigated the timing of remapping as a function of saccade length. We predicted that if remapping occurs through a one-step process, the remapped response will align more closely with saccade onset, independent of saccade length. Alternatively, if remapping involves a wave moving across cortex over time, we anticipated that the remapped response will better align with saccade offset and will occur later for longer saccades. We recorded the activity of LIP neurons in animals performing a saccade task. In the task, the animals fixated before executing a visually guided saccade to a target located 7, 14, or 21 degrees away. In 55% of trials, a task-irrelevant probe appeared in the post-saccadic RF while the animal was fixating and remained on throughout the saccade. In 20% of the trials, the animals made the saccade without a probe present and in 25% of trials, the probe appeared in the RF while the animals fixated a point at the original fixation point or at the 3 target locations - no saccade was made. LIP cells were confirmed using a memory-guided saccade task and were only included if they had a remapped response that was not explained by a motor response in the saccade-only control trials. We analyzed the temporal characteristics of the remapped responses and found no correlation between onset latency and saccade length when aligned by saccade offset, but significant correlations when aligned by saccade onset. At the single neuron and the population levels, the confidence intervals of the slopes did not overlap. These results are consistent with the hypothesis that remapping occurs via a cortical wave-like process and may further constrain models of remapping in the future.

Disclosures: Y. Alkan: None. **A. Morris:** None. **J.W. Bisley:** None.

Poster

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Program #/Poster #: PSTR071.13/D38

Topic: D.07. Visual Sensory-Motor Processing

Title: Investigating the Neural Correlates of Immersion in Virtual Reality

Authors: *A. LITOVCHENKO[1], M. GRANSON[2], M. FAUST[1];
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Abstract: Immersion is a mental state in which an individual becomes deeply engaged or absorbed in an activity, often resulting in a diminished awareness of the external world. This state involves a series of cognitive processes, including attention, perception, and memory, which work together to create an integrated experience of being involved in a particular environment or task. While frequently achieved in interactive media environments such as video games, immersion lacks robust theoretical underpinnings. Our study tested the 3-dimensional framework for psychological immersion proposed by Nilsson et al. (2016) by identifying the EEG neural correlates associated with immersive experiences. Participants engaged with a driving simulator game displayed on a traditional flat computer screen and through a more immersive 3D virtual reality (VR) headset, with varying difficulty levels across sessions. The findings indicate a notable increase in theta (4-8 Hz) wave amplitude during 3D VR gameplay compared to 2D screen gameplay, particularly on the easier racetrack, suggesting that task complexity and the immersive quality of the display technology significantly influence neural engagement. Both theta and beta (15-30 Hz) bands displayed higher amplitudes in the 3D VR condition, underscoring the enhanced immersion depth facilitated by VR. The study cross-validated findings using subjective (immersion surveys) and objective (EEG) measures. Such triangulation helped confirm that the observed brain activity correlated with participants' immersion experiences. Combined, the EEG data and survey responses supported the distinction between challenge-based and system/perceptual-based dimensions of immersion. These results contribute to the theoretical development of immersion by empirically validating specific dimensions within the framework and establishing theta band activity as a reliable neural indicator of increased immersion across digital media. This study fills a critical gap in immersion research and clarifies the psychological and neural mechanisms underpinning immersive experiences in virtual environments.

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Poster

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Title: Persistent effects of multiple-day state-dependent parietal intermittent theta burst stimulation on sensorimotor control networks.

Authors: *J. A. DELUISI[1], E. R. GOLDENKOFF[2], T. G. LEE[3], J. A. BRISSENDEN[4], S. F. TAYLOR[5], T. A. POLK[4], M. VESIA[6];
[1]Univ. of Michigan, Ann Arbor, Ann Arbor, MI; [2]Sch. of Kinesiology, Univ. of Michigan, Ann Arbor, MI; [3]Dept. of Psychology, Univ. of Michigan, Ann Arbor, Ann Arbor, MI; [4]Psychology, Univ. of Michigan, Ann Arbor, MI; [5]Psychiatry, Univ. of Michigan Dept. of Psychiatry, Ann Arbor, MI; [6]Sch. of Kinesiology, Univ. of Michigan, Ann Arbor, Ann Arbor, MI

Abstract: Transcranial magnetic stimulation (TMS) can alter cortical excitability and functional connectivity in brain networks differentially depending upon the neural activity state during stimulation. Our group and others have shown that the functional interactions between the posterior parietal cortex (PPC) and primary motor cortex (M1) derived from dual-site TMS are context-dependent. We have recently shown that controlling the brain state with a grasping task during multiple-day parietal stimulation sessions can induce immediate changes in the motor cortex and improve manual dexterity. The current study examined whether multiple-day state-dependent parietal stimulation can affect downstream motor activity and targeted parietal-motor functional connectivity related to goal-directed actions beyond one week. Forty-eight healthy adults aged 18-50 were randomly assigned to one of three groups. Participants received five daily sessions of intermittent theta burst stimulation (iTBS) to the left PPC to enhance activity in the sensorimotor control network. One group underwent iTBS to the left PPC while concurrently performing a grasping task. A second group underwent iTBS to the left PPC while in an unconstrained rest state. The third group underwent iTBS to a left parietal region outside the grasping network while performing the grasping task concurrently. Motor-evoked potentials (MEPs) elicited by single-pulse TMS and task-evoked connectivity during a fMRI precision force tracking task were collected before (baseline) and about one week after the final stimulation session. Plasticity changes in M1 were assessed by quantifying motor cortical excitability (e.g., MEP size) following multi-day iTBS stimulation compared to baseline. Functional connectivity analysis was conducted on fMRI data to measure task-related parietal-motor connectivity changes after stimulation sessions relative to baseline. State-dependent parietal stimulation had a lasting effect on motor cortical excitability, as MEP amplitudes remained significantly higher than baseline after a week of multiple-day stimulation sessions. These neuroplastic changes in M1 were not observed after the other two iTBS protocols. Preliminary results suggest differential changes in task-evoked fMRI activity patterns in a parietal-motor circuit associated with action control after state-dependent stimulation. We conclude that multiple sessions of state-dependent TMS have long-lasting plasticity-like effects within the targeted grasping network. These findings have implications for the development of stimulation-based interventions for sensorimotor disorders.

Disclosures: J.A. Deluisi: None. **E.R. Goldenkoff:** None. **T.G. Lee:** None. **J.A. Brissenden:** None. **S.F. Taylor:** None. **T.A. Polk:** None. **M. Vesia:** None.

Poster

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Topic: D.07. Visual Sensory-Motor Processing

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NSF GRFP

Title: Saccadic modulation of visual neurons in the superior colliculus

Authors: *A. BUTEAU[1], J. HUNT[1], A. POLEG-POLSKY[2], G. FELSEN[2];
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Abstract: Animals use ballistic reorienting movements called saccades to actively explore their environment for salient visual targets. Saccades result in a transient modification of visual perception such that it becomes difficult to perceive stimuli that appear around the time of saccades, a phenomenon referred to as saccadic suppression. Saccadic suppression is associated with a decrease in responsiveness across the visual system including the midbrain superior colliculus (SC), a highly conserved visuomotor structure required for generating saccades. In primates, studies have shown that visual responses in SC neurons are significantly attenuated around the time of saccades, but the neural circuitry that generates this suppression is not well understood. Ex vivo slicework in mice has identified a putative circuit for saccadic suppression in the SC in which the saccade motor program is used to drive inhibition of visual SC neurons via local inhibitory (GABAergic) neurons; however, this circuit has never been examined in-vivo. The goal of this research is to dissect this circuit to better understand how saccadic suppression arises in the SC. Using Neuropixels probes, we collected extracellular recordings of single-unit activity within the superficial layers of the SC while mice made saccades. Head-fixed mice were placed within an immersive visual arena and shown a low-contrast drifting grating stimulus to elicit saccades via the fast phase of the optokinetic reflex. Periodically, the contrast of the grating was briefly elevated to evoke discrete visual responses from visual SC neurons. Peri-saccadic visual responses were compared to extra-saccadic visual responses to assess single-units for saccadic modulation. Across the population, we found that visual SC neurons exhibited peri-saccadic modulation; the probe-related activity of most neurons was suppressed, but was enhanced in some. To examine whether saccade-generating circuitry in the SC contributes to this modulation, we performed two follow up experiments. First, we simulated the visual experience of saccades and observed that modulation cannot be completely explained by a feedforward, visual mechanism. Second, to directly test the role of a corollary discharge in saccadic modulation, we chemogenetically inactivated GABAergic neurons in the intermediate/deep SC. We are currently assessing the effect of inactivating these GABAergic neurons on saccadic modulation. These data demonstrate that saccadic modulation in the SC is a conserved neural phenomenon and establish a platform for studying peri-saccadic phenomena in mice.

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Poster

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Topic: D.07. Visual Sensory-Motor Processing

Title: Proximal medium-range neural feedback improves grasp planning under noise

Authors: *R. KHAN[1], H. ZHONG[1], S. DAS[1], J. CAI[1], M. NIEMEIER[1,2];
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Abstract: Top-down predictions from generative models in the brain are conveyed through cortical layer-specific feedback connections during visual recognition tasks. However, there is a dearth of understanding of the contribution of feedback for visually guided action planning. Recent object grasping studies show that advanced object shape and movement representations also involve the reactivation of earlier visual areas, indicating that feedback connections carry information from downstream stages of visuomotor processing to the earlier stages in the visual stream. We investigated the contribution of such neural feedback to the visuomotor control of grasping by using convolutional neural networks, trained to compute grasp positions for real-world objects, as a modelling framework. To make these models computationally and structurally more similar to the human cortex, we added generative feedback loops to a custom feedforward backbone, carrying advanced representations to early layers of the network. When evaluated on images with additive Gaussian noise, after multiple forward and backward passes through the network, we observed an improvement in performance for the network with predictive coding dynamics in comparison to the feedforward baseline. We also found that this performance-enhancing effect under adverse conditions is optimal for (1) medium-range feedback, (2) originating at a proximal level of abstraction. To conclude, our simulations show that introducing biologically plausible, layer-specific predictive coding dynamics improves model robustness to noisy visual stimuli in a neural network model optimised for grasp detection.

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Poster

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Topic: D.07. Visual Sensory-Motor Processing

Title: Emergence Of Dorsal-like And Ventral-like Properties In Artificial Neural Network

Authors: *T. B. REZA;
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Abstract: The brain processes visual information through two neural streams: the ventral stream for perception and the dorsal stream for action. The dorsal stream translates visual features into motor commands, like grasping, modeled as regression tasks in Artificial-neural-network (ANN). Grasp representation involves identifying suitable grasp points on objects. In contrast, the ventral stream converts retinal images into abstract representations for object recognition, framed as object-recognition tasks in ANNs. One hypothesis posits that disparities between the two streams arise from distinct optimization approaches. Supporting this notion, neural networks trained for object classification or robotic grasp control exhibit varying response characteristics. However, these networks typically vary in architecture and training methodologies. To assess the impact of task-specific training disparities, we developed a unique map-based artificial neural network (ANN) and a task-agnostic double-log loss function capable of analyzing both object-recognition and visual grasp tasks. Representational similarity analysis showed our classification model had activation patterns similar to state-of-the-art classification models, while our grasp network resembled leading grasp models. Visualizing saliency maps using Guided Backpropagation revealed the classification network emphasized local object parts and surface features, whereas the grasp network emphasized global features. Moreover, we've trained a network with the ability to execute both object recognition and grasping tasks concurrently. This emphasizes that even within a single network, the unique characteristics of these tasks persist as distinct streams. The emergence of dorsal and ventral stream-like properties suggests our approach offers a fair and task-agnostic means of comparing optimization trends across action-oriented and perception-oriented learning agents.

Disclosures: T.B. Reza: None.

Poster

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Title: Deconstructing the brain-wide organization underlying optomotor responses

Authors: *Y. WANG[1], L. BREZOVEC[2], M. CHOI[3], I. ZUCKER-SCHARFF[1], T. CLANDININ[3];

[1]Stanford Univ., Stanford, CA; [2]Neurosci., Stanford, Stanford, CA; [3]Neurobio., Stanford Univ., Stanford, CA

Abstract: The optomotor response (OMR) is a reflexive behavior, present in many species, in which animals move their bodies in the direction of a moving visual pattern to correct any relative motion between the animal and the visual motion. Although the OMR has been used extensively to investigate visuomotor neural circuits, the brain-wide organization underlying this critical reflex is poorly understood. In this study, we use volumetric two-photon imaging to map the spatial topography and temporal dynamics of this visuomotor transformation across the entire brain of walking Drosophila. We characterize the global brain dynamics associated with wide-field motion stimuli and dissect the interaction between sensory input and motor output across the brain. Our analysis reveals neural correlates that predict, on a trial-to-trial basis, the strength of the OMR. Overall, our work reveals how many functionally diverse brain regions cooperate to implement this visuomotor transformation.

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Poster

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Title: Mapping Finger-Specific Neural Networks Insights from Whole-Brain Connectivity at the Mesoscale

Authors: *T. HE[1,2,3,4], B. QU[2,4,3], H. WANG[2,4,3], Z. TANG[4,3], Z. LYU[4,3], A. W. ROE[2,4,3], H.-Y. LAI[2,4,3,5];
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Abstract: The ability to move each finger individually is crucial for daily hand functions. Although previous research has established the existence of somatosensory pathways within and between the somatosensory and motor cortices, the specific brain networks dedicated to each finger have not been thoroughly explored. This study used pulsed near-infrared neural stimulation combined with 7T functional magnetic resonance imaging (INS-fMRI) as a novel method for network mapping. This approach provides focal stimulation at functional-column level and insights into whole-brain mesoscale connections. Our aim was to unravel mesoscale connections associated with finger-specific neural circuits. We used a lab-designed MR-compatible tactile stimulator to functionally map the locations of individual finger, including thumb (D1), index (D2), middle (D3) and ring (D4) fingers, in the cortical areas 3b of two monkeys using a 7T MRI system. INS stimulated these areas to induced blood oxygen level dependent (BOLD) responses, exploring the functional network of different fingers. The INS-evoked BOLD responses revealed significant overlaps in sensorimotor and multisensory connections among the digits (D1, D2, D3 and D4), particularly within the motor and visual cortices. This suggests that sensory inputs from different fingers may process through both shared and distinct circuits, each reflecting its functional significance. Moreover, the response areas induced by INS-D2 were significantly larger than those related to D1 and D3, indicating a more complex connections for the index finger. The connectivity pattern of NS-D4 is similar to that of INS-D3, with a few notable differences in the connections. Although INS-D1 elicited fewer and weaker activations compared to INS-D2 and INS-D3, it uniquely projected to higher-level somatosensory areas, including SII and area 7a. This distinct projection pattern suggests that the thumb serves a different functional role compared to the other fingers. In conclusion, our study is the first to reveal whole-brain network connectivity at the mesoscale for specific fingers, uncovering d distinct and complex activation patterns for each finger. This research enhances understanding of finger-specific networks and provide novel insights into neurological and rehabilitative medicine.

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Poster

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Location: MCP Hall A

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Program #/Poster #: PSTR071.20/D45

Topic: D.07. Visual Sensory-Motor Processing

Support: TUBITAK Grant 221K283

Title: Mu suppression during action observation only in the lower, not in the higher, frequency subband

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Abstract: Mu suppression - desynchronization of neural oscillations in central EEG electrodes during action execution and observation - has been widely accepted as a marker for neural mirroring. It has been conventionally and predominantly quantified in the 8-13 Hz range, corresponding to the alpha frequency band, although few studies reported differences in lower and higher subbands that together constitute the mu frequency band. In the present study, we adopted a comprehensive analytical approach to examine the spectral and temporal dynamics of mu suppression when participants watched videos depicting hand and face actions and artificial pattern movements. Our analyses in central EEG electrodes revealed that neural oscillations were significantly suppressed during action observation only in the lower (8-10.5 Hz), not in the higher (10.5-13 Hz), subband. No such subband differentiation was observed for the alpha oscillations in the occipital electrodes. In addition, in the lower subband, significantly stronger suppressions were selective for hand actions in the central EEG electrodes placed over the hand region of the sensorimotor cortices and for facial actions in the frontotemporal electrodes placed over the face region of the sensorimotor cortices. In the higher subband, such stimulus selectivity was only observed for facial actions in the frontotemporal electrodes. Furthermore, the neural oscillations in the lower, but not the higher, subband followed the precise temporal patterning of biological motion in the videos. These results indicate that neural oscillations in the lower subband show the characteristics of neural mirroring processes, whereas those in the higher subband might reflect other mechanisms.

Disclosures: E. Soyman: None. **A. Badakul:** None.

Poster

PSTR071: Sensorimotor Transformation: Neuroprocessing

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR071.21/D46

Topic: D.07. Visual Sensory-Motor Processing

Support: Harvey Karp Discovery Award (L.F.)
UC MEXUS-CONACYT Postdoctoral Fellowship (L.F.)
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NSF 1707287 (M.G.)
Larry L. Hillblom Foundation (M.G.)
Whitehall Foundation (M.G.)

Title: Differential Stability of Task Variable Representations in Retrosplenial Cortex

Authors: *L. FRANCO[1], M. GOARD[2];
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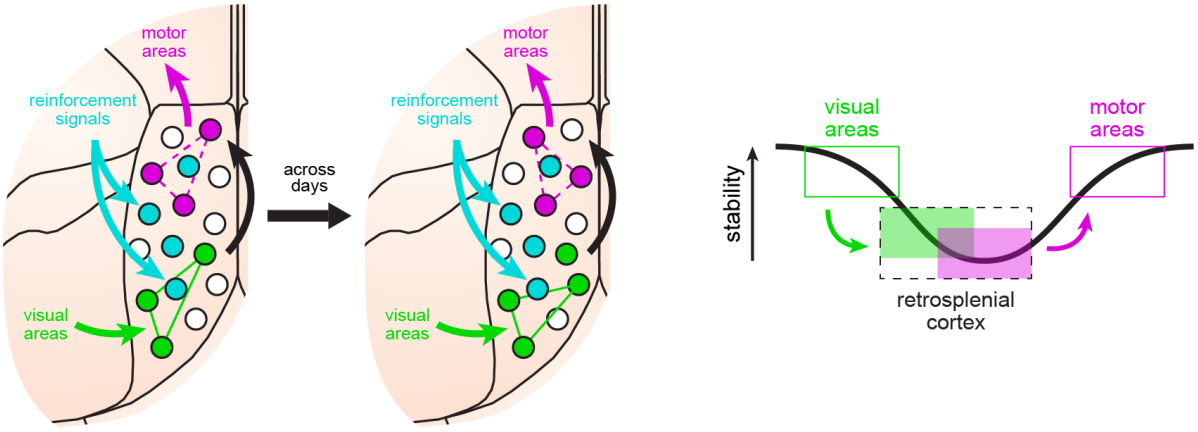
Abstract: Cortical neurons store information across different timescales, from seconds to years. Although information stability is variable across regions, it can vary within a region as well.

Association areas are known to multiplex behaviorally relevant variables, but the stability of their representations is not well understood. Here, we longitudinally recorded the activity of neuronal populations in the retrosplenial cortex (RSC) during the performance of a context-choice association task. We found that the activity of neurons exhibits different levels of stability across days. Using linear classifiers, we quantified the stability of three task-relevant variables. We find that RSC representations of context and trial outcome display higher stability than motor choice, both at the single cell and population levels. Together, our findings show an important characteristic of association areas, where diverse streams of information are stored with varying levels of stability, which may balance representational reliability and flexibility according to behavioral demands.



Disclosures: L. Franco: None. **M. Goard:** None.

Poster

PSTR071: Sensorimotor Transformation: Neuroprocessing

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR071.22/D47

Topic: D.07. Visual Sensory-Motor Processing

Support: CORE Grant P30EY08098
NIH grant R01EY024831

Title: The influence of circular moving trajectories on interceptive eye movements

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Abstract: Accurate saccades to moving targets are important for effective interactions with dynamic environments. Interceptive saccades, compared to saccades aimed at stationary targets, encounter challenges from the changing stimulus location that impact movement preparation and

are compounded by neuronal processing delays. Studies in non-human primates indicate that interceptive saccades can land near the predicted target location despite sensorimotor delays, suggesting that the brain integrates target motion to guide eye movements. However, as the target eccentricity increases, an increased offset at saccade end is observed, potentially due to oculomotor limits. To dissociate these factors, we employed a task that requires interceptive saccades to a circular moving target. The task holds constant saccade amplitude (i.e., the radius of the circle) while varying saccade direction. Human subjects (n=11) observed a stimulus moving clockwise or counterclockwise at three speeds (randomly interleaved) on a circular path at a fixed radius. We also included trials that required a saccade to a stationary target (speed = 0) as control. The fixation point turned off after a delay (0-1200 ms) and served as the cue to initiate a saccade. We characterized saccade endpoint density and ending errors across conditions. Compared to stationary target conditions that had uniform saccades endpoint and ending error distributions, saccade endpoints to moving stimuli were “tilted” by the target’s trajectory on the circular path. Specifically, for clockwise-moving targets, saccade density was higher in the first and third quadrants, whereas for counterclockwise-moving targets, it was higher in the second and fourth quadrants. In addition, the magnitude of the ‘tilt’ increased with target speed. However, the distribution of ending errors showed a pattern opposite to that of saccade density. For clockwise-moving targets, interceptive saccades targeting the second and fourth quadrants tended to lead the target, while those in the first and third quadrants often lagged it. For counterclockwise motion, saccades tended to lead in the first and third quadrants and lag in the second and fourth quadrants. The distribution was also more concentrated in the leading quadrants for faster target speeds. We propose two explanations for the tilting effect on circular target trajectories: 1) interceptive saccades generally occur in cardinal directions but are skewed by initial target velocity parameters, or 2) interceptive saccades anticipate the target's location when it moves across the visual field but are biased to land at a lagged location within the same visual hemifield.

Disclosures: Z. Xiao: None. **N.J. Gandhi:** None. **J. Mayo:** None.

Poster

PSTR071: Sensorimotor Transformation: Neuroprocessing

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR071.23/D48

Topic: D.07. Visual Sensory-Motor Processing

Support: NIH Grant EY024831
NIH Grant EY030667
NIH Grant EY022854

Title: Functional connectivity within and between the superior colliculi explored using current source density analysis

Authors: *C. BOURRELLY[1], N. J. GANDHI[2];
[1]Univ. of Pittsburgh, Pittsburgh, PA; [2]Bioengineering, Univ. of Pittsburgh, Pittsburgh, PA

Abstract: The superior colliculus (SC) is an important brain area that mediates visually-guided saccades. The sensory-motor transformation (along its dorsoventral axis) and the spatial topography (along its rostrocaudal and mediolateral dimensions) have been well characterized for spiking activity, and more recently for the local field potential (LFP). While the spiking activity represents the output of neurons, the LFP signal presumably reflects integrated activity including input signals within a volume of tissue surrounding the recording site. In this work, we evaluate the visuomotor features of the LFP signal during saccades directed toward and away from the optimal location. We applied current-source density (CSD) analysis to LFP signals and identified source and sink patterns across the SC layers for different saccade directions to assess functional connectivity during sensation and action. It has been proposed that intracollicular circuitry is dominated by local excitation and distal inhibition connectivity of SC neurons, particularly in the intermediate layers. Given this hypothesis, we expected to observe inhibitory signatures during the movement epoch, especially between the two SC. Using multi-contact laminar electrode inserted orthogonally to the SC, we simultaneously recorded spiking and LFP activities in rhesus monkeys performing a visually guided delayed saccade task. Using CSD analysis, we compared LFP activities during the visual, the motor and the post-motor epochs across depth for each saccade direction. During the sensory period, a strong sink (putative excitation) in the CSD signal was found after the appearance of the target in the receptive field (RF but not when the target was presented outside the RF. During the motor epoch, when the saccade was made toward the RF, a strong sink coupled with a deeper source (putative dipole effect) was observed around the time of the saccade. Interestingly, when the saccade was directed outside the RF, we observed solely a source in the CSD signal. This source activity appears later in time than the sink observed for the saccade directed toward the RF and likely reflects an inhibitory input present in the LFP activity. Moreover, after saccade completion, sink activities were found at the same time for all target locations, revealing a disinhibition of both SCs. These results suggest a global inhibition followed by a broad disinhibition in the SCs during saccade generation. They also support the hypothesis that the observed LFP in SC likely reflects the input signal locally. All together, these results are informative about spatial and temporal processing in the SC during the production of a saccade.

Disclosures: C. Bourrelly: None. **N.J. Gandhi:** None.

Poster

PSTR071: Sensorimotor Transformation: Neuroprocessing

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR071.24/D49

Topic: D.07. Visual Sensory-Motor Processing

Support: NIH Grant EY024831
NIH Grant EY030667
NIH Grant EY022854

Title: Dorsoventral organization and characterization of the post motor response in spiking activity in the superior colliculus

Authors: *E. AYAR[1], C. BOURRELLY[2], N. J. GANDHI[2];
[1]Carnegie Mellon Univ., Pittsburgh, PA; [2]Bioengineering, Univ. of Pittsburgh, Pittsburgh, PA

Abstract: For visually-guided saccades, neurons in the superior colliculus (SC) emit a burst of spikes to register the appearance of a visual stimulus (visual response), and many of the same neurons discharge another burst to initiate an eye movement (motor response). It has been well characterized that neurons in superficial layers of the SC have stronger visual responses and neurons deeper along the dorsoventral axis have stronger motor responses. In intermediate layers of the SC, neurons contain both visual and motor responses. Previous studies have reported a modulation in spiking activity following the motor burst, often manifesting as a second burst. Although labeled as the post saccadic visual response, the systematic characterization of the post motor modulation needs to be expounded upon to consider potential contributions of non-sensory processes. In this work, we aim to fill this gap in knowledge. Spiking activity along the dorsoventral axis was recorded with a laminar probe as Rhesus monkeys performed the visually-guided and memory-guided delay saccade task with targets presented inside and outside the receptive field. With this paradigm, we often observed strong post motor modulations across channels during the visually-guided saccade tasks and less so for memory-guided. Interestingly, the detection and peak firing time of this post motor response varied along the dorsoventral axis of the SC. On more superficial channels, the post motor response occurs later and is more reliably detected. In intermediate layers, the response occurs closer to the motor burst and is less reliably detected. This result implies that the post motor burst originates in visuomotor layers and then propagates along the dorsoventral axis. As this response does not originate in more visual layers, it likely does not originate from the visual cortex or the retina. In addition, the presence of a visual target may not necessarily be a requirement for the detection of a post motor response, further suggesting the role of non-sensory processes. Subsequent analyses will assess whether saccade kinematics impact the likelihood of detecting a second response following the motor burst.

Disclosures: E. Ayar: None. **C. Bourrelly:** None. **N.J. Gandhi:** None.

Poster

PSTR071: Sensorimotor Transformation: Neuroprocessing

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Program #/Poster #: PSTR071.25/D50

Topic: D.07. Visual Sensory-Motor Processing

Support: R01EY024831

Title: Visual Receptive Fields of Monkey Superior Colliculus Neurons in Response to Moving Targets

Authors: *F. YANG, N. J. GANDHI;
Bioengineering, Univ. of Pittsburgh, Pittsburgh, PA

Abstract: The superior colliculus (SC) is a subcortical structure essential for converting visual inputs into motor commands for eye movement generation. The spatial topography along its rostrocaudal and mediolateral dimensions have been well characterized for individual neurons in response to stationary targets. Each neuron fires more vigorously in response to a preferred target location (visual burst), while discharges significantly less to targets away from this location. This relationship can be illustrated by plotting the firing rate as a function of the target eccentricity, commonly referred to as a receptive field (RF). Illustrating RF of a SC neuron in response to a moving target remains a challenge, leaving us with an incomplete understanding of the RF of SC neurons to moving stimuli. Our task involves monkeys intercepting moving targets at various speeds or saccade to a stationary target, each presented along the horizontal meridian regardless of the optimal responses of individual cells. This setup allows us to study not only individual neurons but also to gain insight into pseudo-population activity. Here, at a single-unit level, we aim to better characterize the RF for moving targets and compare them with the RFs for stationary targets. Likely due to the presence of inhibition from neighboring neurons following the onset of a moving target and variations in RF sizes across different locations within the SC, we anticipate observing changes in moving target RF. For a given neuron, the RF made by plotting the earliest visual burst as a function of the initial location of the moving target is like the conventional RF (i.e., from the stationary target). To better understand how visual RFs are modulated during target motion, we plotted the neural activity as a function of the positions spanned by a target within a trial, while incorporating an afferent delay. Our findings indicate that target speed, motion direction, and neuron location significantly influence the RFs of SC neurons. Thus, the RFs for motion are different from conventional RFs. A burst is often absent when target motion starts outside the conventional RF. The visual activity gradually increases shortly after the moving target enters the RF but does not exceed the conventional RF. Relative to the optimal stationary target position, the moving target position producing the maximal visual response was generally shifted and dependent on motion direction. Noticeably, the most pronounced changes in the RFs were observed in caudal SC neurons. In conclusion, we observed the moving target RF starts the same as for stationary stimulus but then shifts and attenuates its spiking activity depending on the target motion.

Disclosures: F. Yang: None. **N.J. Gandhi:** None.

Poster

PSTR072: Motor Planning and Flexible Execution in Health and Disease

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR072.01/D51

Topic: E.04. Voluntary Movements

Support: F31DC020648

Title: Cortical dopaminergic signaling mediates planning of directional movements

Authors: *J. CHEN[1,2], A. FONTANINI[1,2];
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Abstract: The anterior-lateral motor cortex (ALM) has been extensively studied as a model for understanding the cortical mechanisms for planning directional movements. ALM neurons show characteristic patterns of preparatory activity that predict whether the mouse will produce a left- or right-directed lick. While the neural mechanisms underlying ALM dynamics and their links to behavior are beginning to be elucidated, the sources of such directional activity remain unclear. Here, we examined the role of ALM dopaminergic circuits in mice performing a task requiring directional licking. In this task, mice must use two taste cues to guide different licking actions (lick left vs lick right) after a delay period. Fiber photometry recordings using dopamine (DA) fluorescence sensor, GRAB-DA2h, revealed cortical DA signals tracking the preparation and execution of licking and represented a bias for contralateral lick decisions. We next examined if the activity of neurons expressing DA D1 receptors (D1R+ neurons) within ALM were consistent with local dopamine release dynamics. Cell-type specific two-photon calcium imaging in ALM was performed using transgenic D1R reporter mice to simultaneously record and identify populations of D1R+ neurons and non-D1R expressing neurons (D1R-). Individual D1R+ and D1R- neurons exhibited task-specific responses during each of the behavioral epochs in the task. We found that D1R+ neurons exhibited earlier preparatory responses with faster ramping compared to D1R- neurons during lick preparation. Furthermore, D1R+ neurons encoded a stronger bias for contralateral licking that persisted during delay and choice periods of the task at the single-neuron and population levels. Unilateral optogenetic inhibition of the D1R+ population during the delay period of the task disrupted contralateral lick performance, suggesting activity of D1R+ neurons is required in the planning of contralateral licks. Conversely, unilateral optogenetic stimulation of DA afferents in ALM during the delay period disrupted ipsilateral lick performance, consistent with the patterns of DA release and D1R+ neural activity. Altogether, these results show that cortical DA modulation is required in the motor preparation of lateralized movements.

Disclosures: J. Chen: None. **A. Fontanini:** None.

Poster

PSTR072: Motor Planning and Flexible Execution in Health and Disease

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR072.02/D52

Topic: E.04. Voluntary Movements

Support: NSF NCS DRL-2123911

Title: Encoding of reward in the motor cortex depends on task context

Authors: *M. ZAMBRE[1], S. SNYDER[2], E. R. OBY[1], A. L. SMOULDER[3], S. M. CHASE[4], H. SCHWERDT[5], A. P. BATISTA[5];
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Abstract: Expected reward impacts the execution of skilled movements. Neural signals of anticipated reward magnitude are pervasive in the brain, including in the motor cortex, where they can affect the quality of movement signals (Smoulder, et. al. 2023). Here we sought a fuller characterization of reward signals in the motor cortex by studying its encoding in a different task where motor cortex signals control a cursor without eliciting physical movement. We report that reward information was represented differently in the motor cortex when animals performed these different tasks.
We implanted two "Utah" multielectrode arrays (Blackrock Neurotech, Inc.) in dorsal premotor cortex (PMd) and primary motor cortex (M1) of a Rhesus monkey. To compare the encoding of reward across tasks in these areas, we instructed a monkey to perform two different tasks in the same session. One task was a delayed center-out reaching task in which the animal reached to one of eight targets. The other task was a center-out brain-computer interface (BCI) task in which the monkey controlled the velocity of a cursor on the screen by volitionally modulating its neural activity in real-time. The animal could earn one of three reward amounts on each trial. The reward amount was cued at the beginning of each trial by the color of the target and the same color cues were used in both tasks. To probe how reward expectation modulated neural activity, we used principal component analysis to identify a dimension in the neural population state space that captured the most reward-related variance. We identified this dimension, termed the "reward axis", individually for each task condition.
The individual reward axes found in the reaching and BCI tasks captured most of the reward variance within each task (72+-12% in reach; 90+-6% in BCI). We projected neural activity from the BCI task onto the reward axis of the reaching task and saw that the reach reward axis captured very little reward variance from the BCI task (17+-11%). The inverse was also true: the reward axis in the BCI task did not capture much of the reward variance in the reaching task (14+-8%). The principal angles between the reward axes in the reaching and BCI tasks ranged from 65 to 90 degrees, and in comparison randomly drawn dimensions were distributed from 61 to 89 degrees. Hence, reach and BCI reward axes were not closely aligned within the high-dimensional neural space. Altogether, these results suggest that although reward information is present in the motor cortex in different types of tasks, its representation is not fixed.

Disclosures: M. Zambre: None. **S. Snyder:** None. **E.R. Oby:** None. **A.L. Smoulder:** None. **S.M. Chase:** None. **H. Schwerdt:** None. **A.P. Batista:** None.

Poster

PSTR072: Motor Planning and Flexible Execution in Health and Disease

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR072.03/D53

Topic: E.04. Voluntary Movements

Support: Achievement Rewards for College Scientists, Pittsburgh Chapter Award
Bradford and Diane Smith Graduate Fellowship in Engineering
NSF Grant DGE1745016
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NIH Grant CRCNS R01NS105318
NIH Grant R01NS129584
NIH Grant R01NS129098

Title: Reward improves movement vigor through multiple motor cortical mechanisms

Authors: *A. L. SMOULDER[1], P. J. MARINO[2], E. R. OBY[3], S. E. SNYDER[4], A. P. BATISTA[2], S. M. CHASE[5];
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Abstract: When greater rewards are at stake, animals tend to quicken the speed and latency of movements without sacrificing their accuracy - that is, they act with enhanced vigor. How does the brain translate changes in motivation into increased movement vigor? We trained three rhesus monkeys to perform a delayed reaching task in which we cued the reward that would be given upon trial success. In population recordings from primary motor cortex (M1) and dorsal premotor cortex (PMd) we identified multiple neural correlates of motor vigor affected by reward. First, we found that reward drove movement preparatory neural activity along a monotonic "reward axis" irrespective of upcoming movement direction, and that for any given reward, the projection of neural activity onto the reward axis correlated with the vigor of the movement. Also, the size of the anticipated reward influenced reach direction-dependent patterns of neural activity in a manner correlated with vigor: greater reward made reach directions conditions more separable in neural activity, and greater separability correlated with greater vigor. Second, we found that reward facilitated the transition from preparation to movement. We calculated a neural changepoint time for each trial and saw that it decreased with greater reward. We also found that the neural speed (time derivative of firing rates) preceding movement onset was faster for greater rewards. Within each reward condition, both of these metrics were correlated with the animals' movement vigor. Third, we saw that reward altered neural trajectories. Greater reward appeared to "stretch" trajectories even though their shape and timecourse were conserved. These changes are similar to prior work where animals reached at greater speeds based on a cue (Churchland et al., 2012). This stretching implies gain-like effects of reward on motor cortical activity, hinting at potential underlying mechanisms of the effects we observed (e.g., neuromodulatory drive). Overall, we find reward affects multiple aspects of motor cortical activity that relate with movement vigor. Future work will seek to model the effects of reward to study the mechanisms driving this diversity of neural effects.

Disclosures: A.L. Smoulder: None. **P.J. Marino:** None. **E.R. Oby:** None. **S.E. Snyder:** None. **A.P. Batista:** None. **S.M. Chase:** None.

Poster

PSTR072: Motor Planning and Flexible Execution in Health and Disease

Location: MCP Hall A

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Program #/Poster #: PSTR072.04/D54

Topic: E.04. Voluntary Movements

Support: NSF NCS DRL
NIH NINDS T32
NSF GFRP
NIH NIBIB T32

Title: Reward, perceptual difficulty, and motor difficulty drive distinct changes in cortical activity and sensorimotor behavior

Authors: *A. CHANDRASEKARAN[1], M. MCDONNELL[2], C. KI[3], A. L. SMOULDER[4], A. P. BATISTA[5], B. M. YU[6], S. M. CHASE[3], M. A. SMITH[7];
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Abstract: Our behavior depends on both external factors, such as sensory stimuli, and internal factors, like motivation. We may expend more effort when the potential payoff is greater. We may also expend more effort when the task is more demanding. Do different contexts, like reward and difficulty, engage a common motivational drive? To investigate, we trained three monkeys on a novel sensorimotor task where they had to detect a difficult perceptual change and report it with a fast and accurate reach to a peripheral target. We varied the context of the task in the following three ways. First, we varied the reward offered on each trial. We also manipulated motor difficulty by varying the size of the reach target. Finally, we manipulated perceptual difficulty using blocks of hard- or easy-to-detect changes. These contextual changes could modulate the animal's performance by either leading to shifts in their perceptual sensitivity (ability to detect changes), impulsivity (tendency to respond), and/or motor accuracy. We found that perceptual sensitivity increased both when larger rewards were offered and when the difficulty of the perceptual task was greater. In contrast, motor accuracy and impulsivity were differently impacted by reward and difficulty: First, motor accuracy improved for larger rewards, but it was unaffected by the perceptual difficulty context. Second, monkeys were more impulsive when the perceptual difficulty was greater, but less impulsive for larger rewards and greater motor difficulty. How do contextual changes impact different brain regions? If reward and difficulty engage a common drive, we might expect that they have overlapping neural correlates. We simultaneously recorded from populations of neurons in four relevant cortical areas: visual

cortex (area V4), prefrontal cortex (area 8Ar), premotor cortex, and primary motor cortex. We found that activity in each brain region was modulated by reward, perceptual difficulty, and motor difficulty. Further, we performed a cross-context decoding analysis, where we identified a dimension that could decode a given context and tested how well it performed at decoding a different context. Our analysis revealed that different contexts drove changes along distinct context-specific dimensions of neural activity. In summary, our results suggest that reward, perceptual difficulty, and motor difficulty drive distinct patterns of neural activity and have dissociable effects on sensorimotor behavior. Our work provides insight into how the brain flexibly guides behavior in response to a changing environment.

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Poster

PSTR072: Motor Planning and Flexible Execution in Health and Disease

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Program #/Poster #: PSTR072.05/D55

Topic: E.04. Voluntary Movements

Support: NSF NCS DRL
NIH NINDS T32
NIH NIBIB T32
NSF GFRP

Title: Distinct sensory and motor components of choking under pressure

Authors: *M. MCDONNELL[1,2], A. CHANDRASEKARAN[4], C. KI[2], A. L. SMOULDER[3], B. M. YU[1], A. P. BATISTA[5], S. M. CHASE[2], M. A. SMITH[3,2];
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Abstract: In both humans and animals, performance tends to improve when increased incentives are at stake. However, there can be a paradoxical decrease in performance when rare and large jackpot rewards are offered, which is known as “choking under pressure”. We recently reported that monkeys choke under pressure when performing a difficult motor task. It is plausible that high stakes may influence many factors beyond the motor system, including sensory processes and internal states such as impulsivity. Here, we asked whether various aspects of sensorimotor behavior are also susceptible to choking under pressure. To study this, we trained rhesus monkeys to perform a challenging visual change detection task, where they reported the change with a fast and accurate reach to a peripheral target. Because both sensory and motor processes were required to be successful, the task allowed us to separately study the effects of reward on each. At the start of each trial, a reward cue was presented which indicated the volume of juice that the animal would receive upon successfully completing the trial. This was either a small

(1x), medium (3x), or large (8x) amount, with equal probability (~31.6% of trials). On rare occasions (5% of trials), we offered exceptionally large "jackpot" rewards (40x). We found that monkeys exhibited a performance decrement on trials where a jackpot reward was offered, i.e., they choked under pressure. In dissecting precisely how their behavior changed with reward, we noted the following three effects. In accordance with our previous study, we observed that animals decreased their motor accuracy for their reaches to the target on jackpot trials compared to large reward trials. Additionally, animals also became more impulsive and tended to initiate movement before the go cue during jackpot trials more often than large reward trials. Finally, animals exhibited decreased perceptual detection accuracy during jackpot trials compared to large reward trials. In sum, we observed three distinct adverse behavioral effects due to jackpot rewards across both sensory and motor systems. Given our rich task, we next seek to understand potential neural bases for the behavioral effects we observed. To this end, we simultaneously recorded from relevant regions across visual, motor, and prefrontal cortices, which will allow us to dissociate the neural correlates of both perceptual and motor components of choking under pressure.

Disclosures: M. McDonnell: None. **A. Chandrasekaran:** None. **C. Ki:** None. **A.L. Smoulder:** None. **B.M. Yu:** None. **A.P. Batista:** None. **S.M. Chase:** None. **M.A. Smith:** None.

Poster

PSTR072: Motor Planning and Flexible Execution in Health and Disease

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Topic: E.04. Voluntary Movements

Support: NSF-M3X-1825942
NIH-R37-HD087089

Title: The Role of Preparation in the Control of Complex Objects

Authors: *R. LOKESH[1], M. EDRAKI[1], A. KROTOV[2], D. STERNAD[3];
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Abstract: Humans display remarkable ease tying shoelaces or folding a piece of cloth. Manipulating such deformable objects presents challenges by their mathematically infinite number of degrees of freedom and their underactuation, i.e., they cannot be controlled directly. Our previous work on the rhythmic manipulation of a whip has shown that humans prepare the whip for striking even when embedded in the continuous dynamic action. Building upon this work, we investigated the role of preparatory actions by studying humans striking a target with a whip. To reduce the dimensionality of the problem, we constructed a whip by connecting 25 light-weight 3D-printed links constrained to move in two dimensions. In the human experiment,

subjects held the handle of the whip and started with the whip fully extended vertically by their side. They were instructed to strike a target located in front of them with the tip of the whip. Two distinct strategies were observed: i) “strike only” - only a single forward movement of the hand and whip; ii) “prepare and strike” - a backward preparatory movement followed by the forward striking movement of the hand and whip. The two strategies were evaluated by simulating a mathematical model of the simplified whip using a human-inspired controller. The dynamics of the whip was modeled as a set of differential equations derived with the Euler-Lagrange formalism. The controller for the discrete point-to-point movements of the handle employed minimum-jerk trajectories in the position space. The “strike only” strategy was generated using a single minimum jerk trajectory, while the “prepare and strike” strategy was generated by connecting two minimum jerk trajectories. The parameters of the minimum jerk trajectories were optimized using a grid search to minimize the distance between the tip of the whip and the target. A hit was defined when the whip's tip came within a predefined distance from the target. The optimization procedure was repeated for different target locations using both strategies. Results indicated that when preparing the action, the whip achieved a greater reach and could hit more target locations compared to the “strike only” strategy. It is likely that the preparatory movement imparted energy into the whip to increase the reach of the tip of the whip. Preparing the energy of the whip is analogous to a golfer preloading their back muscles to generate more power during the swing. Moreover, these preparatory movements could create initial whip configuration that simplified the subsequent action. These insights into the benefits of preparation during manipulation of deformable objects can inform the development of robotic controllers.

Disclosures: R. Lokesh: None. **M. Edraki:** None. **A. Krotov:** None. **D. Sternad:** None.

Poster

PSTR072: Motor Planning and Flexible Execution in Health and Disease

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR072.07/D57

Topic: E.04. Voluntary Movements

Title: Intuitive and non-intuitive motor skill learning of a racing video game

Authors: *Z. RILEY[1], J. FEIGH[1], B. J. POSTON[2], D. GREENWELL[1];
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Abstract: Motor skill learning requires repetition of a skill combined with feedback of the skills performance. Video games provide the perfect model for studying motor skill learning as they use consistent gameplay features, along with a progression that is based on your success. This study sought to examine what happens when you flip gameplay controls (e.g. joysticks) to non-intuitive controls. 22 subjects participated in the study where they played an open-source racing game (SuperTuxKart), completing three blocks of 5 laps each on an enclosed game course. For the first and last blocks (intuitive control, I1, I2), the left joystick controlled left and right

turning, while the right joystick controlled forward and backward motion. For the second block (non-intuitive control, N1), the left joystick controlled forward and backward motion, while the right joystick controlled left and right steering. Mean lap times and the number of times hitting the wall of the course were recorded and analyzed with one-way ANOVAs. The mean lap times were significantly different between I1 (61.3±12.1s) and N1 (110.3±54.9s, $P<0.001$). Similarly, N1 lap times were different from I2 (60.2±15.0s, $P<0.001$). I1 and I2 were not significantly different ($P=0.91$). The same pattern emerged for the number of times hitting the wall, where N1 (18.9±10.3) was significantly higher than both I1 (7.9±3.9, $P<0.001$) and I2 (6.9±3.3, $P<0.001$). The number of times hitting the wall was not different between I1 and I2 ($P=0.63$). As expected, traditional gameplay mode was more successful than when the controls were randomly flipped. Furthermore, there were no after-effects of switching back to normal controls. Additional analysis of within-block lap times showed that subjects significantly improved from lap 1 to lap 5 within the I1 and N2 blocks. However, when subjects repeated regular controls (I2), they did not improve lap times any further, suggesting a ceiling to learning within a single session. No matter an individual's level of gaming experience, the traditional controls of a joystick (forward/back, left/right) are commonly known. We can expect that with additional trial blocks of the non-intuitive controls that subjects would perform closer to what is observed in I1 and I2. However, the learning that occurs will not just be novel, but will also have to supplant the long-standing motor programs that have developed to control a normal joystick.

Disclosures: Z. Riley: None. **J. Feigh:** None. **B.J. Poston:** None. **D. Greenwell:** None.

Poster

PSTR072: Motor Planning and Flexible Execution in Health and Disease

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR072.08/D58

Topic: E.04. Voluntary Movements

Support: Velux Stiftung Pr.1283

Title: Smartphone behavior is supported by flexible neural processing

Authors: *W. WAN[1,2], A. GHOSH[1];
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Abstract: In the real world, the human brain produces a broad array of behaviors. The complex train of behavioral events may be supported by adaptive neural processes resulting in distinct neural population activity from one behavior to the next. Here we recorded neural population activity by using scalp electrodes (EEG) while people (N = 64) were immersed in smartphone touchscreen interactions. We separated the diverse smartphone behaviors according to the next interval dynamics, with the intervals spanning from hundreds of milliseconds to several seconds. The smartphone touchscreen event related potentials revealed an adaptive chain of neural events that varied according to the behavioral state. Furthermore, we explored the links between this

variation and prior experience in terms of the smartphone behavioral dynamics expressed in the weeks before the neural recordings. We propose that the flexible nature of neural processing enables the brain to rapidly meet the processing demands imposed by the real world - from sustaining the same behavior to switching from one behavior to the next.

Disclosures: W. Wan: None. **A. Ghosh:** F. Consulting Fees (e.g., advisory boards); A.G. is scientific advisor of Axite. Axite provides a telemonitoring solution for cognitive functions by linking consumer-grade EEG and smartphone behavior.

Poster

PSTR072: Motor Planning and Flexible Execution in Health and Disease

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR072.09/D59

Topic: E.04. Voluntary Movements

Support: Louisiana Board of Regent Research Competitiveness Program (award number: AWD-004500)

Title: The Neuromodulatory Effects of Personalized HD-tACS over Left SMA on Speech and Limb Motor Planning

Authors: *F. TABARI[1], J. I. BERGER[2], K. JOHARI[1];
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Abstract: The supplementary motor area (SMA) plays a crucially important role in planning and execution of speech and limb movement. SMA demonstrates abnormal beta activity (13-30 Hz) during speech and limb tasks in neurological conditions such as Parkinson's disease. Noninvasive neurostimulation protocols have shown some improvement in speech and limb deficits. However, these improvements are somewhat limited due to significant variability between subjects, highlighting the importance of personalized protocols. The present study examined the application of personalized beta-band high-definition transcranial alternating current stimulation (HD-tACS) over the left SMA prior to a speech and limb movement task. Twenty-two neurotypical adults participated in four stimulation conditions: sham, untuned (transcranial random noise stimulation: tRNS), HD-tACS tuned to each individual's maximal frequency of SMA beta (between 13-30 Hz) activity during the sham speech condition (tuned-to-speech), and during the sham limb movement condition (tuned-to-limb). For untuned conditions, random noise stimulation with a fixed frequency but unpredictable waveform was administered. EEG data were collected following stimulation while participants vocalized speech sounds or pressed buttons for limb movement. Analyses revealed prominent alpha (9-12 Hz) and low beta (13-15 Hz) activity over prefrontal and frontocentral electrodes during speech and limb tasks, regardless of stimulation type. Compared to the sham and untuned conditions, HD-tACS tuned-to-speech significantly modulated pre-movement alpha and beta activity for both speech and

limb movement. Consistent with the neural findings, behavioral analyses revealed that the tuned-to-speech condition significantly influenced reaction times in both speech and limb movement responses. For the first time, we showed that personalized beta HD-tACS over the left SMA yielded stronger modulations in endogenous neural oscillations associated with speech and limb motor planning compared to sham and tRNS. Moreover, results revealed that beta HD-tACS tuned-to-speech over left SMA has greater modulatory effects on pre-movement alpha and beta oscillations compared to other stimulation conditions, suggesting its efficacy in facilitating complex speech processes as well as less demanding motor tasks (i.e. limb movement). These findings have significant implications for neurological conditions such as Parkinson's disease, which are characterized by deficits in speech production and limb motor control.

Disclosures: F. Tabari: None. **J.I. Berger:** None. **K. Johari:** None.

Poster

PSTR072: Motor Planning and Flexible Execution in Health and Disease

Location: MCP Hall A

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Program #/Poster #: PSTR072.10/D60

Topic: E.04. Voluntary Movements

Support: NIH Grant R01 NS058487
NIH Grant T32 NS082168

Title: Force control deficits in Rapid Eye Movement Behavior Disorder and Parkinson's Disease

Authors: *E. R. TOBIN[1], S. DELMAS[1], J. HUBBARD[1], J. J. KIM[1], B. YACOUBI[1], R. B. BERRY[2], M. S. JAFFEE[3], E. A. CHRISTOU[1,4], D. E. VAILLANCOURT[1,3,4];
[1]Applied Physiol. and Kinesiology, [2]Medicine, Div. of Pulmonary, Critical Care and Sleep, [3]Fixel Inst. for Neurolog. Dis., [4]Biomed. Engin., Univ. of Florida, Gainesville, FL

Abstract: It is established that one of the best predictors of a future diagnosis of Parkinson's disease (PD) is a current diagnosis of Rapid Eye Movement Behavior Disorder (RBD). About 50-60% of individuals with RBD will convert to PD with a median conversion rate of 10-14 years. A key question in RBD is what motor deficits are observed in these patients before receiving another neurological diagnosis? Our goal is to determine if force control deficits are unique to PD and RBD, or if there are overlapping deficits of variability, error, rate of force production, and rate of force relaxation. Here we investigate 25 controls, 24 RBD, and 38 PD, for the finger force study and 24 controls, 24 RBD, and 37 PD for the ankle force study. Each study contained a maximal voluntary contraction (MVC) task, constant force task, and goal-directed force task. ANCOVA was used to examine each task, separately, covarying for age and sex. In the constant force task, we found that PD had a significantly higher coefficient of variation of force and a higher root mean square error of force ($p's<0.05$) compared with controls in the finger study and ankle force study, respectively. In the goal-directed task, we found that PD had significantly longer times to peak force and longer relaxation times ($p's<0.01$) compared

with RBD and controls during the finger force study. In addition, PD had a significantly greater relative error of time (p's<0.05) during both the finger and ankle force study. Controls had the most FDI muscle activity (p's<0.05) compared with RBD and PD during the goal-directed force task. These findings provide evidence that individuals with PD have greater variability and error compared with controls. In addition, individuals with PD have deficits in modulating time compared with controls and RBD. We found no evidence that RBD patients have force control deficits compared with controls.

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Poster

PSTR072: Motor Planning and Flexible Execution in Health and Disease

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR072.11/E1

Topic: E.04. Voluntary Movements

Support: Newcastle Neuroscience Fund

Title: A novel method to quantify motor planning deficits in Parkinson's disease

Authors: *N. J. MAFFITT[1], S. BANERJEE[2], S. SARKAR[2], S. MAJUMDAR[2], S. CHOUDHURY[2], H. KUMAR[3], D. S. SOTEROPOULOS[1], A. KRASKOV[1];
[1]Biosci. Inst., Newcastle Univ., Newcastle Upon Tyne, United Kingdom; [2]Inst. of Neurosciences Kolkata, Kolkata, India; [3]Inst. of Neurosciences, Kolkata, Kolkata.

Abstract: In addition to presenting with motor disorders, patients with Parkinson's disease (PD) may also exhibit behaviours of cognitive dysfunction. Although some studies have investigated motor prediction in tasks of working memory and action imitation, how motor planning performs in the context of ambiguity, and how this relates to the severity of motor symptoms, remains unclear. To investigate and quantify potential deficits in motor planning in PD, we recruited 32 patients (19 males; 60 ± 11 years; UPDRS (part 3) motor score 25.3 ± 11.6) and 15 healthy controls (7 males; 52 ± 10 years) to perform a novel precision-grip task. Subjects were presented with a triangular prism block that afforded only two possible grasp configurations, distinguished by subject wrist orientation. The grasp chosen depended on the orientation of the target object, with each target orientation yielding either one consistent choice of grasp (i.e. certain), or switching between both grasps (i.e. ambiguous). The range of ambiguous target orientations reflects the degree of uncertainty in motor planning, quantified by the half-width of a sigmoid curve (HW) fitted for grasp choice across all target orientations. Whilst healthy controls had a smaller HW (6.4° ± 0.7), indicative of a sharper transition from one wrist posture to another, PD patients typically had a significantly shallower transition (9.8° ± 0.6; P < 0.005) suggesting greater motor planning uncertainty. Interestingly, performance did not correlate with UPDRS

(part 3) score. These results suggest that the motor planning deficits revealed by our task may arise from separate pathological sequences to that of motor execution dysfunction in patients with PD.

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Poster

PSTR072: Motor Planning and Flexible Execution in Health and Disease

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Program #/Poster #: PSTR072.12/E2

Topic: E.04. Voluntary Movements

Support: NIH Grant R21NS119849

Title: The Effect of Deep Brain Stimulation on Motor Learning in Essential Tremor

Authors: *J. J. KIM[1], S. DELMAS[1], Y. CHOI[1], J. C. HUBBARD[1], M. S. OKUN[2], B. YACOUBI KEYHANI[1], E. A. CHRISTOU[1];
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Abstract: Deep brain stimulation of the ventralis intermedius nucleus of the thalamus ($_{VIM}$DBS) has been an effective treatment for suppressing upper limb tremor in individuals with essential tremor (ET). Little is known whether $_{VIM}$DBS affects motor learning. Here, we aimed to characterize the effects of $_{VIM}$DBS on consolidation, an important motor learning component that quantifies the ability of the participant to retain the practiced task on a different day. We tested 16 ET participants undergoing $_{VIM}$DBS (65.2 ± 6.5 years; 6 F), who performed a goal-directed ankle dorsiflexion task in two consecutive days. Half of the ET performed the task with DBS ON (Day 1) followed with DBS OFF (Day 2) and this group was termed DBS-ON1st. The rest followed the opposite pattern of testing order and this group was termed DBS-OFF1st. The order of $_{VIM}$DBS activation was counterbalanced among the 16 ET participants. They were instructed to exert 50 trials of goal-directed ankle dorsiflexion on the most tremor-affected side, aiming to match a spatiotemporal target of 9 degrees in 180 ms. We selected this task because it is not influenced by tremor. We quantified endpoint error and endpoint inconsistency (spatial, temporal, and overall). In addition, we quantified movement unsteadiness as the change in acceleration (*a*), calculated by the first derivative of *a* (d*a*/dt; *Jerk*). We compared consolidation (performance of the first block on Day 2, relative to the last block on Day 1 - practice) of endpoint error, endpoint inconsistency, and *Jerk* magnitude for the DBS-ON1st and DBS-OFF1st groups. The difference of spatial accuracy between the two groups on Day 2 approached significance ($p=0.13$, $d=2.2$), suggesting that consolidation was better for the DBS-ON1st group. Consolidation of movement smoothness was significantly better for the DBS-ON1st group. This was shown with maintenance of the *Jerk* magnitude from practice for the DBS-ON1st group and

a significant increase in *Jerk* magnitude for the DBS-OFF1st group. This result suggests that neurostimulation ($_{VIM}$DBS) improves consolidation of goal-directed movements by retaining *Jerk* control. These findings present a compelling new insight into the effect of $_{VIM}$DBS on motor learning in ET, highlighting the importance of controlling *Jerk* magnitude toward controlling endpoint accuracy.

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Poster

PSTR072: Motor Planning and Flexible Execution in Health and Disease

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR072.13/E3

Topic: E.04. Voluntary Movements

Support: NRT (2152260)

Title: The quantification of pathological tremor across movement disorders and its impact on motion-dependent learning

Authors: *K. FORAY[1], W. ZHOU[2], J. FITZGERALD[3], W. M. JOINER[4];
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Abstract: The quantification of pathological tremor across movement disorders and its impact on motion-dependent motor learning
AuthorsKatherine Foray*, Weiwei Zhou, Justin Fitzgerald, Pierre Gianferrera, and Wilsaan M. Joiner; Department of Neurobiology, Physiology, and Behavior, University of California Davis, Davis, CA
DisclosuresKatherine Foray: None. **Weiwei Zhou:** None. Justin Fitzgerald: None Pierre Gianferrera: None **Wilsaan M. Joiner**: None
AbstractPatients with either Parkinson's Disease (PD) or Essential Tremor (ET) often experience pathological tremor—involuntary, rhythmical movements of the body that interfere with daily living. This rapid, rhythmic contraction and relaxation of muscles is associated with impaired motor control and learning. While such impairments are well-documented, the specific characteristics of tremor, such as magnitude, are not well quantified making it difficult to definitively connect these characteristics of tremor severity with deficits in motor learning. Additionally, it is unclear which underlying mechanisms pathological tremor impacts to subsequently impair motor learning and control. As a first step, we trained PD and ET patients, and age-matched neurologically intact control subjects to use a robotic manipulandum to move a screen cursor between two targets. Following a baseline period, reaching arm movements were perturbed by a velocity-dependent force-field during training. On these force-field trials, the

robot perturbed the hand motion with forces that were proportional in magnitude and perpendicular in direction to the velocity of hand motion. We used error clamp trials to assess the feedforward adaptive changes in motor output. Motor compensation to the force-field perturbation was quantified on these trials with an adaptation coefficient: the linear regression of the measured lateral force profile on each error clamp trial onto the ideal force profile required for full force-field compensation on that trial. Previous studies have shown that learning to compensate for the movement perturbation is the result of two concurrent learning processes: one process that responds quickly to movement errors, but has poor retention and another that responds slowly to movement errors, but retains the learning well from one trial to the next. We hypothesized that patients with greater magnitudes of tremor would have lower learning rates, specifically due to an impaired fast learning process. Preliminary results suggest that, while there are no differences in learning rate across groups, patients with ET have impaired better long-term decay , which may be due to deficits in specific learning mechanisms.

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Poster

PSTR072: Motor Planning and Flexible Execution in Health and Disease

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Program #/Poster #: PSTR072.14/E4

Topic: E.04. Voluntary Movements

Support: NIH Grant UH3NS100544

Title: Deep brain stimulation modulates cortico-basal ganglia movement-related synchronization in Parkinson's Disease

Authors: *D. LAWRENCE[1], P. STARR[2], S. LITTLE[3];
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Abstract: The cortico-basal ganglia motor network plays a crucial role in integrating dynamic processes involved in movement initiation and execution. However, the impact of deep brain stimulation (DBS) on this network remains unclear. In this study, we collected intracranial signals from 15 patients (27 hemispheres) with Parkinson's Disease (PD) during unsupervised daily activities within naturalistic settings while simultaneously measuring forearm speeds using wrist-worn accelerometers. Neural data was streamed from the subthalamic nucleus (STN) or the globus pallidus internus (GPi), as well as the somatosensory (S1) and motor (M1) cortices, during DBS. We observed that mobile states had lower cortical and subcortical beta power and higher broadband gamma power than stationary states. We also developed classifiers (AUC > 0.8) and regressors (r statistic > 0.6) to differentiate between stationary and mobile states and forecast forearm speed during naturalistic motion. The models trained on data from all sites showed the highest performance ($p < 0.05$), followed by models trained only on signals from the

S1 ($p < 0.01$). Permutation feature importance analysis revealed that cortical high beta power was the best predictor of movement, and S1 gamma power was more influential than M1 gamma power ($p < 0.03$). These findings suggest that different sites within the cortico-basal ganglia motor network generate signals with complementary information that can be leveraged to enhance movement prediction. Additionally, we explored the effects of stimulation amplitude on movement-related beta desynchronization (MRD) and gamma synchronization (MRS). We found that in the STN/GPi, beta MRD ($p < 0.0001$) and gamma MRS ($p < 0.001$) were negatively correlated with stimulation amplitude. This indicated that patients could achieve the same movement speed at higher stimulation levels with reduced subcortical beta MRD and gamma MRS. Based on the gating theory of basal ganglia function, stimulating the STN or GPi is hypothesized to lower the barrier to movement execution. Our work suggests this might be associated with decreased subcortical beta MRD and gamma MRS. We also found that models trained on subcortical signals showed reduced performance with increased stimulation ($p < 0.001$). In contrast, changes in DBS amplitudes did not significantly affect cortical biomarkers and their respective predictive models. These findings provide insights into the potential mechanism by which DBS alleviates hypokinetic symptoms in PD and highlight the utility of machine learning models for predicting naturalistic movement during DBS.

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Poster

PSTR072: Motor Planning and Flexible Execution in Health and Disease

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Program #/Poster #: PSTR072.15/E5

Topic: E.04. Voluntary Movements

Support: NRCRSP-EX23010

Title: Reliability and Validity of Korean Version of Fall Efficacy Scale for Stroke and Brain Injury Patients

Authors: *S. HWANG[1,2], S. KIM[3];
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Abstract: Running title 1: Reliability and Validity of Korean Version of Fall Efficacy Scale for Stroke and Brain Injury Patients
Running title 2: Development and Validity of Modified Fall Efficacy Scale for Stroke and Brain Injury Patients

Sujin Hwang, P.T., Ph.D.[12]†, Sujin Kim, P.T., Ph.D.[3] [1]Department of Physical Therapy, Division of Health Science, Baekseok University[2]DGraduate School, Baekseok University[3]Department of Physical Therapy, College of Medical Science, Jeonju University
Objective: This study was to evaluate the reliability and validity of Korean version of fall efficacy scale for stroke and brain injury patients and to develop modified fall efficacy scale for stroke and brain injury patients. **Methods:** This study involved seventy-nine stroke or brain injury patients from five rehabilitation facilities of five regions of south Korea. This study examined three different versions of Korean version of fall efficacy scale (K-FES) for stroke patients twice 3 days apart. We also measured four outcome measures including Berg balance scale (BBS), modified Barthel index (MBI), functional ambulation classification (FAC), mini-mental state examination (MMSE), and motor assessment scale (MAS) to evaluate the validity of three different versions of K-FES. **Results:** As a result of the confirmatory factor analysis of the K-FES, the Kaiser-Meyer-Olkin measure was 0.865 for the original version, 0.890 for the second version, and 0.888 for the third version. Bartlett's test of sphericity yielded an approximate chi-square of 441.242 with 45 degrees of freedom (p=.000) for the original version, 498.521 with 45 degrees of freedom (p=.000) for the second version, and 502.088 with 45 degrees of freedom (p=.000) for the third version. Cronbach's alpha values were 0.908 for the original version, 0.921 for the second version, and 0.925 for the third version. All three versions of the K-FES showed a negative correlation with both the Berg Balance Scale (BBS) and the Modified Barthel Index (MBI). The intraclass correlation coefficients were 0.954 (F=21.682, p=.000) for the original version, 0.963 (F=26.706, p=.000) for the second version, and 0.993 (F=135.696, p=.000) for the third version. Additionally, the K-FES demonstrated negative correlations with the BBS, MBI, and MAS.**Conclusions:** All three versions of the FES demonstrated high structural validity, and internal consistency, as well as high test-retest reliability. They also exhibited medium criterion validity. Therefore, the FES can be recommended as an appropriate outcome measure for measuring fall efficacy in stroke and brain injury rehabilitation patients receiving treatment at rehabilitation facility.

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Poster

PSTR072: Motor Planning and Flexible Execution in Health and Disease

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Program #/Poster #: PSTR072.16/E6

Topic: E.04. Voluntary Movements

Title: Decoupling Force Variability and Force Unsteadiness: Evidence from Visual Feedback Manipulations

Authors: *V. SHANKAR, J. J. KIM, S. DELMAS, J. HUBBARD, R. J. MALIK, B. YACOUBI, E. A. CHRISTOU;
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Abstract: Recently, we challenged the use of the coefficient of variation of force (CVF) as an appropriate metric of force unsteadiness during the commonly used constant isometric force task. We argued that the CVF quantifies the deviation from the average force, whereas metrics of unsteadiness should quantify the smoothness of the force output. Force variability (CVF) is mostly influenced by low-frequency oscillations, whereas force unsteadiness is more influenced by higher-frequency oscillations. We proposed that "*yank*" - the first derivative of force - as an appropriate metric of force unsteadiness. Here, we manipulated the amount of visual feedback (low-gain (LG) vs. high-gain (HG) visual feedback) to determine its effects on force variability and force unsteadiness. We hypothesized that with HG visual feedback participants would reduce force variability (CVF) but increase force unsteadiness (*yank*), due to visuomotor corrections that reduce the power of low-frequency force oscillations but increase the power in higher-frequency force oscillations. Fifteen healthy young participants (20.1 ± 1.4 years; 5 M) performed a constant ankle dorsiflexion task for 30 seconds at 10% maximum voluntary contraction (MVC). The participants performed 3 trials each for LG (0.1º) and HG (2.0º) conditions. We quantified force variability as the CVF and force unsteadiness as the normalized root-mean-square of *yank* to the standard deviation of force (nYank). We decomposed the frequency structure of the force oscillations during LG and HG conditions with a power spectral density (PSD) analysis of the force from 0 - 2 Hz (0.1 Hz resolution). As expected, the force PSD was significantly different ($p<0.05$) for the LG and HG visual feedback conditions. Compared with LG visual feedback, when participants received HG visual feedback they reduced power from 0-0.5 Hz (60% from 85%) and increased power from 0.5-2 Hz (40% from 15%). Consistent with the greater power in force oscillations from 0-0.5 Hz, participants exhibited greater CVF during the LG condition than the HG condition ($p<0.05$). In contrast, participants exhibited greater nYank during the HG condition ($p<0.05$). The results demonstrate that HG visual feedback reduces force variability but increases force unsteadiness in young adults, due to differential effects on the frequency of force oscillations. These findings highlight that force variability and force unsteadiness are distinct concepts and advocate that these concepts should not be used interchangeably.

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Poster

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Topic: E.04. Voluntary Movements

Support: Canadian Institutes of Health Research (CIHR) rewarded to C.M.S.
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Title: Postural demand does not modulate the StartReact effect

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Abstract: While it is well known that corticospinal pathways are the primary contributor to voluntary movement, the role of the reticulospinal tract is less clear. One novel method to investigate reticulospinal contribution is the delivery of a startling acoustic stimulus (SAS) during a simple reaction time (RT) task, which elicits a startle reflex, and can also result in the early and involuntary release of a pre-planned movement. This "StartReact" phenomenon is thought to be mediated by reticular structures due to its strong correlation with the presence of a startle reflex and the magnitude of RT reduction has been used as a surrogate measure of reticulospinal contributions. Data from recent studies have suggested that the contribution of reticular centres to voluntary action may depend on anatomical and/or functional characteristics of the movement, as shown by a larger magnitude StartReact effect for bimanual versus unimanual movements and for proximal versus distal movements. Given that posture is largely controlled by the reticulospinal tract, the present study investigated whether voluntary movements with greater postural demand would exhibit greater reticulospinal drive (as evidenced by a larger StartReact effect) as compared to movement counterparts with less postural demand. Participants (n = 30, F = 20) performed upper and lower limb simple RT tasks with high postural demand (hiPos) and low postural demands (loPos), where the auditory go-signal was occasionally replaced by a loud (115 dB) SAS. In the upper limb task, participants gripped a weighted handle, and released the handle upon presentation of the go-signal, while maintaining a 90 deg elbow angle (hiPos), or while the forearm was supported (loPos). For the lower limb task, a calf raise task was performed either while standing (hiPos) or seated (loPos). RT on SAS trials where reticulospinal activation was confirmed with an observed startle reflex (SCM+) was compared to that on trials without an observed startle reflex (SCM-). Results of the grip release task showed that SCM+/- RT differences were observed for both the hiPos and loPos tasks; however, the magnitude of the differences was similar between the tasks (p=.99). In the calf raise task, no SCM+/- RT differences were observed for the loPos task, and although a difference was observed in the hiPos task, the RTs observed were substantially longer than those typically seen in StartReact studies. These results suggest that postural demand may not be a parameter that modulates reticulospinal drive. One explanation of this may be that postural demands increase task complexity, which has previously been shown to increase RTs and reduce the StartReact effect.

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Poster

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Topic: E.04. Voluntary Movements

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Title: Cortical involvement in the initiation of voluntary, but not involuntary movements of StartReact: EEG-based evidence supporting subcortical mechanisms underlying the StartReact phenomenon

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Abstract: The reticulospinal system is an important subcortical motor system controlling movements, yet its precise role in motor control remains poorly understood. The primary tool for assessing reticulospinal motor control in humans is the StartReact effect, however its underlying physiological mechanism is still debated. This study aimed at investigating a debated contribution of the motor cortex to the StartReact phenomenon. The StartReact paradigm was applied to 22 healthy participants performing wrist extension movements cued by imperative stimuli (IS). IS consisted of either loud acoustic stimuli (LAS) or moderate acoustic stimuli (MAS). IS order and timing was pseudorandomized. Muscular and cortical activity were investigated by electromyography (sternocleidomastoid and extensor digitorum muscles for assessing startle incidence and reaction times, respectively) and electroencephalography (EEG, 64 channels). Reaction times were significantly reduced following LAS compared to MAS, reflecting the StartReact effect. Neural activity in the motor cortex was lateralized towards the hemisphere contralateral to the movement (channel C1). Reversed lateralization of motor cortex activity during non-dominant wrist movements corroborate the assumption that EEG signals reflect movement-related cortical potentials. Whereas movement-related cortical activity preceded voluntary muscle activation following MAS, it appeared only after muscle activation in LAS trials. Assessment of contingent negative variation (CNV) and event-related desynchronization (ERD) revealed minimal preparatory motor cortex activity before movements. The findings of this study suggest that while the motor cortex plays a significant role in driving voluntary movements following MAS, it seems not involved in the initiation of fast, involuntary movements induced by LAS. Additionally, only low levels of motor cortex preparation were observed prior to IS application. These results indicate that the StartReact effect in setups with unpredictable IS timing is mainly driven by the reticulospinal system, thereby affirming the utility of the StartReact paradigm as a valuable tool for gauging reticulospinal motor control and plasticity, for example following spinal cord injury.

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Topic: E.04. Voluntary Movements

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Title: Mapping reticulospinal control of single joint movements: a comprehensive analysis of StartReact effects in upper and lower extremity muscles

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Abstract: The reticulospinal (RS) system is a key descending motor tract whose functional role is still poorly understood. Previous findings suggest that the RS system controls elementary movements like posture and locomotion. Studies assessing RS control of single joint movements primarily focused on upper extremity muscles, where stronger RS drive was observed in (1) proximal vs. distal, and (2) flexor vs. extensor muscles. However, a systematic assessment of RS drive across multiple upper and lower extremity muscles is lacking.
RS drive was assessed by the StartReact paradigm which is characterized by a shortening in motor reaction time (RT) when the cue initiating movement is paired with startling, loud acoustic stimuli (LAS) compared to moderate acoustic stimuli (MAS). Twenty-nine healthy subjects participated in two visits separated by 14 days. In each visit, the StartReact paradigm was applied to seven muscles of the upper or lower extremity. RT was assessed by electromyographic recordings from a total of fourteen muscles. RT shortening between MAS and LAS trials served as a measure of RS drive to the specific muscles.
Significant RT shortening in response to LAS was observed across all single joint movements, suggesting that all muscles receive some inputs from the RS system. The extent of RS drive was significantly lower in the first dorsal interosseous vs. biceps brachii, the extensor hallucis brevis vs. the vastus medialis, and the tibialis anterior vs. the vastus medialis. Therefore, in both upper and lower extremities the most distal muscles exhibited reduced RS gain compared to more proximal muscles. A significant difference in RS drive to flexors vs. extensors was observed only in the lower extremities, with extensors (gluteus maximus, vastus medialis, and gastrocnemius) displaying higher RS gain compared to flexors (rectus femoris, semitendinosus, and tibialis anterior).
Our findings provide supporting evidence for a reduced RS drive to distal muscles of the upper and lower extremities, which are likely controlled by the CS tract. However, a continuous proximal-distal gradient of RS drive was not evident and seems to reflect an oversimplified view of RS motor control, portrayed in literature. While our data did not reveal increased RS gain in upper extremity flexors vs. extensors, there was enhanced RS drive to extensors vs. flexors of the lower extremity, affirming a critical role of the RS system in posture. Overall, this study provides novel, systematic information on RS motor control and aids our understanding of RS involvement in motor recovery after central nervous system injury.

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Title: Validation of a novel cognitive-motor integration balance task

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Abstract: Introduction: Many skills that are necessary to perform activities of daily living require individuals to think and move at the same time; otherwise known as cognitive-motor integration (CMI). Importantly, deficits are not apparent in individuals with concussions when performing motor or cognitive tasks separately. An upper extremity CMI assessment task has been developed and validated to demonstrate how CMI performance can break down with neurotrauma. As balance issues are a common problem associated with concussion, the addition of a full-body CMI assessment would provide a more comprehensive analysis. Here we investigate the efficacy of a balance related CMI task involving integration from visual, vestibular, and proprioceptive systems, which are known contributors to postural control. Prior to utilizing this task with clinical populations, the current study assessed healthy participants to validate this novel task. **Methods:** Two CMI assessment tasks were used: Task A used a laptop to assess upper extremity CMI (validated task) and Task B used a television monitor, 3D motion capture, and a force plate to assess full-body CMI (novel task). In both tasks, the goal of the participant was to move a cursor from a central target to one of four peripheral targets as quickly and accurately as possible. The cursor was controlled using finger position in Task A and trunk position in Task B. Both CMI tasks consisted of 2 conditions: 1) Standard (S), where movements were congruent with visual information (ex. leftward lean would move the cursor to the left) and 2) Feedback reversal (FR), where the visual feedback was rotated 180° (ex. leftward lean would move the cursor to the right), requiring increasing CMI. Performance in both tasks were quantified using reaction time (RT), movement time (MT) and path length (PL). **Results:** Task A was completed faster and with less movement than Task B (MT: $p < 0.001$; PL: $p < 0.001$). In addition, there were significant effects of condition for Task A (RT: $p = 0.008$; MT: $p < 0.001$; PL: $p = 0.011$) and Task B (RT: $p = 0.045$; MT: $p = 0.034$; PL: $p = 0.036$), where better performance was observed in the S condition compared to FR condition, independent of task. **Significance:** We suggest the extended full-body task is able to detect performance deficits that arise with multi-domain integration. The addition of a full-body CMI task provides a more comprehensive analysis of sensory contributions to coordination tasks. This study provides additional insight into how balance is affected and controlled when CMI is challenged. The use of this task in clinical populations has the potential to uncover differences that might not be apparent in the standard assessment protocol.

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Title: Investigating Eye Tracking Metrics in a Digital Trail Making Test

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Abstract: Tailoring interventions for neurological impairment relies on precise diagnosis of deficits across multiple functional domains. Existing clinical scales to assess cognitive-motor function typically offer limited performance metrics in a single domain. By digitizing these tools, it is possible to capture the spatial-temporal aspects of behavior, providing insight into domain-specific deficits. Furthermore, quantitative capture of eye-hand coordination can provide unparalleled insights about the interplay of the cognitive-visual-motor triad that is so critical for complex behavior. With this aim, we developed a novel digitized TMT (dTMT) with integrated eye tracking to allow for the extraction of more in-depth outcome measures, necessary for multi-domain assessment. This dTMT shows strong criterion validity in young healthy individuals in comparison to the original paper TMT. Healthy young participants completed the eye tracking-integrated dTMT. Numeric test types TMT-A and TMT-C (1-2-3-4...) and alphanumeric test types TMT-B and TMT-D (1-A-2-B...) were grouped together for analysis, creating two groups based on test complexity. Eye movement-related measures showed strong significant correlation $p < 0.001$ with total completion time: number of fixations ($r = 0.8799$), fixation duration ($r = 0.9238$), pathlength of gaze ($r = 0.8530$), and the total gaze to hand distance ($r = 0.9257$). These metrics were also strong predictors of TMT performance in the more difficult alphanumeric TMT. The number of fixations during search and dwell times were significantly larger in the alphanumeric versus numeric tests ($p < 0.001$), indicating the greater cognitive resources required for the alphanumeric test. Overall, the alphanumeric TMT was characterized by more complex spatial planning, less attention to the peripheral visual field, and a greater strain on working memory. No significant effects were observed in motor metrics (i.e. mean speed, acceleration and mean squared jerk) indicating that both test complexities demanded similar motor control. These results lay the foundation for the utilization of an eye-tracking integrated digitized trail making test for the detection of individualized domain-specific deficits in neurologically impaired populations.

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Title: Hormone levels and movement control network connectivity affect visuomotor behaviour in working-aged women

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Abstract: Interactions with our environment require intact connections between frontal, parietal, and subcortical brain regions. While some of these interactions are direct, others require cognitive-motor integration (CMI), where the guiding visual information and motor action are decoupled. Our group has shown sex differences in the networks controlling these visuomotor skills. However, most of this research is based on data from pre-menopausal college-aged women. To address the knowledge gap around the impact of sex hormones on the neural control of movement, we examined 19 females between the ages of 34 and 63 in their pre, peri, and postmenopausal stages. We previously observed a significant relationship between hormone levels and connectivity strength of the brain networks for skilled performance. Here, we hypothesized that both CMI performance and the underlying neural control activity would differ as a function of hormone concentrations. Participants completed a CMI eye-hand coordination task, where there was a spatial decoupling of the hand motion and a reversal of visual feedback. Next, participants underwent MRI scanning, during which they performed this task using an MRI-safe touchscreen. Participants were trained on the MRI task until performance reached greater than 90% success. Estrogen, progesterone, and testosterone levels were also collected. A generalized psychophysiological interaction (gPPI) analysis was implemented to examine how functional connectivity between regions known to be involved in our CMI task may be related to kinematic performance and sex hormone concentrations. Our linear regression analysis showed that elevated levels of estrogen and testosterone were associated with improved movement time and precision scores ($p<0.05$), after accounting for age and frontoparietal connectivity. Further, precision scores were associated with increased left prefrontal cortex-inferior parietal lobule connectivity ($p<0.05$), after accounting for age and progesterone levels. Finally, after accounting for both age and all 3 hormones, reaction times were associated with increased precuneus-left superior parietal lobule connectivity ($p<0.05$). These data show that the performance of visually-guided movement is differentially affected by sex hormone levels and connectivity strength of the brain networks controlling skilled performance. We suggest that the structure of the networks

required for accurate movement performance changes with the fluctuations in progesterone, estrogen, and testosterone that occur later in life, and that this may affect one's cognitive-motor integration abilities.

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Title: Uncovering neural dynamics of reach perturbations induced by cortical optogenetic inhibition using a large-scale optogenetic interface in non human primates

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Abstract: Neruomodulation has emerged as a leading therapy for neurological disorders, yet little is known about how neural circuits respond to elicit this therapeutic potential. As precious and powerful translational models, non-human primates (NHPs) have long been recognized for their utility in neuroscience and neuropathology. In recent years optogenetic tools have been adapted from rodent models to NHPs to probe neural circuits in larger brains with higher spatiotemporal resolution. Despite this progress, the technical feasibility to implement optogenetics in NHPs still faces several challenges which include delivering opsin encoded viral vectors over a wide cortical area, maintaining chronic large-scale optical access, and administering network-wide optical stimulation during simultaneous electrophysiological recording. To address this technological gap, we present an optogenetic interface designed to increase accessibility of NHP optogenetic experiments for a diversity of expertise and experimental needs. Specifically, we present 1) an efficient optogenetic viral vector delivery technique that does not require live magnetic resonance imaging (MRI) during infusion, 2) a

modular cranial interface suitable for diverse experimental needs and rapid iteration, 3) a multi-modal artificial dura (MMAD) for long-term optical access with 4) chronic electrocorticography (ECoG), and 5) a scalable cortical illumination setup for patterned optogenetic stimulation. We demonstrate the potential of this interface by delivering the inhibitory opsin JAWS (AAV8-hSyn-Jaws-GFP) throughout the post parietal cortex of two adult rhesus macaques. We observe significant delays in reaching during an instructed delay center outreach task, the first behavioral change in the context of a reach in NHPs to our knowledge. Analysis of local field potentials recorded by the MMAD during optical inhibition reveal an evoked response of increased broadband power localized to cortical areas expressing the opsin. Using logistic regression we further reveal a low dimensional subspace of neural activity that can predict reach direction under both naturalistic (78% accuracy) and inhibited (65% accuracy) neural states. These results demonstrate this interface's ability to overcome current technological limitations of large scale optogenetics, realize spatiotemporal cortical dynamics, and uncover neural state space perturbations during neuromodulation. This interface serves as a valuable tool to uncover neruomodulation's therapeutic potential by directly observing the changes in cortical dynamics during the modulation period.

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Title: Emg-emg coherence: a novel biomarker for reticulospinal motor drive?

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Abstract: The reticulospinal (RS) system is a key motor tract involved in movement control. Nevertheless, the RS is still poorly understood, likely due to methodological challenges in assessing its physiology. The StartReact paradigm is used to assess RS motor control in humans and is characterized by a fast release of a planned motor program when movement initiation is coupled to loud acoustic stimuli (LAS). However, the StartReact paradigm is limited to reaction time tasks and requires application of LAS. This study aimed at investigating EMG-EMG

coherence as potential biomarker for RS motor drive. EMG-EMG coherence has previously been used to measure common neural drive reflecting corticospinal commands. Less is known about its ability to assess RS motor drive. In a first project of the study, we assessed EMG-EMG coherence of the acoustic startle response, a motor response known to be mediated by RS neurons. EMG-EMG coherence of the left and right sternocleidomastoid (SCM) was analyzed in 10 healthy subjects. In a second project, we investigated EMG-EMG coherence of the left and right tibialis anterior (TA) during StartReact. The StartReact paradigm was applied to bilateral ankle dorsiflexion in 16 healthy subjects that reacted to either LAS or moderate acoustic stimuli (MAS). In a third project, we examined RS motor control during dynamic motor tasks reflecting movements of daily life. EMG-EMG coherence between the left and right TA, gastrocnemius medialis (GM), and soleus (SO) was investigated in 16 healthy subjects.Startle responses in the SCM revealed a prominent peak in intermuscular coherence at 15.6 Hz. The same coherence peak was observed in the left and right TA during StartReact, with LAS trials showing enhanced coherence at 15.6 Hz compared to MAS trials. During dynamic ankle movements, enhanced coherence was observed in the TA at 15.6 Hz during synchronous vs. asynchronous bilateral ankle movements. Additionally, EMG-EMG coherence was increased between 11.7 and 19.5 Hz in the TA, GM, and SO during postural adjustment tasks. Our findings support the assumption that RS drive underlying the startle response is reflected by enhanced intermuscular coherence in the range of 10-20 Hz. Interestingly, LAS trials of the StartReact paradigm demonstrated enhanced coherence in the same frequency range, supporting the assumption that the StartReact effect is primarily mediated by the RS system. Moreover, enhanced EMG-EMG coherence in the 10-20 Hz frequency range was observed during low complexity ankle movement and postural adjustment tasks. These findings provide evidence that EMG-EMG coherence might be a promising tool to measure RS motor drive during dynamic movements.

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Poster

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Topic: E.04. Voluntary Movements

Title: Deep Brain Stimulation Improves Speed-Accuracy Tradeoff in Children with Dystonia During a Continuous Motor Task

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Abstract: Childhood dystonia involves involuntary intermittent or sustained muscle contractions which can lead to repetitive and twisting movements. Deep brain stimulation (DBS), as a neuromodulatory intervention, has proven to have profound impact on treatment of childhood dystonia. However, how DBS alters movement accuracy in pediatrics diagnosed with dystonia is not yet understood. In this study, we aim to investigate task performance in a group of pediatric patients performing a continuous figure-eight writing task under three conditions: 1) without stimulation, 2) with stimulation using suboptimal clinical setting, and 3) with stimulation using optimal clinical setting identified by clinical experts on effective deep brain targets. The figure-eight writing task was performed while the subjects were participating in an inpatient Neuromodulation Monitoring Unit (NMU). During the NMU, up to 10 temporary depth electrodes were implanted in the basal ganglia and thalamic regions, specifically targeting the Globus Pallidus internus (GPi), subthalamic nucleus (STN), Ventral oralis anterior/posterior (VoaVop), ventral intermediate nucleus (VIM), and pedunculopontine nucleus (PPN) to apply stimulation to find the best effective clinical settings and targets. The subjects were asked to perform multiple trials of the continuous writing task with and without stimulation with each hand on an iPad while kinematic trajectories and electromyographic (EMG) signals were recorded. Our results indicate that DBS with optimal clinical settings yields improvement of speed-accuracy tradeoff in both hands compared to other conditions. Further, our results demonstrated that for subjects with optimal stimulation settings, percent improvement of accuracy compared to off stimulation for each hand is higher than that of movement speed. Additionally, our results evaluate trajectory smoothness, indicate the presence of task-related frequencies in EMG activity, consistent with previous studies, and demonstrate how pattern of muscle activation changes when stimulation is applied.

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Topic: E.04. Voluntary Movements

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Title: Neural recordings in healthy macaques suggest that the post-stroke flexor synergy may not originate from the reticulospinal tract

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Abstract: Stroke survivors are typically left with residual deficits which include negative signs like weakness and loss of dexterity, but also positive signs such as spasticity and synergies. Synergies are co-contractions of muscle groups, such as between shoulder abductors and elbow, wrist and finger flexors (the flexor synergy). We hypothesised that the flexor synergy arises from a neural circuit which is present in healthy individuals. Such a circuit would be activated when co-contraction of these muscle groups is required to complete a task goal, but inhibited when independent muscle activation is required. Losing the ability to control this circuit after a stroke would result in the obligate co-contractions which can be such a significant contributor to disability. Previous work has suggested that the flexor synergy in stroke survivors might originate from the reticular formation (RF) in the brainstem and its descending reticulospinal projections. To examine this hypothesis, we trained two macaque monkeys on a task requiring in and out of synergy movements. The forearm was held in a cast attached to a six-axis force transducer, allowing us to calculate torques around the elbow and shoulder joint. The x axis of an on-screen cursor was controlled by shoulder abduction/adduction; the y axis by elbow flexion/extension. Sixteen targets were positioned concentrically around a centre (rest) location; the monkey moved the cursor to targets in turn to obtain a food reward. After training was complete, single unit recordings were made from the primary motor cortex (M1) and RF. Within M1, some neurons were identified as corticospinal cells by antidromic activation from the pyramidal tract. Peri-event time histograms were calculated for each cell separately for each target, and the dependence of firing rate on elbow and shoulder torques determined using regression analysis. Both M1 and RF contained cells which coded the torque level around the elbow joint alone, the shoulder joint alone, or co-activation around both joints. Of the latter cells, the majority fired with shoulder abduction/elbow extension, or shoulder adduction/elbow flexion. This is the opposite of what is expected for a region which produces the flexor synergy. Similar results were obtained when considering firing rates during the phasic movement into target, or the static holding phase of the task. The similarity of our results between M1 and RF, both of which coded primarily out-of-synergy movements, does not agree with the idea that the flexor synergy arises from reticulospinal pathways.

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Title: A weak auditory prepulse mitigates motor performance decrements following a startling stimulus.

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Abstract: An unexpected, startling stimulus can lead to disruptions in both cognitive and motor performance. Early work in military pilots showed that manual tracking was degraded for up to 10 seconds following a startle, and other work has shown long-lasting decrements in cognitive performance such as mental subtraction and decision making. A low intensity non-startling stimulus (i.e., prepulse) presented shortly (e.g., 100 ms) prior to a startling stimulus has been shown to diminish both the probability of observing a startle reflex as well as its magnitude. The present experiment investigated whether this "prepulse inhibition" of startle would similarly diminish the deleterious effect of startle on motor performance and/or reduce the duration of these decrements. Participants performed six trials of a 6-min duration manual tracking task using a computer mouse to maintain a cursor over a target that moved in an unpredictable pattern. Three different stimuli were each presented twice at approximately 1 min intervals during each 6-min tracking trial, and participants were instructed to react as fast as possible by clicking the mouse button as soon as possible upon presentation of the stimulus in four of the trials. The three stimuli included a non-startling 80 dB acoustic stimulus, a 120 dB startling acoustic stimulus (SAS), and an 80 dB acoustic prepulse delivered 100 ms prior to a 120 dB SAS. Results showed that presentation of a prepulse prior to a SAS decreased the probability of eliciting a startle reflex. More importantly, however, when a prepulse stimulus was presented prior to a SAS, the magnitude of the initial tracking error in the 1-sec following the stimulus was significantly smaller compared to when the SAS was presented alone, and tracking performance also returned to baseline faster when the SAS was preceded by a prepulse. These results indicate that prepulse inhibition of startle can diminish not only the startle reflex itself, but also any negative effects on motor performance arising from the startle.

Disclosures: A. Bui: None. **D. Maslovat:** None. **A.N. Carlsen:** None.

Poster

PSTR072: Motor Planning and Flexible Execution in Health and Disease

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR072.28/E18

Topic: E.04. Voluntary Movements

Support: R21NS119849

Title: Unique agonist beta-band activation underlies dysmetria in Essential Tremor

Authors: *S. DELMAS, Y. CHOI, B. YACOUBI, J. J. KIM, J. HUBBARD, M. S. OKUN, E. A. CHRISTOU;
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Abstract: Essential Tremor (ET) is the most prevalent movement disorder, characterized by a bilateral 4-8 Hz upper limb action tremor. Despite being primarily associated with tremors,

individuals with ET also experience dysmetria, inaccuracy during targeted movements. Despite dysmetria representing a cardinal sign of cerebellar dysfunction, the underlying neuromuscular control parameters associated with dysmetria in ET remain poorly understood. Sixteen ET patients who underwent thalamic deep brain stimulation (tDBS) surgery and 17 healthy controls (HC) volunteered in the study. Each participant completed 3 trials of an upper limb tremor task, and 50 trials of unloaded, ankle dorsiflexion goal-directed pulse movements with a spatial/temporal target of 9 degrees in 180 ms. ET patients performed experimental procedures with tDBS OFF and tDBS ON in a counterbalance order in two consecutive days. We quantified (1) upper limb tremor, (2) goal-directed accuracy as spatial and temporal bias error and absolute error, (3) goal-directed trajectory smoothness as jerk magnitude, and (4) agonist muscle frequency structure from 12-100 Hz during the goal-directed task. ET patients exhibited greater tremor, spatial and temporal errors, and jerk magnitude than HC. Greater jerk magnitude was associated with greater spatial and temporal errors but not tremor. The greater jerk magnitude observed in ET associated with lower agonist 12-35 Hz power but not 35-100 Hz. Moreover, although tDBS supressed tremor, it did not affect any goal-directed outcomes. Here, we show that ET patients exhibit unique agonist activation associated with dysmetria relative to healthy controls that is not attributed to tremor. These insights provide a deeper understanding of the neurophysiological mechanisms underlying dysmetria in ET.

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Poster

PSTR072: Motor Planning and Flexible Execution in Health and Disease

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Topic: E.04. Voluntary Movements

Support: NSERC Grant RGPIN 2017-04717

Title: An electrically-induced startle reflex is not attenuated by an acoustic prepulse

Authors: *E. DAHER, A. N. CARLSEN;
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Abstract: The startle reflex is a whole-body reflexive response that can be elicited by stimuli of various modalities. Presenting a loud (e.g., 120 dB) startling acoustic stimulus (SAS) during reaction time (RT) tasks has become an increasingly employed technique to elicit a planned movement in research settings. It is now recognized that this technique may also have beneficial clinical applications. However, presenting a loud SAS repeatedly in either setting can be both disruptive to nearby workers, and risks damage to the auditory system from excessive exposure. Thus, alternative methods of reliably eliciting a startle reflex would be preferable in these cases. Some previous studies have employed an electrical-tactile stimulus (startling electric stimulus,

SES) to elicit a startle reflex; however, an effectiveness comparison performed previously in our lab indicated that startle reflexes were elicited much less frequently as compared to a SAS when applied to the biceps-brachii. The present experiments aimed to 1) test the effectiveness of a SES presented at various body locations to establish an optimal stimulation site; and 2) to determine if a SES is susceptible to attenuation by a weak acoustic prepulse, as these types of stimuli are omnipresent in various settings. In the first experiment, a SES with an intensity of 25-times the electrical perceptual threshold was presented coincident with a visual go-signal in a simple RT task requiring targeted right wrist extension. The SES was delivered on selected trials via surface electrodes placed at one of six contralateral locations (index finger, ulnar-styloid-process, biceps-brachii, upper-trapezius, lower-trapezius, gastrocnemius). Results (n=27) showed that a startle reflex was observed significantly more often (~50% of trials) when a SES was applied over the biceps or wrist as compared to other locations. In the second experiment, a weak acoustic prepulse (80 dB) was occasionally presented 100 ms prior to either a SAS or a SES presented over biceps during a simple RT task. Results (n=26) showed that the incidence of eliciting a startle reflex following a SAS was significantly diminished ($p = .012$) by the prepulse, and when a startle was elicited, its amplitude was significantly reduced ($p < .0034$). However, no attenuation effect of the SES-induced startle reflex was observed (all $p > .35$). Thus, it appears that an electrically-induced startle reflex was not substantially attenuated by an acoustic prepulse, which could be partially explained by the use of cross-modal prepulse and startle stimuli which have been shown to have a weaker inhibitory effect than unimodal stimuli.

Disclosures: E. Daher: None. **A.N. Carlsen:** None.

Poster

PSTR072: Motor Planning and Flexible Execution in Health and Disease

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Program #/Poster #: PSTR072.30/E20

Topic: E.04. Voluntary Movements

Support: NRF-2021R1A6A3A14045108

Title: Revealing the interaction between beta oscillations and population spikes during movement in non-human primate

Authors: *H. CHOI[1], J. KIM[2], S. M. GRIFFIN[1], L. NOVIK[3], K. GANGULY[1];
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Abstract: Neural populations in movement-related brain areas are known to support reliable transitions from movement preparation to execution. Increases in beta oscillations' amplitude have also been heavily implicated in neural processing during periods of preparation. Interestingly, recent work suggests that this beta dynamics may be better represented by short-duration transient changes rather than overall changes in power (beta burst). While it is well-

established that these signals are changed during the movement, the precise nature of their interaction and its implications for functional roles remain unexplored. Investigating this interaction is essential, as it could reveal the brain mechanism of the movement. Furthermore, it could provide critical insights into the treatment that drives the functional recovery of movement disorders, such as stroke or Parkinson's disease, so that it may uncover key biomarkers that could significantly enhance rehabilitation strategies. Through a combination of recordings from both recovering from cortical injured and intact non-human primates, mathematical modeling, as well as causal manipulations using electrical brain stimulation, we find a striking non-linear interaction between transient changes in beta amplitude and the activation of neural population dynamics. More specifically, we find that during movement sequences, there is rapid switching between two stable states: a state with activated beta and a state with activated task-related ensembles. This indicates that the system can exist in two stable configurations and reliably oscillate between them (referred to as 'bistable oscillatory dynamics'). Interestingly, these bistable oscillatory dynamics change is the result of the movement-related and beta-related spike activity change. We verified this brain mechanism through the spike subspace analysis. Moreover, we demonstrated that the restoration of such bistable oscillatory dynamics strongly predicts recovery of prehension after cortical injury. Also, we could find the specific modulated frequency that interacts with both beta and spike signals. Using that frequency, we could reliably manipulate the timescale of bistable oscillatory dynamics through alternating current electrical stimulation. Overall, our results suggest that bistable oscillatory dynamics can govern transitions during movement, and this could be the key biomarker of stroke recovery not only in the diagnosis aspect but also in the treatment aspect. Importantly, the restoration of bistable dynamics appears to be critical for functional recovery and transitions between states after brain injury.

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Poster

PSTR073: Multiregion Pathways in Movement Control

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Topic: E.04. Voluntary Movements

Support: JSPS KAKENHI 22K19592
JSPS KAKENHI 18J11989
AMED-CREST JP16gm0310008

Title: Cerebellar output to spinal motoneurons via corticomotoneuronal cells in primary motor cortex of macaque monkeys

Authors: *Y. NAKAYAMA[1,2], N. SANO[2], M. SUZUKI[2], S. CHIKEN[3], A. NAMBU[3], Y. NISHIMURA[2];

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Abstract: Dysfunction of the cerebellum (Cb) can cause motor deficits. Anatomical studies have shown that the cerebellar nuclei project to the primary motor cortex (M1) through the motor thalamus. In addition, the M1 projects monosynaptically to spinal motoneurons in primates, which impact on muscle activity. Since motor deficits are manifested in muscle activity, cerebellar outputs should eventually reach the muscles. However, the neural pathways that enable the Cb to control muscle activity are still unknown. In the present study, we investigated whether the M1 cells that causally generate muscle activity receive cerebellar outputs. We recorded neuronal activity in the M1 and electromyographic (EMG) activity in the forelimb muscles while monkeys (*Macaca fuscata*) performed an arm reaching task to investigate M1 cell responses to electrical stimulation of the dentate nucleus (DN) in the Cb, and muscle responses to its M1 spikes. We found that the majority of M1 cells either increased or decreased their neuronal firing in response to DN stimulation. By analyzing the spike-triggered averaging of the EMGs, we identified 60 corticomotoneuronal (CM) cells, which have monosynaptic connections with spinal motoneurons. Of the 60 CM cells, 38 (63%) responded to the DN stimulation. These results provide direct evidence for a pathway from the Cb to the spinal motoneurons via the M1 in which the Cb is capable of controlling muscle activity. Taken together, the present findings suggest that the network originating from the Cb through the M1 to the muscles plays an important role in the realization of motor behavior.

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Poster

PSTR073: Multiregion Pathways in Movement Control

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Topic: E.04. Voluntary Movements

Support: 1F30EY035603-01
TL1 TR003169

Title: Executive Regions Encode Movement of Individual Body Parts in Macaque Monkeys

Authors: *M. B. SLAPIK[1], X. NIU[2], A. G. MCCONNELL[4], M. FRANCH[5], V. DRAGOI[3]; [1]McGovern Med. Sch., Houston, TX; [2]Rice Univ., Houston, TX; [3]Neurobio. and Anat., Rice Univ., Houston, TX, TX; [4]Houston Methodist Res. Inst., Houston, TX; [5]Neurosci., Baylor Col. of Med., Houston, TX

Abstract: The brain has a highly modular architecture with specialized regions for vision, hearing, decision-making, and so on. However, the extent of this modularity differs significantly across species. Previous research has shown that body movements in mice drive neural activity

across the entire cortex, including early visual areas. Conversely, work in restrained monkeys has shown the opposite: that body movements do not drive neural activity across the entire brain. In this study, we explore this question with unrestrained macaque monkeys to capture a full spectrum of natural behaviors. We employ wireless recordings to monitor neural activity in V4 and dlPFC areas while monkeys move freely within an enclosure. Additionally, we use an overhead camera coupled with DeepLabCut to precisely track the movements of individual body parts in tandem with neural activity. Here, we confirm that body movements do not drive widespread neural activity in monkeys, even in a freely moving setting. Conversely, these movements do drive activity in higher brain regions such as dlPFC, which is traditionally associated with executive functions. Moreover, we find that dlPFC tracks the movement of individual body parts, and that it specifically encodes their velocities, rather than their location or acceleration. This work further reveals how modularity varies across species and highlights the importance of studying primates to understand the human brain. Furthermore, we identify dlPFC as a key area for the encoding motor variables, providing an additional target for movement-decoding in prosthetic devices.

Disclosures: M.B. Slapik: None. **X. Niu:** None. **A.G. McConnell:** None. **M. Franch:** None. **V. Dragoi:** None.

Poster

PSTR073: Multiregion Pathways in Movement Control

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Topic: E.04. Voluntary Movements

Support: Simons Collaboration on the Global Brain

Title: Using Interpretable Generative Models to Probe the Multiregional Interactions Underlying Movement Initiation

Authors: *M. AGRIOS[1], A. KRISTL[2], S. P. SAVYA[2], N. KOH[2], S. HSU[3], S. A. SOLLA[4], J. A. MIRI[1];
[1]Northwestern Univ., Evanston, IL; [2]Neurobio., Northwestern Univ., Chicago, IL; [3]Princeton Neurosci. Inst., Princeton, NJ; [4]Neurosci., Northwestern Univ., Chicago, IL

Abstract: While many previous studies have identified numerous brain circuits involved in initiating specific movements in response to cues, the precise neural mechanisms associated with a spontaneous decision to act remain unknown . Traditionally, experiments studying this question have been hampered by a limited ability to capture the simultaneous activity of a large number of neurons. We addressed this challenge by performing simultaneous recordings using four neuropixels in a head-fixed mouse; this allowed us to record the activity of hundreds of neurons in premotor cortex, primary motor cortex, primary somatosensory cortex, striatum, and thalamus, while mice perform a self-initiated naturalistic climbing task. We have implemented

generalized linear models (GLMs) and demonstrated that they can be a powerful tool for building generative models that can capture the observed neural dynamics across large populations, while maintaining fidelity to first and second order statics of the recorded population activity. The spiking activity of each neuron is used as input to a GLM that learns pairwise statistical relationships between individual neurons and describes how the activity of one neuron excites or inhibits the activity of the other across varying time lags. Once trained, these models can be used to simulate each individual neuron's activity adhering to the learned relationships between neurons. We sought to validate these models by comparing the first and second order spiking statistics of the simulated activity against the experimentally measured activity and found that our models are able to produce spike trains with striking similarity to what we observe in the real data. Interestingly, spontaneous ramps in the simulated neural activity are produced with similar frequency and duration as those observed in the neural recordings during climbing. This observation implies that the complex neural dynamics that drive the behavioral switching between non-movement and movement states are captured by our GLM. Additionally, we leverage the interpretability of GLMs by performing analyses directly on the set of pairwise neuron-to-neuron relationships learned by the model during training to test hypothesized interactions across brain regions underlying movement initiation. Our results shed light on the interactions that underlie volition and motor planning, from the level of single neurons to large multiregional populations. Our results indicate that large scale neural recordings combined with powerful data analysis methods provide a unique tool for investigating the mechanisms that underlie neural system function in cognition, motor behaviors, and beyond.

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Poster

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Topic: E.04. Voluntary Movements

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Title: Cortical and Collicular role in multimodal self-initiated sequential behaviors

Authors: *M. HAMON[1,2], T. LUPASHINA[3], J. SIBILLE[3], M. E. LARKUM[2], R. N. SACHDEV[2], J. KREMKOW[3];
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Abstract: The plans to move and execute a behavior in pursuit of a goal arises from activity in a distributed set of neural networks and normally / naturally involves multiple sensory motor modalities. The underlying patterns of neural population activity can be related to the planning and decision to move a particular part of the body at a particular time. Here we trained headfixed mice in self-initiated behavior, that engages multiple sensory motor modalities, as mice plan, decide and execute whisker, eye, and body movements through a naturalistic maze -- the Airtrack system -- that has physical walls. The key questions we hope to address here are whether the plan to move can be revealed in the activity of cortical and collicular neurons, whether individual neuron activity is related to a single dimension in behavior -- whisking, eye movement, body movement -- or is related to a sequence of related behaviors that occur in our task -- whisking followed by movement of the animal followed by eye movement and turning. Our recordings in the superior colliculus and motor cortex (M2) reveal that in both areas neurons are best related to a single dimension of behavior -- eye movement, or turning or onset of movement. For both colliculus and M2, activity could be related to eye movement in multiple directions. In a second set of experiments we used VGAT-ChR2 mice to activate inhibitory neurons in colliculus unilaterally. Activating inhibitory neurons in single ~200 micron spot in colliculus generated contraversive eye, body and whisker movement. This work suggests that even though both M2 and Colliculus contain a sensory motor map that encompasses the entire spectrum of planning, and movement of the entire body, individual neurons are tuned to single class of movements in particular contexts.

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Poster

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Topic: E.04. Voluntary Movements

Support: HHMI

Title: Dynamic heterarchical control of mouse hindlimb extension

Authors: *J. KELLER[1], K. M. BRANSON[2], M. PACHITARIU[3], J. T. DUDMAN[4];
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Abstract: Innate wiring patterns in the brainstem and spinal cord enable a wide variety of coordinated loops through the environment, independent of the forebrain. However, in adult mammals the forebrain (specifically neocortex) is believed to sit atop a control hierarchy, and how it arbitrates for control with these caudal neuraxis circuits remains an open question. To

address this question, we study hindlimb extension in mice, which is expressed both stereotypically in fetal animals and flexibly in adults. We developed a head-fixed task in which mice turn off a cold air stimulus applied to the hindlimbs by vigorously extending them against a counterweight. In this context, naive mice produce *reactive* extensions within seconds, and given the presence of a predictive cue, learn to produce anticipatory extensions to *avoid* the cold air in ~100 trials. Using 3D kinematic tracking, we show that these avoid hindlimb extensions have subtle kinematic differences from their reactive counterparts, suggestive of a learned parameterization of the unlearned reactive movement. Either focal optoinhibition of motor cortex or broad optoinhibition of frontal and parietal cortex has minimal effects on the kinematics and latency of reactive extensions, but largely prevents avoid extensions. To understand this dual cortical and subcortical control of vigorous hindlimb extension, we recorded neural activity from multiple Neuropixels probes in several brain areas relevant to hindlimb movement, across learning and cortical inhibition. These data revealed prevalent frontal cortex activity that precedes extension, even during reactive extensions in naive mice, suggestive of strong ascending efference from subcortical areas. Patterns of activity in the hindbrain were more similar across anticipatory and reactive extensions than in the forebrain, where a subset of neurons tuned to predictive cues (and sensitive to optical inhibition) specifically increased their activity before anticipatory extensions. Our analysis suggests that the control of kinematically similar hindlimb extensions in mice is dynamic and heterarchical, with neocortex playing a role in fast learning of non-dexterous movements.

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Poster

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Title: Computational model to predict motor performance through the activity of corticospinal neurons

Authors: *N. MARTÍNEZ-HERNÁNDEZ[1], M. ALTAMIRA[1], R. OLIVARES-MORENO[1], M. LOPEZ-HIDALGO[2], G. ROJAS-PILONI[1];
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Abstract: Corticospinal neurons (CSp), located in layer 5B of the sensorimotor cortex (SMC) are essential for motor performance and learning. CPs neurons are functionally diverse participating in the initiation and fine-tuning of voluntary motor movements. Despite its importance in motor control and extensive research on CSp neurons, is poorly known if they are organized into neuronal ensembles. Moreover, no computational models have been developed to predict or describe aspects of motor learning and control through a unitary CSp neuronal activity approach. In this study we used miniaturized microscopy and calcium imaging with cellular resolution to analyze the motor-related Ca^{2+} transient dynamics of CSp neurons from SMC while mice learned and performed a cued lever-press task. To perform this analysis, we developed a recurrent neural network (RNN) architecture designed to capture the intricate temporal dependencies of neural activity. The efficacy of this network was tested using data obtained from mice in beginner and expert stages of the cued lever-press task. Furthermore, we investigated the effects of randomly altering calcium activity, both temporally and spatially, on the accuracy of the network predictions. Preliminary results suggest that our model may offer new insights into the individual role of CSp neurons in motor circuits, providing a valuable tool for advancing our understanding of motor circuit functions in behavioral neuroscience.

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Poster

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Title: Parafascicular nucleus inputs role during initiation and updating of actions

Authors: *E. M. ÁVILA, J. O. RAMIREZ-JARQUIN, F. TECUAPETLA;
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Abstract: The parafascicular nucleus (PF) is part of the intralaminar thalamic nuclei and receives inputs from different modality processing areas. Cortical, basal ganglia (BG), cerebellar (CB), and mesencephalic regions (MLR) of the brain contribute to the whole PF innervation.

Classically, PF function has been related to rule updating and cognitive flexibility. More recently, a motor role in sequence initiation was reported for PF's projections to BG. Optogenetic inhibition of PF thalamic inputs to the striatum affects the initiation during a self-paced lever pressing task as if thalamic signals convey relevant information for movement initiation. To understand the role of the PF nucleus during the cognitive and motor roles previously described, we investigated the specific contributions of PF and its inputs during the execution of two different tasks. RESULTS: To select the presynaptic targets for the study, we tracked presynaptic PF neurons by retrograde labeling. Cells from diverse brain regions were labeled. In *ex vivo* brain slices, we investigated the presynaptic inputs from the major glutamatergic areas by expressing and activating channelrhodopsin 2 (ChR2) into the PF. These recordings demonstrated a greater connection probability for the MLR in comparison with inputs from the CB or the cingulate cortex regions. Next, we trained groups of vGLUT2-cre mice in either a fixed ratio lever pressing (FR8) or a set-shifting task (SS). FR8 task asked mice to self-paced press a lever to receive a reinforcer. SS task asked mice to detect rule-related changes in environmental cues to obtain a reward. First, we confirmed the role of the PF nucleus during both tasks [optogenetic inhibition of the PF during the FR8 task increased the latency for the initiation of lever pressing; Inhibiting PF's activity during updating in the SS task impaired mice capacity for exploration of alternative strategies to obtain reward]. To evaluate the contribution of presynaptic inputs to the PF in both tasks, we optogenetically inhibited the presynaptic PF inputs from CB or the MLR. Inhibition of MLR but not CB inputs during the FR8 task increased the latency to initiate the lever press. Contrarily, Inhibition of CB but not MLR inputs during the SS task increased mice perseverative errors and affected rule updating. These results suggest that information incoming from different sources to the PF is necessary during different types of PF-related roles. Particularly, MLR projections to the PF seem to be sending motor information related to the initiation of actions while CB inputs to the PF seem to be more related to the cognitive role of this nucleus during the exploration and updating of actions.

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Poster

PSTR073: Multiregion Pathways in Movement Control

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Topic: E.04. Voluntary Movements

Title: Simultaneous Targeting of Cortical Depths in Premotor and Primary Motor Cortices

Authors: *E. SPERRY, R. CANFIELD, A. L. ORSBORN;
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Abstract: Goal-directed movement is largely the result of two steps: planning and execution. For example, to pick an object off a table, the brain must first plan how far and fast to reach, and must then send the signals to arm muscles to correctly execute the movement. Research shows

that different parts of the motor cortex are involved in planning and execution, with planning-related activity generally seen in the premotor cortex (PMd), and execution-related activity in the primary motor cortex (M1) [1]. However, it is unclear how information is transferred and transformed from planning through to execution across these functionally and anatomically different cortical regions. Structurally, mammalian cortices exhibit well-defined layers, where inputs and processing are concentrated in the superficial layers, while outputs are localized in the deeper layers. We predict that planning information is transformed into execution information between the output layers of PMd and the input layers of M1.
To test this hypothesis, we performed simultaneous PMd and M1 recordings in one male rhesus macaque as he performed an arm reaching (center-out) task. We developed a custom fixture that is able to move in three dimensions across a 2 cm chamber, and is capable of holding multiple high density, laminar, microelectrode arrays to capture neural signals at known depths from PMd and M1. This design allows us to flexibly adjust to target populations of neurons across different locations within primary and premotor cortex, allowing for a more comprehensive characterization of the shared computations between these regions.
We assessed interactions between regions by computing pairwise coherence between local field potentials measured at different depths in PMd and M1. Our preliminary analysis revealed that coherence between a small area in PMd and most depths of M1 increased with the onset of peripheral targets. This suggests that PMd-M1 coordination may differ between superficial vs deep layers of PMd. Such findings could imply that upstream computations are performed in one area, and then the rest of the motor cortex primarily relays these computations downstream. This research holds implications for understanding motor control and may contribute to the development of novel strategies for neuroprosthetics and rehabilitation therapies.
References:[1] M. Godschalk, R. N. Lemon, H. G. J. M. Kuypers, and V. Der, “The involvement of monkey premotor cortex neurones in preparation of visually cued arm movements,” Behavioural brain research, vol. 18, no. 2, pp. 143-157, Nov. 1985, doi: https://doi.org/10.1016/0166-4328(85)90070-1.

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Poster

PSTR073: Multiregion Pathways in Movement Control

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Title: Dynamic changes in information interaction between the primary motor cortex and primary somatosensory cortex in initiation of reaching movement in monkeys

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Abstract: The interaction between the primary motor cortex (M1) and the primary somatosensory cortex (S1) during voluntary limb movements is widely acknowledged, yet the dynamics of their information exchange remain elusive. In this study, we scrutinized the temporal, spectral, and directional aspects of information flow between M1 and S1 during voluntary movements. Electrocorticographic (ECoG) activity was recorded from multiple sites within the forearm regions of both M1 and S1 while monkeys performed an arm-reaching task. By employing a time-resolved, spectral Granger causality analysis, we elucidated the intricate patterns of information transfer. Notably, during the interval when the subject awaited a visual cue to initiate movement, a pronounced information flow from S1 to M1 predominated in the beta band (15-22 Hz) of the ECoG activity. Conversely, upon the onset of the cue and just before movement initiation, this flow decreased, while a heightened information flow from M1 to S1 emerged, particularly in the theta band (3-7 Hz) of the ECoG activity. The observed beta band information flow from S1 to M1 during the pre-movement period may signify the transmission of essential information regarding the body's resting state such as limb position and posture, crucial for generating precise motor commands. Conversely, the theta band information flow from M1 to S1 immediately preceding movement initiation may reflect efference copy signals. These findings underscore the notion that distinct frequency bands serve as conduits between M1 and S1 for different types of information pertinent to somatosensory and motor functions. Moreover, our results highlight the dynamic interplay between these cortical regions in anticipation and execution of voluntary movements.

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Poster

PSTR073: Multiregion Pathways in Movement Control

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR073.10/E30

Topic: E.04. Voluntary Movements

Support: NIH grant DP2 NS120847

Title: Preparatory activity is distributed across multiple motor system regions during self-initiated movement

Authors: *N. KOH[1], A. KRISTL[2], M. AGRIOS[3], S. P. SAVYA[2], A. MIRI[1];
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Abstract: Movement preparation is an integral component of voluntary movement, with preparatory activity in the primary motor cortex having been shown to be particularly important for task performance and online error correction. This preparatory activity, while commonly studied in the context of instructed-delay tasks, is also observed in the motor cortex during self-initiated movement. By acquiring simultaneous neuropixel recordings across several brain areas in mice during a naturalistic climbing paradigm, we show that preparatory activity before self-initiated movement is not only robust and present in a large percentage of motor cortex neurons - including those in the caudal forelimb area (CFA M1) and rostral forelimb area (RFA), but is also prominent in the forelimb somatosensory cortex (CFA S1) and the basal ganglia-recipient portion of forelimb motor thalamus (bgfMT). The prevalence of preparatory activity across these motor system regions suggests that preparatory activity in the primary motor cortex might not simply be generated locally but may instead arise through network interactions. To test this, we first decomposed preparatory neural population activity from each region into principal components. To then ascertain the contribution of each region to preparatory activity in CFA M1, we fit nested linear regression models to establish whether predictions of preparatory activity in CFA M1 are significantly better when using both time-lagged components from each region and CFA M1 as compared to predictions based only on CFA M1's own preceding activity. We find that activity in RFA, CFA S1 and bgfMT provide additional and statistically significant information about CFA M1 preparatory activity beyond that afforded by past activity of CFA M1 alone (mean Δ weighted R^2 = 0.164, 0.160, 0.136; Wilcoxon signed-rank, $p < 0.05$ for all; 5-fold CV). However, no one region contributed significantly more to CFA M1 preparatory activity than another. To further assess the uniqueness of the information provided by each region, we fit a full model using preparatory principal components from all regions, and compared the predictions from this model to models where a single region was left out. From these analyses, we find that the information provided by each region is small but unique (mean Δ weighted R^2 = 0.03, 0.03, 0.02; Wilcoxon signed-rank, $p < 0.05$ for all; 5-fold CV). Our results suggest that preparatory activity in CFA M1 is unlikely to stem from a single source or be primarily hierarchically organized, but is instead distributed across multiple motor system regions.

Disclosures: N. Koh: None. **A. Kristl:** None. **M. Agrios:** None. **S.P. Savya:** None. **A. Miri:** None.

Poster

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Topic: E.04. Voluntary Movements

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Title: Mapping forelimb-related M2-to-M1 synaptic circuit connections in the mouse

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Abstract: The planning and execution of hand and forelimb movements during goal-directed behaviors involves cortical activity across multiple areas, particularly primary and secondary motor (M1, M2) and primary somatosensory (S1) cortices. We recently mapped synaptic connectivity in the forelimb-related S1-to-M1 sensorimotor pathway. Here, to explore cellular-level mechanisms underlying inter-areal communication on the premotor side of this cortical network, we investigated the synaptic circuit organization in the forelimb-related M2-to-M1 corticocortical pathway. In acute brain slices from adult animals, we optogenetically photostimulated M2 inputs while electrophysiologically recording responses in identified subtypes of M1 neurons. In one series of experiments, we targeted recordings to cervically projecting corticospinal neurons, located in layer 5B, and for comparison, layer 2/3 pyramidal neurons. Photostimulation of M2 inputs evoked excitatory postsynaptic potentials and currents in corticospinal neurons, and strong disynaptic inhibitory inputs, while pyramidal neurons in layer 2/3 received lower amplitude excitatory and inhibitory inputs. We also characterized inhibitory mechanisms in this pathway by directly sampling M2 input to multiple M1 inhibitory interneuron types, and by mapping inhibitory inputs from these interneuron classes to corticospinal neurons. Our findings help to define a working model for the cell-type-specific circuits mediating M2-to-M1 communication.

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Poster

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Topic: E.04. Voluntary Movements

Support: NCFA-F32

Title: The role of spinal cells and circuits during jumping behavior

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Abstract: Movement is fundamental to support animal behavior and critical for environmental interaction. While substantial research has elucidated many aspects of motor control, significant gaps exist in understanding the spinal cord's role in movement execution and coordination. Here, we focus on jumping, a highly conserved, innate, and discrete behavior, to understand how the spinal cord encodes movement. It is a complex, reliable, and robust full-body behavior with multiple coordinated symmetric movements across the joints and can be invoked as part of locomotion, escape, predation, or play. We have developed a horizontal gap jumping assay in which behavior can be divided into four phases: preparatory, propulsive, flight, and landing. Our

behavioral quantitative measures include eleven landmarks with five mouse joints tracked using three high-speed cameras aligned with electromyography recordings, which allow us to extract the joint position, angles, velocity, acceleration, and muscle activity. This robust set of features enables sophisticated high-dimensional analysis using machine learning and classification algorithms to identify jumping phases or features that can be assigned to a specific spinal cell type or circuit. We also developed a closed-loop system to perform close-loop optogenetic perturbations and test when a cell type or circuit is required for jumping. This research not only fills a significant gap in our understanding of the spinal cord functionality in movement but also sets a foundation for future investigations into neural control mechanisms.

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Poster

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Topic: E.04. Voluntary Movements

Support: NIH

Title: Functional role of excitatory brainstem neurons in motion control

Authors: *M. B. SEO[1], J. J. HUANG[2], H. W. TAO[3], L. I. ZHANG[4];
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Abstract: The brainstem serves as a crucial pathway between upper motor centers and the spinal cord to execute coordinated movement. Despite advancements, understanding the precise roles of specific brainstem regions in motion control remains incomplete. Recent investigations suggest the presence of specialized modules within the brainstem dedicated to executing distinct motor commands. However, the functional role of the caudal portion of the pontine reticular nucleus (PRNc) remains poorly understood. In this study, utilizing cell-type specific optogenetic modulation in adult mice, we investigate the role of excitatory neurons expressing the Vglut2 marker within the PRNc. By optogenetically manipulating the activity of Vglut2+ PRNc neurons and monitoring their activity in freely moving mice with microendoscopic calcium imaging, our preliminary results suggest that this brainstem region may be involved in controlling specific body movement of the animal in daily life.

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Poster

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Title: Network switching to rescue skilled reaching behavior

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Abstract: Acute optogenetic inactivation of the sensorimotor cortex paralyzes skilled reach-to-grasp actions in mice. However, with prolonged exposure to cortical inactivation, we discovered that mice can dramatically regain successful motor function. To elucidate the neural substrate underlying this recovery, we targeted extracellular electrodes to several structures implicated in forelimb control including the caudal forelimb area, rostral forelimb area, striatum, and motor thalamus. Surprisingly, the kinematic encoding of the recovered reaching action was absent in each of these areas, as if each was ignorant to the ongoing movement. This suggests that a loss of motor cortical dynamics may result in the transfer of control to a network that diverges greatly from the typical circuit. To illuminate its location, we used a silent fMRI technique to obtain a whole-brain map of motor activity. This map suggested a potential upregulation in ipsilateral sensorimotor cortical activity as mice attempted to regain motor function. Subsequent electrode recordings revealed an ipsilateral copy of the reach-to-grasp commands that were missing from the contralateral circuit. Moreover, the optogenetic inactivation of the ipsilateral sensorimotor cortex partly reversed recovery. Together, our experiments suggest that reaching actions are flexibly and robustly supported by parallel contralateral and ipsilateral pathways in the rodent. Deterioration in contralateral control may be compensated in part by changes in the ipsilateral cortex.

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Poster

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Title: Traveling waves enable reliable volitional motor movement

Authors: *O. T. KOLHE[1], H. F. KHAN[1], M. HABIBIMATIN[1], E. F. TANASE[2], K. JAYANT[1];
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Abstract: Traveling waves (TWs) are an emergent phenomenon observed in dynamical systems throughout nature. Recent advances in high-density neural recording technologies have allowed scientists to record traveling waves throughout the mammalian brain. These TWs mediate various aspects of animal cognition, such as stimuli perception, volitional movement, and working memory. Theoretical studies have suggested that these TWs play an important role in preserving time during information transfer between two brain regions and for plasticity across long-range neural circuits. Yet their potential functional and behavioral relevance remains unknown. In this work, by implementing custom-designed flexible high-density NeuroGrids, we demonstrate that traveling waves distinctly reflect task-relevant information in mice performing a contextual volitional motor task. Specifically in the primary motor cortex, propagating traveling wave phase-directionality reflected impending movement after an external stimulus. In contrast, the propensity of precise wave generation relied on the presence of external context. This was reflected by changes in the reliability of local spiking populations of cortical neurons across task conditions, which tightly coupled with ongoing wave dynamics within a lower dimensional state-space. A 3D temporal convolutional neural network trained on just the phase gradients of surface LFP accurately predicted behavioral outcomes, indicating that the surface TWs carry behaviorally relevant information. Using focal cooling and optogenetic inhibition, we show that the secondary motor cortex modulates the structured generation of traveling waves and correct motor execution via distinct pathways: cortical and subcortical through the motor thalamus. Thus, our results suggest that traveling waves predict task-specific computations

required for reliable volitional movement and can dynamically coordinate activity between distinct brain regions via bottom-up and top-down pathways.

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Poster

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Topic: E.04. Voluntary Movements

Support: NIH RO1 NS108424
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Title: A Window into Skilled Motor Behaviors using Optogenetic Holography

Authors: *H. PANCHOLI[1], M. TRUSEL[2], T. F. ROBERTS[1];
[1]UT Southwestern Med. Ctr., Dallas, TX; [2]Neurosci., UT SouthWestern Med. Ctr., Dallas, TX

Abstract: Neural sequences of activity underlie the precise production of learned motor behaviors. How different neurons participating in neural sequences may uniquely contribute to aspects of motor actions, such as the timing or trajectory of movements, is unknown. Male zebra finches produce a stereotyped courtship song and have a well-defined neural circuit controlling this song. Here we examine how different excitatory neurons in HVC, the premotor cortical analog that generates patterns of activity during song, influence song motor production. HVC contains two principal classes of projection neurons, intratelencephalic neurons (IT) projecting to a pallial motor region, and corticostriatal neurons (CST) innervating the basal ganglia. These neurons produce temporal sequences of activity underlying stereotyped song production. However, it remains unclear how they may uniquely contribute to song. With the goal of editing connectivity in HVC, we used two-photon optogenetics to play sequences of activity into IT or CST neuron populations in offline states, and examined how these manipulations impacted song production. Previous studies indicate that HVC might encode song timing and it has also been suggested to control spectral-acoustic song gestures. We find that song timing is influenced by manipulating either IT or CST neurons. Crucially, the acoustic structure of song is also altered, but only when manipulating the CST neurons. This suggests that HVC can control both song timing and song gestures via partially overlapping circuits. Thus, cellular-resolution, subtype specific manipulations reveal that different cell-types within a neural sequence can uniquely contribute to aspects of skilled motor actions.

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Poster

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Program #/Poster #: PSTR073.17/E37

Topic: E.04. Voluntary Movements

Title: Testing Hierarchical Models of Self-Driven Action Decisions

Authors: *S. SAVYA[1], M. AGRIOS[2], N. KOH[3], A. KRISTL[3], S. HSU[4], A. MIRI[5]; [1]Northwestern Univ., Chicago, IL; [2]Neurobio., Northwestern Univ., Evanston, IL; [3]Neurobio., Northwestern Univ., Chicago, IL; [4]Princeton Neurosci. Inst., Princeton, NJ; [5]Northwestern Univ., Evanston, IL

Abstract: Several brain regions have been implicated in self-driven action decisions, and several hierarchical models have been proposed to explain the neural dynamics across these regions. One model concerns the initiation of movement, where the striatum is thought to integrate inputs from multiple regions of frontal cortex, leading ultimately to selective disinhibition of output from the motor thalamus that in turn drives motor cortical output. We set out to quantify interactions between multiple brain regions implicated in self-driven action decisions and test this existing hierarchical model using metrics that enable assessment of neural interactions on the timescale of synaptic communication. Head-fixed mice engaged in a self-paced climbing paradigm where they frequently decided when to initiate climbing over continually varying terrain with all four limbs. Four Neuropixels coated in CM-DiI were used to simultaneously record neural activity in medial prefrontal cortex (mPFC), forelimb M1 (fM1), forelimb S1 (fS1), forelimb M2 (fM2), dorsolateral and ventromedial striatum (DLS, VMS), and the basal ganglia (BG) recipient region of forelimb motor thalamus (bgfMT) along with electromyographic recordings from the right forelimb muscles and video recording of the right forelimb and hindlimb. To verify recording sites, mice were injected with an AAV1 that drives neuronal expression of Cre recombinase in the entopeduncular nucleus (BG output) and with another AAV that drives Cre-dependent neuronal expression of green fluorescent protein (GFP) into thalamus to label thalamic neurons that receive basal ganglia input. Alexa fluor-conjugated cholera toxin subunit B (CTB) was then injected into spinal segments C4-C8 to retrogradely label the fM2, fM1, and fS1 areas. CTB was also injected into fM1 to retrogradely label the bgfMT. Brain sections were imaged to visualize the CM-DiI, CTB, and GFP and then registered to the Allen common coordinate framework (CCF). Each recorded unit is associated with a centroid located along the Neuropixel shank, enabling units to be localized within the CCF. Subsets of neurons were also localized to backlabled fM1, fM2, fS1, and bgfMT. These experiments yielded data from 14 sessions across 8 mice. The average cell yield per session were 170 in mPFC, 128 in fM2, 115 in fM1, 132 in fS1, 234 in DLS, and 52 in bgfMT. In current work, we are using transfer entropy, point-process Granger causality, and convergent cross mapping as firing pattern predictivity metrics to elucidate imbalances in the ability of one region to predict the activity of another. This will allow us to test predictions of hierarchical models during self-driven action decisions.

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Poster

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Topic: E.04. Voluntary Movements

Title: Hierarchical motor cortical population dynamics across control modalities during complex movements

Authors: *A. AGARWAL[1], M. RIGOTTI-THOMPSON[3], B. KARPOWICZ[3], F. PEI[3], N. EVEN-CHEN[4], C. PANDARINATH[3,2];
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Abstract: Our motor system is remarkably flexible in its ability to perform movements with different effectors. For example, we can produce strikingly similar handwriting using a pen on paper or a fingertip on a tablet screen. How does motor cortex perform computations that precisely generate movements while preserving flexibility in control modality? Previous work has revealed coarse structure in motor cortical population activity that is shared across different constrained movements. Yet, it is unclear if such structure is present during more complex movements. Additionally, behavioral and physiological evidence suggest that the motor system uses a hierarchical encoding, where representations of abstract action goals can be shared even for movements that are executed with very different muscle commands. Here we ask whether this hierarchy is implemented by neural population dynamics within motor cortex. We recorded motor cortical activity from a macaque performing a cursor control task that elicited diverse movements (35x35 grid of start/target positions) using either a joystick or mouse for control (>400 trials per modality). Spike counts (15ms bins) were collected from 1024 electrodes distributed in area and depth across motor cortex (Neuralink N1). Trial-averaging is challenging given the scarcity of repeated movement conditions, so we used latent factor analysis via dynamical systems to obtain denoised firing rates for each trial. We then tested whether a subset of the population's activity was modality-independent. For single channels, activity exhibited a wide range of dependence on control modality. To quantify this at the population level, we applied a task kinematics-agnostic decomposition of single-trial activity, which revealed that a substantial portion of the total variance (TV) was explained by a modality-independent neural subspace (>50%). Within this subspace, single-trial dynamics and kinematic encoding were remarkably similar across modalities. This method also revealed neural subspaces where activity was control modality-specific (>15% and >8% of TV in joystick and mouse subspaces, respectively). We also applied dPCA - a supervised method that requires trial-averaging - and consistent with the above, found that substantial variance was either unrelated to the control modality (>35% TV) or dependent on it (>25% TV). These results suggest that the execution of

complex movements using different control modalities is implemented through flexible recruitment of a hierarchy of motor cortical population dynamics tied to different levels of abstraction. Further analyses will aim to disentangle information flow between subspaces.

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Poster

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Topic: E.04. Voluntary Movements

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Title: Trial-by-trial modulation of somatosensory signals to the sensorimotor cortices upon the initiation of dynamic wrist movement in macaque monkeys

Authors: *W. HASEGAWA[1], J. YOSHIDA[2,3,1], S. KIKUTA[1], S. KUBOTA[1], K. SEKI[1]; [1]Natl. Ctr. of Neurol. and Psychiatry, Tokyo, Japan; [2]Tokyo university of agriculture and technology, Tokyo, Japan; [3]Natl. Ctr. of Neurolgy and Psychiatry, Tokyo, Japan

Abstract: Changes in sensory evoked potentials (SEPs) provide insight into the complex sensory gating process, a critical mechanism governing perception and motor control. Sensory gating involves the brain's ability to filter and prioritize crucial sensory information, shaping our interactions with the environment. Understanding the dynamic modulation of SEPs during voluntary movement is crucial for unraveling the complex mechanism coordinating between sensory input and motor output. Previous studies on SEP responses have indicated that afferent signals are gated during movement, as averaged across multiple trials. However, it remains unclear whether this gating is regulated moment-to-moment to enhance the performance of each trial. To address this question, we examined how the primary motor cortex (M1) and primary somatosensory cortex (S1) exhibit trial-by-trial modulation of SEPs in monkeys (n=2) performing ramp-and-hold tasks using wrist flexion and extension movement. We recorded the SEPs, evoked by electrical stimulation of implanted nerve cuff electrodes on the superficial radial and median nerves applied repetitively during the task, from M1 and S1 activities with S-probe multiple channel electrodes (32 or 64 channels, Plexon). Then, we analyzed how the trial-by-trial variations in the SEPs are correlated with the behavioral performances in each trial. The preliminary results from 8 recording sites each for M1 and S1 showed significant correlations between SEP modulation before movement onset and the onset timing of wrist movement.

Specifically, the closer to the movement onset, the greater the sensory gating observed in both M1 (8 out of 8 sites) and S1 (8 out of 8 sites). However, following movement onset, sensory gating gradually diminishes during dynamic wrist motion exclusively in M1 ($r = 0.58$, $p < 0.05$; 6 out of 8 sites), but it was sustained in S1 ($r = 0.44$, $p < 0.05$; 1 out of 8 sites). These results suggested that the somatosensory afferent signals are gated to make better top-down preparation for movement initiation, which commonly occurs in both M1 and S1. It could be specifically advantageous to suppress the transcortical reflex that could prevent precise movement onset for the M1 and to suppress the potential task-irrelevant feedback for the S1. However, once movement begins, the afferent input to M1 might have to be disinhibited to take advantage of the transcortical reflex to generate muscle activity. We concluded that sensory input to a wide area of the cortex is suppressed to spare more resources for making proper movement initiation, with M1 relying more on afferent inputs for movement execution.

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Poster

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Title: Thalamic interaction of basal ganglia and cerebellar circuits during motor learning

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Abstract: The ability to control movement and to refine and learn new motor skills is one of the fundamental functions of the brain. The basal ganglia (BG) and the cerebellum (CB) are two key brain regions involved in controlling movement, and neuronal plasticity within these two regions underlies the acquisition of new motor skills. However, how these two critical motor regions interact and orchestrate together to produce a cohesive motor output remains poorly understood. Here, we used an intersectional viral tracing approach to identify neurons in the motor thalamus that receive inputs from BG and CB and found that a subset of neurons in VM and VAL receive

converging BG and CB inputs. Using slice electrophysiology in combination with optogenetic activation of BG and CB projections we show that these thalamic neurons receive functional inhibitory inputs from the BG and excitatory inputs from the CB. Moreover, using chemo-and optogenetic silencing, we demonstrate the role of these thalamic neurons and their inputs in motor learning and motor control. Lastly, using in vivo fiber photometry and two-photon calcium imaging through an implanted GRIN lens in the motor thalamus, we measured neuronal activity in mice learning lever-push and locomotion tasks and found that motor thalamus neurons show distinct movement related activity patterns. These results indicate that neurons in the motor thalamus receive converging input from BG and CB and may play an important role in integrating movement signals during motor learning.

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Poster

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Title: Engineering a faster connectivity between mouse M1 and laryngeal muscles for vocal behavior

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Abstract: The human ability to communicate with learned vocalizations is proposed to be enabled by a robust direct projection from primary cortical motor regions of M1 to nucleus ambiguus (Amb) motor neurons in the brainstem involved in controlling the laryngeal muscles for production of vocalizations. Mice have been found to have a rudimentary version of this projection, which lead to the vocal learning continuum hypothesis, where mice are posited to be limited vocal learners. Several candidate genes have been proposed to play a role in the development of the more robust connection in humans and other vocal learning species, including the gene *PlxnA1*, an axon guidance receptor that is down regulated in human laryngeal motor cortex and the analogous cells types in songbird HVC and RA. Past studies have shown that mice with a *PlxnA1* knockout in cortical neurons display more direct projecting neurons from cortex to forelimb motor neurons and superior manual dexterity. In our lab, we created mice that have a *PlxnA1-Rbp4-Cre* knockout that is specific to layer V pyramidal neurons, which

in turn leads to salient changes in mouse song frequency bandwidth and syllable sequencing, in addition to increased M1 to Amb direct projections. Here, we used intracortical microstimulation (ICMS) in wild-type (WT) and *PlxnA1-Rbp4-Cre* knockout (KO) mice to study whether this enhanced Amb innervation leads to faster control of vocal musculature by cortical populations. We stimulated sites across M1 in a single hemisphere and recorded electromyography (EMG) signals from the contralateral laryngeal cricothyroid muscle (CT) muscle and extensor carpi radialis (ECR) forelimb muscle. We observed significantly shorter CT EMG latencies in *PlxnA1* KO mice as compared to WT counterparts. These shorter latencies were most apparent from the middle and posterior regions of M1. This effect was not observed in the corresponding forelimb EMG latencies. Our findings identify a cortex-specific change in gene expression that drives phenotypic changes in vocalization, increases anatomical connectivity, and induces faster control from cortex to vocal musculature in the mouse. This study provides greater insight into the genetic changes that may enhance vocal control abilities and gives further support for *PlxnA1* as a candidate gene involved in the evolution of human vocal learning.

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Poster

PSTR073: Multiregion Pathways in Movement Control

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Program #/Poster #: PSTR073.22/F2

Topic: E.04. Voluntary Movements

Support: Knight Initiative
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Title: Cortico-striatal neuronal dynamics imaged across motor learning

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Abstract: The motor cortex and dorsolateral striatum (DLS) play crucial roles in motor skill acquisition and execution. Prior studies have revealed sequential neuronal activity patterns in both motor cortex and striatum after the acquisition of a motor task, but how these dynamical patterns jointly evolve over the course of motor learning to encode skilled movements remains poorly understood. To monitor the joint dynamics of motor cortex and DLS, we labeled cortico-

striatal projection neurons and DLS spiny projection neurons with the GCaMP7 Ca^{2+} indicator and imaged neural activity in each brain area using a dual-axis two-photon microscope (Lecoq *et al*., *Nat Neurosci*. 2014; Wagner *et al.*, *Cell* 2019). To apply this imaging approach to the study of motor learning, we trained mice to run under the microscope on a kinematically challenging treadmill, upon which the mice received rewards at evenly spaced positions. Over weeks of training, mice gradually improved their motor performances, and we repeatedly monitored Ca^{2+} activity in the same sets of cortical and DLS neurons. To track motor improvements, we evaluated behavioral metrics, such as kinematic quality and the mouse's running speed, throughout the learning process. Our data reveal dynamic changes in the neural activity patterns and interactions between motor cortex and DLS throughout motor learning. Correlations between cortical and striatal activity via a communication subspace of shared activity patterns increase over learning, as do the abilities to estimate the mouse's speed and position on the treadmill based on the activity in each brain area. The mouse's speed, a kinematic variable, could be decoded well even prior to learning, and speed estimation accuracies improved further over time. Decoding of the mouse's position on the treadmill, a task-related variable, was initially poor but rapidly improved with motor training. Interestingly, representations of both variables stabilized more quickly in motor cortex than striatum, particularly for the encoding of position. Moreover, over the course of learning, a notable subset of neurons in both brain regions developed position-tuning curves. These tuning curves were sharper in the cortex than in DLS, and once developed, remained consistent over days. Overall, our results reveal a temporal progression in the development of neural representations, with cortical encoding maturing faster than striatal representations, especially in the first ~2 weeks of learning. This suggests there are distinct plasticity mechanisms in the motor cortex and DLS and also underscores the complex interplay between brain areas during skill acquisition and execution.

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Poster

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Simons Foundation

Title: The interactions between premotor and motor cortex can be flexible

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Abstract: How is flexible behavior supported by the nervous system? Modular structure in the brain suggests an organization whereby individual regions may emphasize specific processes, and flexibility in behavior is implemented through flexibility in brain-wide interactions. Here, we sought to probe the extent to which interactions between brain areas can be flexible. We compared flexibility in the interactions between brain areas to the flexibility in the interactions within a single brain area. We hypothesize that interactions between brain regions are more flexible than interactions within single regions. The dorsal premotor cortex (PMd) and the primary motor cortex (M1) provided a suitable testbed for interactions, considering their connectivity and well-known differential involvement in motor control.
To probe the limits of flexibility in the interactions between populations of neurons, we developed a novel brain-computer interface (BCI) paradigm using populations of neurons in PMd and M1. In order to characterize functional interactions between separate populations, we used canonical correlation analysis (CCA) to identify the most strongly correlated dimensions of neural activity between the two populations. Then, we designed a novel mapping from neural activity to cursor movements to directly challenge the animal to break the naturally-occurring correlation, and thereby administer a causal test of the flexibility of the interactions between neural populations. Here, we define "breaking a correlation" to mean expressing a distribution of neural activity patterns that were decorrelated across the two populations. To test interactions within single areas, two populations were constructed by randomly splitting the neurons from that area into two groups and then applying an identical procedure to challenge correlations.
We conducted seventy sessions in two monkeys where the animals were challenged to decouple activity either between PMd and M1, or within PMd only or M1 only. We found that correlations between two brain regions were easier to break than correlations identified within either single brain area. In breaking the across-area correlations, both animals generated novel neural population activity patterns that pushed outside of the observed correlation structure. We also found that changes to the correlation structure often extended beyond the specific pair of across-area dimensions that were tested. Together, these results provide causal evidence that the interactions between brain areas can be flexible, and perhaps this supports the vast repertoire of existing behaviors.

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Poster

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Topic: E.04. Voluntary Movements

Support: Lendület Grant HAS

Title: Interaction between the motor cortex, inhibitory rostral brainstem neurons, and the thalamus in movement control

Authors: *E. BOSZ[1], V. M. PLATTNER[2], L. BIRO[1], K. KÓTA[1], M. A. DIANA[3], L. ACSADY[1];
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Abstract: Movement and locomotion are governed by highly specialized subcortical motor networks. Many of these subcortical centers, including the basal ganglia and the cerebellum form nested loops with the cortex and the thalamus. Recently, the rostral pontine reticular formation (PRF) has also been implicated in the coordination of whole-body movements. In this study, we investigated whether a functional cortico-subcortical-thalamic loop can be detected in the case of the inhibitory neurons of the PRF that express glycine transporter type 2 (PRF/GlyT2 cells). Earlier PRF/GlyT2 cells were shown to project to the intralaminar (IL) and parafascicular (Pf) thalamic nuclei and their activation could evoke a strong motor phenotype. Here we first show that layer 5 pyramidal cells of the secondary motor and cingulate cortices (M2/Cg) establish synapses mainly on the mid-caliber dendrites of PRF/Glyt2 cells. Pf/IL projecting PRF/GlyT2 cells were among the targets of M2/Cg fibers. We also found that Pf/IL-projecting M2/Cg cells collateralize to PRF and innervate PRF/GlyT2 cells. Since Pf/IL project back to M2/Cg we could demonstrate that M2/Cg, PRF/GlyT2 cells, and Pf/IL can form nested loops. Next, with optogenetic activation of the M2/Cg-PRF/GlyT2 pathway in vitro and in vivo we disclosed faithful, non-depressing, glutamatergic synaptic responses in PRF/Glyt2 cells that allowed short-latency action potential generation with high probability even at high presynaptic stimulation frequencies and a strong cortical control over the spontaneous activity of PRF/GlyT2 cells during slow cortical oscillation. Finally, we investigated the impact of PRF/Glyt2 cells on thalamic activity and rotational behavior. Activation of PRF/GlyT2 axons in IL/Pf significantly decreased the thalamic firing rate and led to contralateral turning. However, activation of GlyT2 cell bodies in PRF could induce both ipsi- and contralateral turning in different animals. We could explain this heterogeneity by a differential, ipsilateral innervation pattern of the lower brainstem by thalamic projecting PRF/GlyT2 cells. Our results suggest that PRF/GlyT2+ cells play an important role in motor control as part of nested cortico-subcortico-thalamic loop, bridging ascending and descending motor networks in the brainstem.

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Poster

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Topic: E.04. Voluntary Movements

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Title: Task-dependent selective transmission of beta rhythms to muscles

Authors: *M. SARASQUETE MARTINEZ[1], R. HANNAH[2], D. FARINA[3], J. IBANEZ[4]; [1]Univ. de Zaragoza, Zaragoza, Spain; [2]Dept. of Psychology, Univ. of California San Diego, La Jolla, CA; [3]Imperial Col. London, London, United Kingdom; [4]Bioengineering, Univ. of Zaragoza, Zaragoza, Spain

Abstract: Success in motor performance relies on the brain's ability to timely activate and inhibit muscle activity. Movement inhibition is associated with changes in beta activity in the cortex (15-30 Hz), which can be observed in muscles during steady contractions. We took advantage of this to study beta transmission to task-irrelevant muscles during different motor states. Specifically, we used a warned GO/NO-GO task involving a specific (task-relevant) muscle and studied how another (task-irrelevant) muscle reflected modulations in beta activity during the periods after the imperative (GO or NO-GO) stimuli. Doing this, we wanted to study the selectivity of beta activity across muscles and its dependence on motor states. Five healthy adult males completed 160 trials of a version of a GO/NO-GO task in which the effector muscle (first dorsal interosseus, FDI) and a task-irrelevant muscle (tibialis anterior, TA) had to be contracted throughout the entire duration of the trials. In GO trials (70 % of trials), subjects had to briefly increase the level of contraction of the FDI (task-relevant muscle) while maintaining the level of contraction of the TA (task-irrelevant) stable. In NO-GO trials, both muscles had to maintain contraction levels unchanged. Electromyography (EMG) and force recordings were used to analyse early markers of force inhibition and corticomuscular beta transmission. The mean failure rate was 24.5 ± 6.9 % in GO trials (too early or late responses) and 33 ± 22 % in NO-GO trials (force increases above a threshold), with a mean reaction time of 274 ± 35 ms. After the imperative stimulus, we observed a slight force decline peaking at 203 ± 21 ms in the FDI (NO-GO trials) and, at 173 ± 14 ms (GO) and 199 ± 20 ms (NO-GO) in the TA, with an amplitude around -0.2 % of the MVC. Following this initial subtle force deflection, beta activity showed significant variation based on trial type. The TA displayed notably higher beta power in GO trials than in NO-GO trials (97 ± 70 % vs 33 ± 24 %), with all subjects showing an increase in beta power in the GO trials. Interestingly, the marked reduction in beta power in the TA in NO-GO trials was paralleled by a relatively strong increase in beta activity in the FDI (58 ± 17 %). No clear link was found between the force dip's magnitude and the subsequent beta activity, suggesting that the beta rebound was not caused by the force perturbation. Overall, our results show and task-dependent transmission of cortical beta activity to muscles during movement and cancellation.

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Poster

PSTR074: BCI Sensory, Vision, Speech

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Program #/Poster #: PSTR074.01/F6

Topic: E.05. Brain-Machine Interface

Support: NIH Grant T32 NS047987

Title: Causal Decoupling of Intracortical High Gamma Activity and Spikes Using an Orthogonal Neurofeedback Brain Machine Interface

Authors: *T. LEI[1], M. R. SCHEID[1], R. D. FLINT, III[2], J. I. GLASER[2], M. W. SLUTZKY[2]; [2]Neurol., [1]Northwestern Univ., Chicago, IL

Abstract: Cortical local field potentials (LFPs) are produced by multiple brain sources, which are reflected in different frequency bands. Among these bands, high gamma activity (HGA) is widely considered to represent summed local spikes (sometimes called spike "leakage"). If this were true, then the nearest neurons to a given electrode should always contribute most to the HGA recorded on that electrode. We sought to investigate this further using a brain machine interface (BMI) paradigm that required subjects to decouple spiking from HGA recorded on a single (control) electrode in primary motor cortex by mapping these signals to orthogonal components of cursor movement in a 2-target center-out task. Subjects successfully dissociated these two signals, indicating that HGA is not simply a reflection of local spiking. Instead, HGA modulation correlated with neuronal population co-firing (the dominant neuronal subspace) that was widely distributed across a multielectrode Utah array, rather than locally. HGA modulation and spike modulation on the control electrode coincided with population activity that was highly aligned in general, but they were also separable in a smaller subspace of the population. Further, spike-triggered averaging showed that increases in HGA on the control electrode were preceded tightly by neuronal spiking from across the array. Together, these results suggest that HGA appears to be generated by a summation of local postsynaptic activity that is increased due to synchronous firing of presynaptic activity in the intrinsic neuronal manifold, rather than just local averaged spiking.

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Poster

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Department of Veterans' Affairs Merit Review Program – VAMR 5I01RX002654

Title: Aspects of speech production represented in inferior frontal gyrus

Authors: *P. R. PRAKASH[1,2], T. LEI[3], C. FOLI[4], J. I. GLASER[3], B. AJIBOYE[4], M. W. SLUTZKY[5];
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Abstract: Despite numerous hypotheses regarding the role of the inferior frontal gyrus (Broca's area) in speech production, its precise function remains elusive. Lesions in this area can lead to expressive language deficits where patients tend to omit grammatical elements and simplify sentence structure (agrammatism). Grammatical syntax can be defined as the rules that help us transform our nonsequential thoughts into a linear sequence to express our thoughts meaningfully. These rules imbue our words with context that highlight differences in time (e.g., tense), grammatical number (singular vs. plural in English) or semantics. Some imaging studies have reported an association between damage to IFG and syntax comprehension. Some intracranial recordings in IFG suggested some modulation of event-related potentials in IFG (mainly pars triangularis, area 45) with tense processing [Sahin et al, Science 2009]. However, IFG's (in particular area 44's) role in grammatical processing remains unclear in terms of the type of processing in which it participates and the amount of information it contains for single-trial decoding. Here, we recorded broadband activity from a human participant as part of the Reconnecting the Hand and Arm to the Brain (ReHAB) clinical trial. The study participant was implanted with six, 64-channel microelectrode arrays across the sensorimotor network, specifically in primary motor (M1 x2), primary sensory (S1 x2), anterior intraparietal (AIP x1) and left posterior inferior frontal gyrus (IFG x1; anterior border of Area 44 and 6v). As part of a sentence completion task, the participant was instructed to read a sentence with one verb missing. This was followed by a root verb that the participant had to conjugate, in agreement with the grammatical context of the sentence, and then speak aloud. We first extracted power by squaring the analytical amplitude in the spike band [SBP; 300 Hz - 5kHz] range. We saw modulation in SBP that started about 500 ms prior to voice onset. Using SBP in ten, 50-ms causal bins and a support vector machine classifier, grammatical number was decoded with an accuracy significantly above chance level (computed using shuffled labels) starting approximately 450 ms prior to voice onset. This suggests that IFG may play a role in processing syntax during sentence formation preceding speech production. This could potentially be useful in brain machine interface applications.

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Poster

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Support: NIH Grant 1R01NS092894-01
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Title: Production of an Affect Agnostic Somatosensory Neuroprothesis Via Optimized Intrathalamic Microstimulation

Authors: *L. M. DICKEY, B. A. SEE, W. A. WALKER, J. T. FRANCIS;
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Abstract: Somatosensory neuroprosthetics have the capacity to restore touch through the use of a sensitized robotic limb. We andothers have produced optimized somatosensory neuroprosthetics for simple touch force trajectories under simpleexperimental conditions that is without explicitly modulating the subjects affective state via reinforcers. It is known thatcognitive signals modulate the sensory thalamocortical system(1)and the sensorimotor system (2).In this work wedetermine the influence of reinforcers, both positive and negative, on the throughput of a somatosensoryneuroprosthesis (3).We have developed an experimental approach to formulate a model of the thalamocortical circuit(VPL and S1) using biomimetic stimulation protocols(3).To expand our previous work past touch force trajectories wenow include cued levels of expected reward for correct trials or punishment for failed trials. The behavioral task has rat's using a 2-D robotic manipulandum to make reaching movements to spatially cued targets with cues presented in visualspace as well as touch position on the ipsilateral paw while the contralateral paw is used to control the manipulandum.All animal protocols were approved by the University of Houston Institutional Animal Care and Use Committee (IACUC).Four male Lewis rats (9-11 weeks old) were chronically implanted with multi-contact electrode arrays in the upstreamVPL and downstream S1.We administered bipolar biphasic intrathalamic microsimulation (ITMS) in the VPL through amulti-shank multi-electrode array (64 channels) while local field potentials (LFPs)and spikes were recordedsimultaneously from 64 channels in the S1.Thalamic probing protocols and cortical principal components were used intraining a state space model via a linear subspace algorithm(3).These models are utilized with model predictive control(MPC) to optimize VPL-MiSt inputs to neural templates extracted previously in natural taction experiments.References1.Marsh, B. T., Tarigoppula, V. S. A., Chen, C. & Francis, J. T. Toward an Autonomous Brain Machine Interface:Integrating Sensorimotor Reward Modulation and Reinforcement Learning. *J. Neurosci.* **35**, 7374–7387 (2015).2.Guzun, L., Fortier-Poisson, P., Langlais, J.-S. & Smith, A. M. Tactile sensitivity in the rat: a correlation betweenreceptor structure and function. *Exp Brain Res* **239**, 3457–3469 (2021).3.Choi, J. S. *et al.* Eliciting naturalistic cortical responses with a sensory prosthesis via optimizedmicrostimulation. *J. Neural Eng.* **13**, 056007 (2016).

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Poster

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Title: A fast streaming neuroprosthesis for fluent real-time speech synthesis

Authors: *K. LITTLEJOHN[1,2], C. CHO[2], J. R. LIU[1], A. SILVA[1], B. YU[2], V. ANDERSON[1], C. KURTZ-MIOTT[1], S. BROSLER[1], A. KASHYAP[2], I. HALLINAN[1], A. SHAH[2], A. TU-CHAN[1], K. GANGULY[1], D. A. MOSES[1], E. F. CHANG[1], G. K. ANUMANCHIPALLI[2,1]; [1]Univ. of California, San Francisco, San Francisco, CA; [2]Univ. of California, Berkeley, Berkeley, CA

Abstract: Natural spoken communication happens instantaneously. Delays longer than a few seconds can disrupt the natural flow of conversation. This makes it difficult for individuals with paralysis to participate in meaningful dialogue, potentially leading to feelings of isolation and frustration. While speech neuroprostheses aim to restore natural communication, it is unclear whether speech can be synthesized from brain data with low latency, mirroring natural speech production. Here, we used high-density surface recordings of the speech sensorimotor cortex in a clinical trial participant with severe paralysis to drive a continuously streaming speech synthesizer. We designed and employed novel deep-learning transducer models to achieve online large-vocabulary intelligible fluent speech synthesis personalized to the participant's pre-injury voice with neural decoding in 80-ms increments. This resulted in a median latency of 1.1 seconds and 47 synthesized words per minute, making it the fastest synthesis from the brain to date. Offline, the models demonstrated implicit speech-detection capabilities and could continuously decode speech indefinitely, enabling uninterrupted use of the decoder and further increasing speed. Our framework also successfully generalized to other silent-speech interfaces, including single-unit recordings and electromyography. Our findings introduce a new speech-neuroprosthetic approach to restore fast-spoken communication to people with paralysis.

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Poster

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Program #/Poster #: PSTR074.05/F10

Topic: E.05. Brain-Machine Interface

Support: DoD CDMRP SCIRP SC180308
VAMR 5I01RX002654

Title: Dynamic reorganization of local network connectivity during motor and language processing

Authors: *C. FOLI[1,2], E. C. CONLAN[1,2], W. D. MEMBERG[1,2], A. KETTING-OLIVIER[1,2], R. F. KIRSCH[1,3,2], B. A. AJIBOYE[1,3,2];
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Abstract: Contrary to the notion of rigid functional specialization, local populations of neurons in various cortical regions have been frequently found to exhibit an ability to represent multiple tasks concurrently. The underlying organizing principles (neural mechanisms) facilitating such flexibility within biological networks are still unclear. Drawing on insights from graph theory and network science, we analyzed intracortical recordings from the Inferior Frontal Gyrus of a human with tetraplegia to elucidate how the functional connectivities between local multi-unit populations vary across three tasks: open and closed loop virtual hand control, and grammatical inflection. Our analysis revealed that multi-unit populations did not form distinct task-specialized modules but instead demonstrated mixed tuning to multiple components of speech and grasping tasks. This mixed tuning was associated with an increase in network-wide connectivity strength driven by task demands. Furthermore, our analysis of network topology revealed a clustering of pairwise connections by shared response properties. These clusters captured distinct communication patterns across tasks, suggesting that the IFG is organized as a multi-layer network, with each functional layer capturing a unique pattern of selectivity to task components, as quantified by connectivity strength. Importantly, our results imply that the multi-layered organization of IFG facilitates efficient multi-task computation. Rather than recruiting new neuronal populations for each task, overlapping neural ensembles can adapt their connectivity patterns, enabling flexible implementations of new tasks. Taken together, this work contributes a generalizable framework for understanding multi-task representation in complex neural networks, offering insights into neural adaptability.

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Poster

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Topic: E.05. Brain-Machine Interface

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Title: Effect of force-related visual feedback on neural representation of force in the human grasp network

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Abstract: The purpose of this study was to investigate the effect of force-related visual feedback, provided through object deformation, on the neural representation of grasp force during a motor imagery task in virtual reality (VR). Grasp force control is important for dexterous object interaction and manipulation during upper limb movement restoration for people with tetraplegia. A better understanding of the neural representation of grasp force and how it is affected by sensory feedback may lead to development of effective bidirectional BMI controlled neuroprosthetics. Grasp force has been shown to be encoded in the fronto-parietal grasp network in non-human primates, consisting of primary motor cortex (M1), anterior intraparietal area (AIP), and F5 (analog of inferior frontal gyrus (IFG) in humans). It is well known that AIP is involved in visuomotor processing, interpreting visual information into necessary motor commands for downstream processing. We examined if visual inputs (visually deformed vs non-deformed objects) indicating various grasp force levels systematically modulated AIP and additional areas of the human grasp network during motor imagery grasp force task.. The study participant RP1 (motor complete/sensory-incomplete, C3/C4 AIS B SCI) was enrolled into the Reconnecting the Hand and Arm to Brain (ReHAB) Clinical Trial and implanted with six, 64 channel microelectrode arrays (one in AIP, one in IFG, two in M1, and two in S1). Neural activity in the grasp network and S1 was recorded while the participant attempted to exert appropriate force levels using a power grasp for the cue involving everyday objects being grasped by a virtual arm. The trial conditions were randomized between object visualizations with deformable and non-deformable objects and two objects cueing low and high force levels. Each trial was comprised of four epochs, a screen blanking period (2s) a premovement epoch (2-2.5s), a grasp formation epoch (0.8-1s) and hold epoch (3s). Comparison of condition-dependent modulation (force tuning) showed higher number of modulating neural features during tasks involving deformation of objects vs without in AIP and IFG areas during the hold epoch (ANOVA, $p<0.05$). The results from this study suggest inclusion of task-relevant sensory feedback, in this case through force-related visual deformation of objects, can improve the neural representation of grasp force in the human grasp network.

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Poster

PSTR074: BCI Sensory, Vision, Speech

Location: MCP Hall A

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Program #/Poster #: PSTR074.07/F12

Topic: E.05. Brain-Machine Interface

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Title: Spatial filtering for improved brain control of neuroprosthetics

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Abstract: Multichannel intracortical microelectrode arrays have been critical for advancing basic neuroscience studies and are now regularly used in both preclinical and human brain-machine interfacing (BMI) applications. These tiny high-impedance electrodes are prone to electromagnetic noise contamination which is going to become even more of a challenge as BMIs move outside of the controlled laboratory environment and into peoples' homes. BMI-controlled devices that apply stimulation to restore sensorimotor function pose extra challenges due to stimulation artifacts on the recordings. Spatial filtering is a computationally efficient way to remove common noise and improve the quality of the recorded signals before any feature extraction or decoding is performed. Spatial filtering involves subtracting a weighted average of various other channels from the channel of interest. The goal is to make the weighted average reflects the target channel's noise but without overlapping with the target channel's true neural signal. Methods, such as common average or median referencing are seldom optimal due to non-uniformity in the noise across channels. Better options, such as using linear regression to optimize non-uniform weights, can handle non-uniform noise but still may not be using the most beneficial cost function. Here we explore alternative non-uniform weighting options that use different cost functions. Since the optimal cost functions may be different based on the type of neural feature one is trying to extract, we are comparing how well different methods work to remove noise from four types of neural features commonly used in BMIs: (1) sorted spikes, (2)

unsorted threshold crossings, (3) root mean square of the signal in the spiking band (e.g. 300-3000Hz), and (4) local field potentials FFT features. To test the performance of different spatial filtering methods for different feature types, we used simulated data (where ground truth is known) as well as real recorded human and non-human primate data collected in different sensorimotor and BMI tasks where improvements in decoding accuracy was our performance metric. Preliminary results suggest array geometry and features used for decoding will impact which spatial filtering methods should be used.

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Poster

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Topic: E.05. Brain-Machine Interface

Support: R21NS128685
R01NS119160

Title: Restoring Muscle Force Control and Proprioception with Brain Machine Interfaces

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Abstract: Brain-controlled neuroprosthetics and intracortical microstimulation (ICMS) have the potential to enhance the quality of life of individuals with paralysis or neurological disorders by restoring aspects of motor control and sensation. Though kinematic limb control and touch sensation are more commonly studied, muscle-related sensorimotor activity is often overlooked despite being a crucial part of limb control. Our previous studies have shown that modulating limb stiffness throughout reaching can significantly improve the precision and energy efficiency of the movement. Similarly, while the outcomes of limb movement can be observed visually, muscle force cannot be accurately deduced visually. Therefore, we are interested in conveying muscle force via ICMS of area 3a neurons.
In our initial non-human primate study, we recorded upper limb EMGs and intracortical spiking activity from PMd, M1, and the M1-3a border deep in the central sulcus. Rhesus macaques performed a simple motor task to differentiate biceps activation, triceps activation, and cocontraction. Our cross-validated results reliably distinguished EMG states, with the M1-3a border area showing the most units encoding cocontraction. Subsequently, subjects were trained to use their neural signals for simultaneous control of the motion and stiffness of a virtual human arm model. To assess volitional stiffness modulation, we applied an oscillating perturbation to

the arm model which required the animal to increase cocontraction to maintain stability. Subjects were also able to successfully control the same arm model using direct cortical decoding of muscle activations rather than decoding motion and limb stiffness independently.
Next, we identified neuron pools within area 3a that encoded muscle force, length, and change in length. A custom setup was developed to observe the neural responses as the limb was held in specific positions, moved at specific speeds, and when the animal was required to generate specific isometric forces. To test if ICMS could generate sensations of muscle force, the monkeys completed tasks using isometric force to move a force-controlled cursor to hit different force target levels displayed on screen. Once trained in the task, we can hide the force-controlled cursor and apply ICMS to force-encoding neuron pools to see if the animal adjusts its force output to accommodate the change in perceived force. Adjustment to their force output will serve as validation that they not only perceive the stimulation but also integrate the sensation into their motor plan and modify their applied force as a result of this sensation.

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Poster

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Topic: E.05. Brain-Machine Interface

Support: DoD SCIRP SC180308
VAMR 5I01RX002654

Title: The strength-duration curve can efficiently characterize functional electrical stimulation muscle recruitment

Authors: *B. ALEXANDER[1,2,4], R. JAKES[2], W. MEMBERG[2,4], R. F. KIRSCH[2,4,3], D. J. TYLER[2], B. AJIBOYE[2,3,4];
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Abstract: Functional Electrical Stimulation (FES) can restore movement to people affected by paralysis due to conditions such as spinal cord injury or stroke. The muscle activation that FES causes is governed by the relationships between the stimulation parameters, electrode interfaces, and individuals' physiologies. Because of this, the muscle outputs caused by the available range of stimulation inputs must be quantified for each person. This characterization process, while essential for building effective stimulation patterns, is currently time consuming and characterization of the entire stimulation space is often unrealistic. By viewing the muscle recruitment surface as stacked strength-duration curves, and sampling those curves at different

levels of muscle activation, the entire muscle recruitment surface can be constructed from just a few points.
In order to confirm that the strength-duration relationship exists at all levels of muscle recruitment, curves were acquired from multiple muscles and muscle groups using multi-contact nerve cuff electrodes and surface electromyography (EMG). Curves at 10, 30, 50, 70, and 90 percent of a given muscle's maximum twitch EMG response were acquired for each muscle-contact combination. At each pulse amplitude (PA) value, pulse width (PW) was modulated using binary search in order to determine the value at which the desired muscle activation was achieved. This procedure was performed three times for each muscle-contact pair, and the results of those trials were averaged. This was performed for 5 different muscle groups in the human upper extremity.
The sampled points at each level of muscle activation and for each muscle-contact pair showed strong curve fits using the Weiss equation. The average R^2 value for all curve fits was 0.996 ± 0.008. For curve fits created from just the maximum PW point and the maximum PA point and the R^2 values calculated in comparison to all other points, the value was 0.958 ± 0.077. There was no statistical difference between the accuracy of the fits for different levels of activation. Additionally, in most cases, any two points that were not directly next to each other were capable of providing a satisfactory fit.
This newly demonstrated application of the strength-duration relationship will allow for effective characterization of an entire recruitment surface from a minimal number of points. This has the potential to save time and increase the accuracy and functionality of constructed FES patterns. Future work will involve constructing optimized stimulation patterns using these surfaces and determining whether this method can be efficiently used for day to day pattern recalibration.

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Poster

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EPSRC/UKRI Doctoral Training Porgramme
UK Dementia Research Institute

Title: Control of spatial navigation by an optical hippocampal brain-machine interface induces rapid reconfiguration of cognitive maps

Authors: *C. MICOU[1], S. HO[2,3], T. O'LEARY[1], J. KRUPIC[2,3];
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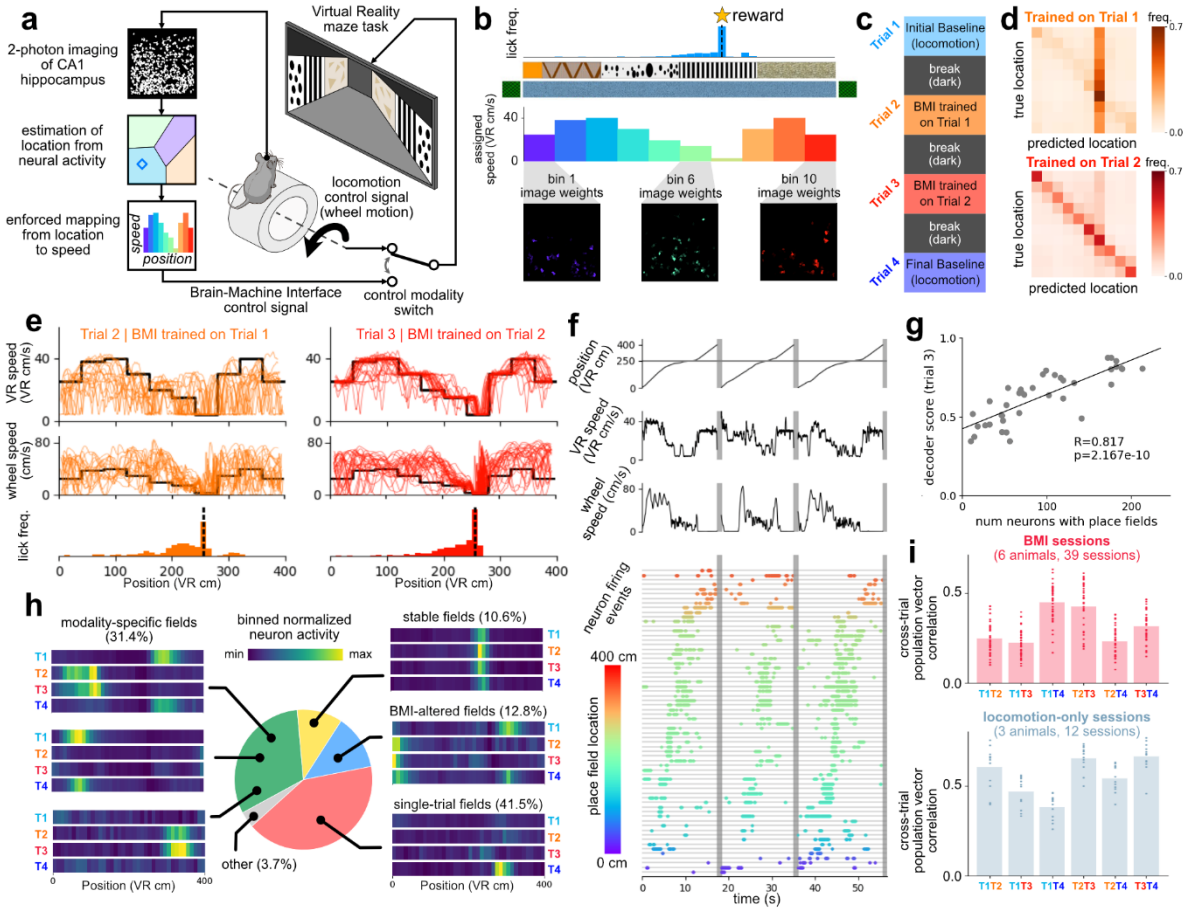
Abstract: The activity of neural populations in CA1 hippocampus exhibits a rich relationship with spatial navigation. However, this navigation is normally yoked to the motor actions responsible for travel. This coupling makes it challenging to distinguish abstract neural representations of travel from concrete motor actions. In this work, we employ a Brain-Machine Interface (BMI) to decouple running locomotion from travel while retaining the importance of CA1 activity in a navigation task (Fig. a). Initially, animals use locomotion to navigate a 1D Virtual Reality (VR) track. This serves as a basis to train a location decoder. In BMI trials, we map decoded locations to actions—choices of forward speed—designed to mimic stereotyped locomotion velocity profiles (Fig. b). Closed-loop decoder performance is initially poor despite high offline decoder accuracy: the change in control modality triggers a population-wide reconfiguration. By re-training the decoder on attempted BMI traversals (Fig. c), we achieve high accuracies in closed-loop decoding (Fig. d) thereby recreating stereotyped navigation trajectories (Fig. e). Animals are free to run or remain stationary on the wheel, and the new representation of the track remains intact (Fig. f). The quality of decoding (and thus trajectories) is determined primarily by the number of place cells in the population (Fig. g). A minority of place cells remain stable across all trials, with far more cells exhibiting place fields that are modulated by control modality. Exposure to BMI trials alters the response of certain cells during locomotion trials, resulting in a superposition of place fields from both control modalities (Fig. h). When we compare the similarity of track representations across pairs of trials within single sessions, we find these alterations visible at the level of population-wide metrics (Fig. i). Taken together, these findings suggest that cognitive maps may be embedding influence over outcomes, whether mediated by concrete motor actions or otherwise.



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Poster

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NWO grant number 024-005-022 'DBI2'
European Union's Horizon 2020 grant number 899287 'NeuraViper'
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Title: A biologically plausible phosphene simulator to facilitate the development of visual prostheses

Authors: *M. L. VAN DER GRINTEN[1], J. DE RUYTER VAN STEVENINCK[2], A. LOZANO[1], C. KLINK[1], B. RUECKAUER[2], L. PIJNACKER[2], P. R. ROELFSEMA[1], M. VAN GERVEN[2], R. VAN WEZEL[2], U. GÜÇLÜ[2], Y. GÜÇLÜTÜRK[2];
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Abstract: Blindness affects millions of people around the world. For some, a promising solution to restore a form of vision are visual prostheses, which convert camera input to electrical stimulation of the retina, LGN or visual cortex to bypass part of the impaired visual system. Electrical stimulation of these structures has been found to produce the perception of dots of light, called phosphenes. By evoking phosphenes in the right patterns, prosthesis wearers can be shown a representation of the outside world. As this representation has a limited resolution, visual prosthetics will need to rely on effective, efficient, and practically useful encoding of visual information. A common method for the optimization of this encoding is non-invasive functional evaluation in sighted subjects or with computational models by making use of simulated prosthetic vision (SPV) pipelines.
We present a biologically plausible, PyTorch-based phosphene simulator for cortical prostheses, that transforms realistic electrical stimulation patterns into biologically plausible representations of what the prosthesis wearer is expected to see. Our simulator integrates a wide range of clinical results with neurophysiological evidence in humans and non-human primates. The pipeline includes a model of the retinotopic organization and cortical magnification of the visual cortex. Moreover, the quantitative effects of stimulation strength, duration, and frequency on phosphene size and brightness as well as the temporal characteristics of phosphenes are incorporated. Our simulator can run in real time and uses differentiable operations to allow for gradient-based computational optimization of phosphene encoding models with machine learning. Our results demonstrate the suitability of the simulator for both computational applications such as end-to-end deep learning-based prosthetic vision optimization as well as behavioral experiments. Incorporation of the simulator in VR environments allows for the assessment of changes in parameters and realistic hardware and energy constraints on functionally relevant tasks such as navigation in naturalistic environments or object recognition. Other possible applications include the optimization of electrode implantation planning, prototyping and evaluation of stimulation protocols and the development of rehabilitation and support methods for prosthesis wearers. The modular and open-source software provides a flexible simulation framework for computational, clinical, and behavioral neuroscientists working on visual neuroprosthetics.

Disclosures: M.L. van der Grinten: None. **J. De Ruyter van Steveninck:** None. **A. Lozano:** None. **C. Klink:** None. **B. Rueckauer:** None. **L. Pijnacker:** None. **P.R. Roelfsema:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Pieter Roelfsema is co-founder and shareholder of a neurotechnology start-up, Phosphoenix (Netherlands). **M. Van Gerven:** None. **R. Van Wezel:** None. **U. Güçlü:** None. **Y. Güçlütürk:** None.

Poster

PSTR074: BCI Sensory, Vision, Speech

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Topic: I.08. Methods to Modulate Neural Activity

Support: VLAIO Grant HBC.2021.0187
HORIZON EIC Pathfinder Grant No101071015

Title: Intracortical current steering to increase the resolution of a visual prosthesis

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Abstract: Electrical stimulation of the visual cortex is known to elicit visual percepts, or phosphenes, which can be used in a visual prosthesis to create artificial vision for the blind. However, these visual prostheses often suffer from a low resolution, due to a limited number of stimulation sites. A usable form of artificial vision requires thousands of pixels, which begs the question if simply increasing the number of electrodes is the preferable strategy from a technical and biological perspective. On the other hand, simultaneous stimulation of multiple electrodes has been shown to create virtual electrodes in cochlear implants and to increase the resolution of deep brain stimulation.
To investigate the neuronal activation from current steering in the primary visual cortex, we used custom intracortical microelectrode arrays. These were implanted in coronal slices from 10 GCaMP6s mice and 2-photon calcium imaging was used to visualize the spatiotemporal response to bipolar stimulation. In each stimulation pattern, current was sent between a central and one or multiple return electrodes, for a total of 13 different directions. The central and return electrodes were located in L4 and L2/3 respectively, spaced 150 µm apart. Furthermore, the amplitude, polarity and asymmetry of waveforms were also varied.
The similarity in spatial activation between two stimulation patterns in the same slice was investigated with the Wilcoxon signed-rank test. This showed only small differences in activation for changing polarity and asymmetry, but significant differences for changing current directions (i.e. a fixed central electrode and a variable return electrode). All activated neuronal populations were characterized by their kernel density estimate, after projection on the two main axes: along the cortical column and along the cortical layers, which allowed us to locate the centre of activation. Due to the cortical columnar structure, this centre of activation was located in L2/3, and its location changed significantly with the direction of the current (i.e. with the location of the return electrode).
These experiments have shown that intracortical current steering can be used to selectively target neuronal populations around the central electrode. The number of different neuronal populations is larger than the number of electrodes, similar to virtual electrodes with cochlear implants. Nonetheless, clinical research is necessary to investigate how these different neuronal populations in the primary visual cortex translate to different phosphenes, and therefore how effectively current steering can indeed be used to increase the resolution of a visual prosthesis.

Disclosures: M. Schelles: A. Employment/Salary (full or part-time):; ReVision Implant. **K. Wierda:** None. **F. Ceyssens:** A. Employment/Salary (full or part-time):; ReVision Implant. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent

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Poster

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Topic: E.05. Brain-Machine Interface

Support: NEI Grant R01EY030569

Title: Minimally invasive photothermal activation of retinal neurons for vision restoration

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Abstract: Restoring vision in irreversible photoreceptor degeneration, such as from age-related macular degeneration or retinitis pigmentosa, is an ophthalmic challenge. Existing retinal prostheses suffer from low visual acuity and necessitate invasive surgical implantation. Our study demonstrates in mice a remote activation of retinal neurons using a near-infrared (NIR) laser following minimally invasive injection of gold nanorods (AuNRs), offering a potential for vision restoration without the need for device implantation or genetic intervention. By intravitreally injecting Thy-1 antibody-conjugated AuNRs into mice, we observed effective delivery of AuNRs to the retina confirmed by confocal fluorescence imaging and two-photon luminescence imaging, and sustained retention of AuNRs over several months. *Ex vivo* analysis revealed that with the injection of AuNRs, live retinal explants from GCaMP3 mice elicited significant Ca^{2+} fluorescence changes of retinal ganglion cells (RGCs) in response to the square pattern of scanning NIR laser (980 nm) stimulation up to 5% $\Delta F/F$ (n=9). The neuronal response precision was greater than 100 μm. Further, pharmacological examination identified the photothermal activation of retinal neurons was induced by transient receptor potential vanilloid (TRPV) 1 channel and primarily mediated by bipolar cells. *In vivo* studies showed that AuNRs-injected mice (n=6) exhibited significant electrocorticograms from the visual cortex under a square pattern of NIR laser exposure, while PBS-injected mice did not respond to the stimulus (n=4). Moreover, the intravitreal injection of AuNRs did not lead to significant systemic toxicity over several months in mice (n=8 per group). Our results underscore the potential of this photothermal technique in developing a high-resolution, minimally invasive retinal prosthesis, without the need for complex surgical procedures and genetic manipulation, and paving the way for a revolutionary approach to treat blindness.

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Poster

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Topic: E.05. Brain-Machine Interface

Support: NIH Grant 4UH3NS095557 – 03

Title: Moving targets: perceptual thresholds in a blind human for the Intracortical Visual Prosthesis (ICVP) require remeasurement in 82% of sessions

Authors: *M. P. BARRY[1,3], R. SADEGHI[4], K. STIPP[2], V. L. TOWLE[5], P. GRANT[6], B. BAK[7], F. J. LANE[2,6], R. W. BYRNE[8], M. J. BAK[7], J. P. SZLYK[6], S. COGAN[9], G. DAGNELIE[3], P. R. TROYK[1];
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Abstract: Sensory neuroprostheses require known perceptual thresholds to ensure stimulation levels are high enough to be perceived. Excessive cortical stimulation, however, can risk damaging tissue or inducing seizures. Thresholds are known to fluctuate over time, but it is not well documented how frequently remeasurement is necessary. One human with bare light perception was implanted with 25 subdural wireless floating microelectrode arrays in dorsolateral visual cortex in February 2022, each with 1.0-1.5 mm 16 iridium oxide film electrodes. Array stimulation has elicited up to 19 independent phosphenes in the lower left visual field that, when driven by a camera, produces some functional vision. Threshold levels (63% chance of producing visual percepts) for each of 687 electrode/parameter combinations were measured up to 28 times across up to 720 days. Current was varied within 1-60 µA, holding other parameters constant. Typical stimulation parameters included: 200 Hz, 400 ms trains, 200 µs cathodic phases in cathodic-first pulses, and 60 µs delays between successive electrode onsets. Up to 10% of trials were catch trials; false positive rates over 10% were rarely observed. Current for camera-based visual tasks was often set to 2x threshold, and the range of 1.5-3x threshold was safely usable. Tolerance for threshold fluctuations was thus defined as ±33%. Each threshold estimate was compared to its immediately preceding estimate for the same electrodes and parameters. Estimates for which 95% confidence intervals extended beyond ±33% were excluded from analysis. Comparisons of estimates within the same week were not considered. Means of relative estimate differences within each trial run were used to determine effects of date on threshold fluctuations; significance was determined by randomly permuting differences across timepoints and computing averages of absolute values of timepoint means 10^6 times. Median time between measurements was 21 (SD = 90) days. Thresholds deviated from previous estimates by over ±33% in 28% of measurements spread across 82% of timepoints. Deviations within trial runs were significantly skewed to be greater or less than 0, with absolute

means averaging 25% (n = 102, SD = 27%, $p < 0.007$, permutation resampling). Average deviation pooled across all trial runs was 5% (SD = 61%). Although little long-term change in thresholds was observed, the high percentage of threshold deviations that exceeded tolerance suggests that users and developers of some sensory cortical prostheses might need to recalibrate stimulation levels at least weekly. It will be important to develop methods to rapidly adjust stimulation levels with little to no user effort.

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Poster

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Topic: E.05. Brain-Machine Interface

Support: NIH BRAIN UG3NS107688
Blackrock Neurotech Contract to University of Utah
Blackrock Neurotech Contract to University of Minnesota
Blackrock Neurotech Contract to West Virginia University

Title: Translation of an intraneural auditory nerve hearing prosthesis

Authors: *L. RIETH[1], I. SONDH[2], K.-H. DYBALLA[3], M. LEBER[4], J. CREW[4], K. HUEBNER[5], A. P. HEILLER[6], W. NOGUEIRA[3], L. A. JOHNSON[7], G. M. GHOSE[8], H. A. HOLMAN[9], R. GURGEL[10], D. J. WARREN[11], S. ZUNIGA[12], A. LOVELAND[13], R. FRANKLIN[4], A. SAMII[14], A. J. OXENHAM[15], S. B. STRAHL[16], F. SOLZBACHER[17], M. ADAMS[13], T. LENARZ[18], H. H. LIM[2];
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Abstract: More than 1 million patients have been treated for hearing loss with cochlear implants [Zeng 2022] making them exemplar neuroprosthetic devices. Despite this success and years of R&D activity, little improvement in crucial tasks such as speech in noise has been achieved in the past two decades. This potentially results from difficulty stimulating the auditory nerve through the bony cochlea with intracochlear electrodes. We seek to evaluate intraneural microstimulation of the auditory nerve using the penetrating Utah slanted electrode array (USEA) driven by a MED-EL SYNCHRONY 2 cochlear stimulator to achieve more natural hearing in a study with three human volunteers. Our pre-clinical chronic cat study to demonstrate safety and efficacy of our auditory nerve implant (ANI) technology is nearly completed. We have also performed multiple first-in-human intraoperative studies with our devices in volunteers to validate our approach to place the array and ability to evoke nerve responses. Pre-clinical studies with 3-month endpoints in cat models involved chronic placement of ANI electrodes, and demonstrated sustained evoked auditory brainstem responses (eABRs) and maintained electrode impedances below <70 kΩ. These studies performed electrical nerve stimulation along with electrode impedance monitoring and evoked auditory brainstem responses (eABRs) to evaluate stability and functionality of the ANI device. They came after successful pilot animals implanted up to 9 months that evaluated impedance, channel independence, level (growth) functions, and masking to characterize nerve engagement. In parallel to these animal studies, ethics approval was received for intraoperative studies with human participants in Hannover, Germany, focused on the surgical approach, device handling, and evaluation of impedances and eABRs in response to nerve stimulation. Eight participants have been stimulated with ANI devices intraoperatively as part of acoustic neuroma resection surgeries. Viability of the nerve and auditory system was first verified using the Auditory Nerve Test System (ANTS) that stimulates the cochlea and remaining auditory nerve fibers. Microstimulation was then performed with ANI electrodes while eABRs were recorded to monitor nerve engagement. High-quality responses were measured from subjects demonstrating viability of the surgical and technology approaches. This preclinical data along with validation and verification testing is being used to build our regulatory submission for our clinical investigation.

Disclosures: L. Rieth: 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.; Blackrock Neurotech. **I. Sondh:** None. **K. Dyballa:** None. **M. Leber:** A. Employment/Salary (full or part-time):; Blackrock Neurotech. **J. Crew:** A. Employment/Salary (full or part-time):; Blackrock Neurotech. **K. Huebner:** A. Employment/Salary (full or part-time):; MED-EL. **A.P. Heiller:** None. **W. Nogueira:** None. **L.A. Johnson:** None. **G.M. Ghose:** None. **H.A. Holman:** 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.; Blackrock Neurotech. **R. Gurgel:** None. **D.J. Warren:** 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.; Blackrock Neurotech. **S. Zuniga:** None. **A. Loveland:** None. **R. Franklin:** A. Employment/Salary (full or part-time):;

Blackrock Neurotech. **A. Samii:** None. **A.J. Oxenham:** None. **S.B. Strahl:** A. Employment/Salary (full or part-time):; MED-EL. **F. Solzbacher:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Blackrock Neurotech. **M. Adams:** None. **T. Lenarz:** None. **H.H. Lim:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Neuromod Devices, SecondWave Systems, UltrHearing Technologies.

Poster

PSTR074: BCI Sensory, Vision, Speech

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR074.16/F22

Topic: E.05. Brain-Machine Interface

Support: Dutch Research Council Gravitation Grant 024.005.022
HORIZON-EIC-2021-PATHFINDER CHALLENGES No 101070939

Title: Optimal positioning and size of high-density electrocorticography grids for speech brain-computer interfaces

Authors: *E. C. OFFENBERG[1], J. BEREZUTSKAYA[1], L. MÜLLER[2], Z. V. FREUDENBURG[1], M. J. VANSTEENSEL[1], N. F. RAMSEY[1];
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Abstract: Speech-based brain-computer interfaces (BCIs) can offer an intuitive way of communicating to people who have lost the faculty of speech due to paralysis. Speech decoding from electrocorticographic (ECoG) recordings on the sensorimotor cortex (SMC) has shown >90% accuracy of decoding individual words (Berezutskaya et. al, 2023). Recent studies show a trend for increasing the number of ECoG electrodes, from 4 (Vansteensel et. al, 2016) to 256 (Metzger et. al, 2023). While potentially ensuring high accuracy of decoding, larger grids require a more invasive surgery, increasing the risks for potential BCI end users. Moreover, many electrodes cover areas that may not contribute to decoding, wasting energy and adding unnecessary device complexity. In this study, we investigate the feasibility of pinpointing which SMC sites are most informative for individual word decoding and whether a smaller grid (32 electrodes) placed over these sites can match the decoding accuracy of larger grids. Eight able-bodied human participants (ages 19-51; 4 female; 7 epilepsy, 1 brain tumor) implanted with high-density ECoG grids of 64 to 128 channels spoke 12 words out loud repeatedly. A t-test comparing high frequency band activity during speech and rest fragments revealed two hotspots: one in the ventral SMC, corresponding to the face area, and another in the dorsal SMC. Using a combinatorics approach, we then show that a smaller subgrid of electrodes (32 channels) can achieve the same accuracy of individual word decoding as using all electrodes (64 to 128 channels): 76±16% and 75±17%, respectively, across subjects (chance is 8.3%). The best

performing subgrids were almost exclusively oriented vertically, so as to cover both hotspots seen in the t-test. Finally, pre-selecting electrodes for word classification based on the t-test resulted in comparable accuracy of word decoding, showing that cortical sites activated by speech/rest contrast discriminated between classes of individual words. This can potentially mean that a simple speech/rest contrast using non-invasive functional magnetic resonance imaging (fMRI) could help plan optimal positioning of a small ECoG grid in individual BCI end users. These results indicate that both dorsal and ventral SMC are crucial for word decoding. Importantly, both locations can be optimally covered by a grid of only 32 electrodes without losing decoding accuracy. Moreover, a simple speech/rest contrast acquired with fMRI can be used to predict optimal positioning of the grid. Altogether, targeted grid placement for speech decoding seems feasible, thereby reducing energy consumption and device complexity associated with high channel counts.

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Poster

PSTR074: BCI Sensory, Vision, Speech

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR074.17/F23

Topic: E.05. Brain-Machine Interface

Support: NIH Grant U01NS098968

Title: Decoding lexical semantics from intracranial sEEG during natural language production

Authors: *H. ZHANG[1], C. R. C. PESCATORE[1], Z. M. WILLIAMS[2,3,4], S. S. CASH[1,3], J. CAI[2];
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Abstract: Brain-Computer Interfaces (BCIs) aim to restore communication in individuals with speech difficulties. While BCIs typically focus on decoding spoken language through phonetic and auditory features, an alternative approach lies in deciphering word meaning directly from neural activity. Here, we directly studied the feasibility of directly decoding word meaning from the neural activity represented in local field potentials recorded across multiple brain areas during natural conversation. We leveraged intracranial stereo-electroencephalography (sEEG) performed in patients with intractable epilepsy for clinical purposes, to record brain activity from 14 participants engaged in natural dialogue, with participants speaking for an average of 10 minutes. Lexical semantic meaning of each word was categorized into 10 clusters based on its vectorized representation. Using a machine learning model, we successfully decoded word meaning from all participants, with an average accuracy of 21%, which is significantly higher

than what is expected from chance (10%). This accuracy of semantic decoding outperformed the phonetic decoding on the same data, demonstrating the semantic decoding accuracies were not driven by the sensory information. Together, this work suggests the potential for BCIs to leverage semantic information as an alternative for speech restoration for individuals with speech production impairments.

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Poster

PSTR075: Kinematics, Muscle Activity, Exercise and Fatigue, and Biomechanics of Posture and Gait

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR075.01/F24

Topic: E.06. Posture and Gait

Support: NIH 1P41EB018783
VA Merit Award 01 CX001812
New York State Spinal Cord Injury Research Board SCIRB C32236GG
New York State Spinal Cord Injury Research Board SCIRB C33279GG
Stratton VA Medical Center, Albany, NY

Title: Short-term adaptation of muscle activity to bidirectional walking

Authors: *R. L. HARDESTY[1,2], H. MOJTABAVI[1,2], J. R. WOLPAW[1,3];
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Abstract: Human locomotion requires complex synchronization of muscles to maintain interlimb coordination and control. Simultaneously, neural control of locomotion must adapt to preserve performance across a diverse range of environments. Studies of locomotor adaptation using split-belt treadmills with asymmetric speeds have demonstrated that people adapt spatiotemporal characteristics of their gait cycle to reestablish step length symmetry. Previously, we reported that people walking on a split-belt treadmill with the belts going at equal speeds, but opposite direction (bidirectional walking) also adapted spatiotemporal parameters, as evidenced by a decreased stride length upon returning to normal locomotion. Here we report, we believe for the first time, adaptation in muscle activity patterns in humans performing bidirectional walking. We asked twelve volunteers to walk on a split-belt treadmill for a single session. First, they performed 2 minutes of normal walking (belts moving in the same direction and speed, at 80% of preferred walking speed. Next, each person performed four 5-min trials of bidirectional walking (20 min total) (belts moving at 80% preferred walking speed in opposing directions (right moving posterior-to-anterior)). The session finished with a 2-min washout period of normal

walking at 80% preferred speed. Body kinematics, treadmill ground reaction forces, and EMG activity of right and left soleus and tibialis anterior were recorded. EMG activity patterns changed progressively over the 20 min of bidirectional walking. For example, in most participants, both right and left TA EMG fell gradually, even though the left belt was moving in the same direction and speed as during baseline, normal walking. During the washout phase, EMG activity patterns returned to baseline, except for the right soleus, which showed an aftereffect of increased activity corresponding to the decreased stride length in the right leg. These results suggest that kinematic adaptations to bidirectional locomotion reflect adaptation by the ankle flexor (soleus) more than by the ankle extensor (tibialis anterior).

Disclosures: R.L. Hardesty: None. **H. Mojtabavi:** None. **J.R. Wolpaw:** None.

Poster

PSTR075: Kinematics, Muscle Activity, Exercise and Fatigue, and Biomechanics of Posture and Gait

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR075.02/F25

Topic: E.06. Posture and Gait

Support: NIH 1P41EB018783
VA Merit Award 01 CX001812
New York State Spinal Cord Injury Research Board SCIRB C32236GG
New York State Spinal Cord Injury Research Board SCIRB C33279GG
Stratton VA Medical Center, Albany, NY

Title: Short-term and long-term impact of a new heksor on an old one: initial results

Authors: *J. R. WOLPAW[1,2], R. L. HARDESTY[3,2], H. MOJTABAVI[4];
[1]Natl. Ctr. for Adaptive Neurotechnologies, Delmar, NY; [2]Samuel S. Stratton VAMC, Dept. of Veteran Affairs, Albany, NY; [3]Res., Natl. Ctr. for Adaptive Neurotechnologies, Albany, NY; [4]Natl. Ctr. for Adaptive Neurotechnologies, Albany, NY

Abstract: The substrate of a skill is a network of neurons and synapses that may extend from cortex to spinal cord. This network has been given the name heksor, based on the ancient Greek word hexis (JPhysiol 2022, DOI:10.1113/JP283291). Each heksor changes through life to maintain the key features of its skill, the attributes that make the skill satisfactory. Muscle activity and kinematics may change; key features are maintained. Heksors overlap; they share CNS neurons and synapses. Thus, the creation of a new heksor (i.e., the acquisition of a new skill) is accompanied by changes in existing (i.e., old) heksors. Normal adults learn to walk on a split-belt treadmill with belts moving at the same speed in opposite directions (right-belt moving forward). We are studying the short-term and long-term impact of this new bidirectional-walking (BDW) heksor on the old locomotion heksor in terms of the behavioral effects and their underlying mechanisms as reflected in spinal reflexes, TMS motor evoked potentials (MEPs),

and sensory evoked potentials (SEPs). Analyses of single-session BDW data from 12 people show: (1) marked change in right-leg kinematics (hip, knee, ankle); (2) minimal change in left-leg kinematics; (3) decreased stride length; (4) gait pattern similar to an oscillating inverted pendulum. Stride length had not fully recovered by 2 min after return to normal locomotion. Analysis of initial long-term (12-session) data suggest that washout of the impact of BDW on return to normal locomotion may occur progressively faster over multiple sessions and that creation of the BDW heksor might be associated with changes in the cortical topography of the MEPs of individual leg muscles. The companion posters present additional important aspects of these short-term and initial long-term results. With further data collection,the long-term effects should illuminate skill acquisition and maintenance in the continually plastic CNS, and could guide development of new methods for restoring skills impaired by CNS injury or disease.

Disclosures: J.R. Wolpaw: None. **R.L. Hardesty:** None. **H. Mojtabavi:** None.

Poster

PSTR075: Kinematics, Muscle Activity, Exercise and Fatigue, and Biomechanics of Posture and Gait

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR075.03/F26

Topic: E.06. Posture and Gait

Support: NIH 1P41EB018783
VA Merit Award 01 CX001812
New York State Spinal Cord Injury Research Board (SCIRB) C32236GG & C33279GG
New York State Spinal Cord Injury Research Board (SCIRB) C33279GG
Stratton VA Medical Center, Albany, NY
New York State Spinal Cord Injury Research Board (SCIRB) C38338GG

Title: Long-term motor learning acquired through repeated locomotor adaptations to bi-directional walking on a split-belt treadmill: protocol and initial results

Authors: *H. MOJTABAVI[1], R. L. HARDESTY, Jr.[2], D. GUPTA[3], J. R. WOLPAW[4]; [1]Natl. Ctr. for Adaptive Neurotechnologies, Albany, NY; [2]Res., Natl. Ctr. for Adaptive Neurotechnologies, Sauquoit, PA; [3]NCAN, Stratton VA Med. Ctr., Natl. Ctr. for Adaptive Neurotechnologies, Stratton VA Med. Ctr., Albany, NY, Albany, NY; [4]Natl. Ctr. for Adaptive Neurotechnologies, Natl. Ctr. for Adaptive Neurotechnologies, Delmar, NY

Abstract: Human locomotion is a highly adaptable task. The use of split-belt treadmill protocols is widely accepted in uncovering the biomechanics of adaptations and motor learning. Studies to date have focused on adaptations that occur in a single session. We previously reported that people quickly adapt to walking on a split-belt treadmill with belts going in opposite directions at equal speed. Adaptation was evident in altered stride length and joint kinematics. We are now

studying the impact of long-term bidirectional training on both bidirectional walking and normal walking. Our long-term protocol begins with a baseline neurophysiological assessment of Motor Evoked Potentials (MEP), Sensory Evoked Potentials (SEP), and H-reflex measurements. Then participants engage in 12 training sessions followed by a second neurophysiological evaluation involving MEP, SEP, and H-reflex recording. Afterward, participants undergo an additional 12 training sessions. It concludes with a final neurophysiological evaluation of MEP, SEP, and H-reflex measurements.In each training session participants start by walking for 2 min on a Bertec split-belt treadmill with both belts at 80% of their self-selected speed. This defines baseline gait for the session. They then walk for four 5-min adaptation blocks separated by 1-min breaks with left-belt movement the same as baseline but right-belt movement in the opposing direction at equal speed. Lastly, they walk for 10 min with both belts in the same direction. We record ground reaction forces; center-of-pressure; soleus and tibialis anterior EMG activity in both legs in all the training sessions and movement using 41 reflective markers with motion capture (Qualysis) in first, mid-training, and last training sessions of each 12-session block. (session number 1,7,12,19,24)Our preliminary results from the first healthy participant, suggest that de-adaptations occur progressively faster in each session, notably evidenced by modifications in stride length. These changes are accompanied by neurophysiological changes such as changes in MEP magnitude. Our findings suggest that repeated adaptation can result in long-term CNS changes that drive sustained behavioral changes. Rehabilitation relies on extended training to improve motor deficits via motor learning. This current study aims to deepen our understanding of the neural mechanisms that underlie this long-term change and guide the development of novel therapeutic interventions and technologies.

Disclosures: H. Mojtabavi: None. **R.L. Hardesty:** None. **D. Gupta:** None. **J.R. Wolpaw:** None.

Poster

PSTR075: Kinematics, Muscle Activity, Exercise and Fatigue, and Biomechanics of Posture and Gait

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR075.04/F27

Topic: E.06. Posture and Gait

Support: NSF 2015317

Title: Characterize rat hindlimb mechanics of various configurations

Authors: *Z. WANG[1], S. TRAN[1], M. C. TRESCH[2];
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Abstract: Dynamic scaling theory stipulates that the dynamical features of animal behaviors are determined by the scale of the limbs and the speed of the movement. The scale of the limbs

regulates the mechanical properties such as elasticity, viscosity and inertia, and the movement speeds determine if the control should be inertia-dominant (accelerating/decelerating) or elasticity-dominant (equilibrium position control). In this study, we aimed to investigate if the mechanics of rat hindlimb is dynamically scaled by its system configurations. We recently established a dynamic perturbation system which can characterize the mechanical properties of the rat hindlimb across various configurations. By perturbing different configurations and quantifying their mechanics, we found that mechanical parameters are similar under similar configurations, indicating the system mechanical properties are constrained by the limb configurations. The limb mechanics vary in a continuum within a continuous range of limb configurations but jump to different mechanical state spaces if the scales of the hindlimb (quantified by the hip height relative to the ground) change. The hindlimb mechanics become more elastic-dominant as the configuration stretches and elongates, while the mechanics become more inertia-dominant as the configuration folds and shortens. To investigate the speed control on limb mechanics, we extracted the limb configurations the animal used during locomotion with fast and slow speeds and reconstructed those configurations on the perturbing platform. Combining the hindlimb mechanics parameters from different system scales and behavioral speeds, we charted a wide range of mechanical state spaces of rat hindlimbs in the workspace and in the temporal domains.

Disclosures: Z. Wang: None. **S. Tran:** None. **M.C. Tresch:** None.

Poster

PSTR075: Kinematics, Muscle Activity, Exercise and Fatigue, and Biomechanics of Posture and Gait

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR075.05/F28

Topic: E.06. Posture and Gait

Support: NIH Grant F32MH122995
NIH Grant DP1 NS137188

Title: Encoding of full-body kinematics and actions in sensorimotor cortex of freely behaving mice

Authors: *K. S. SEVERSON[1], J. LU[1], T. LI[2], T. LOU[1], W. XIAO[1], H. JIANG[1], K. A. CAPLAN[1], T. W. DUNN[2], F. WANG[1];
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Abstract: To actively explore and interact with the world, our brains must orchestrate coordinated movements of multiple body parts. Such complex motor coordination is cognitively demanding and relies on integrating sensory information from multiple modalities, especially proprioception. Previous studies have investigated sensorimotor integration in frontal and parietal sensorimotor cortical regions (sensorimotor cortex, SM), but reduced preparations

restrict the body's natural movement. Therefore, how SM integrates sensory and motor information during natural whole-body movements remains poorly understood. Recent advances in machine learning enable full-body markerless tracking of natural behaviors across animal species. Here, we combined markerless pose estimation, behavior segmentation, and electrophysiological recordings to investigate how SM neurons represent whole-body kinematics in freely behaving mice. We recorded single unit activity across cortical layers using chronic tetrode microdrives and tracked mice freely behaving in an arena using an optimized 3D CNN pose estimation model (DANNCEv2) and geometric models to parameterize full-body posture as Euler angles. We fit GLMs with kinematics variables as predictors and quantified variance in neural firing rates explained by the model (R^2). Strong encoding performance was observed in posterior parietal cortex (PPC, 17.3%), S1-M1 transition zone (S1tz, 18.6%), and S1 dysgranular zone (S1dz, 12.5%). However, weaker encoding performance was observed in S2 (7.7%) and V1 as a control (5.4%). Unexpectedly, rather than simply encoding joint angles, spiking activity in SM primarily reflected behavior. Neurons showed strong modulation by specific behavior syllables, e.g., "rear" or "groom, inferred by an AR-HMM model (keypoint-MoSeq). Just as S1 is somatotopically organized to represent somatosensation of the body, behavior encoding is topographically organized. S1tz strongly represented rearing, whereas S1dz strongly represented grooming. These data suggest specific SM circuits are contextually engaged during stereotyped behaviors. On finer timescales, S1 neurons in functionally-connected ensembles fired in sequence aligned to phases of a specific behavior. We speculate that these behavior sequences in sensorimotor cortex may contribute to "muscle memories" distributed across the cortex. Future work aims to further investigate the role of sensorimotor cortex in flexible control and execution of coordinated full-body movements.

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Poster

PSTR075: Kinematics, Muscle Activity, Exercise and Fatigue, and Biomechanics of Posture and Gait

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR075.06/F29

Topic: E.06. Posture and Gait

Support: P50-AR080581

Title: Reduced loading after sciatic nerve resection impairs hindlimb growth

Authors: *T. JOHNSON[1], N. DYMENT[2], N. FOGARTY[3], E. KOYAMA[4], L. HAN[5], R. MAUCK[2];
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Abstract: Neuromuscular diseases, spinal cord injuries, and peripheral nerve damage often result in reduced or abnormal loading on limbs which can later lead to secondary pathologies, including joint contractures. While mechanical forces are known to influence the growth and maintenance of musculoskeletal tissues, the role of applied mechanical loading on the neonatal growth and maturation, where matrix accrual is highest, has yet to be established. We studied the effects of unilateral sciatic nerve resections (SNR) to better understand the role of mechanical loading on developmental processes of load bearing tissues. SNR was performed in both neonatal (surgery performed on postnatal day 1) and adult (surgery performed at 22 weeks of age) mice. We used video gait analysis to assess limb kinematics, Micro-CT to access trabecular and cortical bone parameters, and cryohistology to assess tendon morphology.SNR limbs exhibited sustained gait abnormalities compared to contralateral limbs, including reduced paw print width (a hallmark of sciatic denervation), increased ankle dorsiflexion and reduced hock height ($p < 0.01$) at both ages. Neonatal SNR significantly decreased Achilles tendon cross sectional area (CSA) at postnatal day 14 (P14) and P42 ($p<0.05$, $p<0.01$) with reduced total number of cells per cross section ($p<0.05$) and an increasing trend in cell density ($p=0.08$). SNR had less of an effect on tendon morphology in adults with only decreasing trends in cells per cross section and cell density at post-surgical day 42 (D42) ($p=0.07$, $p=0.09$).SNR yielded marked alterations in bone parameters at both ages with neonatal limbs having reduced tibial length, trabecular BV/TV, trabecular thickness, and cortical area ($p<0.05$), and adult limbs having reduced trabecular BV/TV, BMD, trabecular number, and trabecular thickness ($p<0.05$). As expected, SNR did not alter tibial length in adults. We also found differences in the onset of bone loss between trabecular (D14, $p<0.05$) and cortical (D42, $p<0.05$) bone corroborating trabecular bone being more sensitive to altered loading.Here, we demonstrate that disruption of mechanical loading by sciatic nerve resection alters tendon and bone growth and maintenance in both neonatal and adult mice. Our data suggest SNR can be an effective model for inducing unilateral bone and tendon changes during peak phases of proliferation and matrix deposition. Thus, this study provides insights on the mechanisms by which mechanical forces regulate tissue growth and maintenance. Future studies will investigate the mechanosignaling events that are altered in this model with the goal of leveraging this knowledge to guide new regenerative strategies

Disclosures: T. Johnson: None. **N. Dyment:** None. **N. Fogarty:** None. **E. Koyama:** None. **L. Han:** None. **R. Mauck:** None.

Poster

PSTR075: Kinematics, Muscle Activity, Exercise and Fatigue, and Biomechanics of Posture and Gait

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR075.07/F30

Topic: E.06. Posture and Gait

Title: The effect of grasping light objects on the motor control of the arms during gait

Authors: *J. LEE-CONFER, M. HELWIG, C. EGGERT, D. GARCIA, R. MARTIN, A. NEFF, C. SPIESS;
Univ. of Arizona, Tucson, AZ

Abstract: Arm movements play a crucial role for maintaining balance and stability while walking. Identifying the neural controls involved with arm movements can help understand how the body adapts to different walking conditions such as when carrying objects. There is evidence that arm swing is initiated from central pattern generators (CPGs) within the spinal cord and a neural connection between the legs and arms exist during walking. Furthermore, gripping with the hand does not establish a connection between the legs and arms as the grasping stems from the motor cortex. This study investigates how grasping light objects while walking affects arm swing, compared to walking without objects or with a wrist weight. We hypothesized that arm swing would reduce in the conditions when participants walked while carrying a light object compared to walking and walking with wrist weight. 4 young adults (n = 4) walked over a 15-meter-long walkway at their self-selected speed. 2 iPhones installed OpenCaps' open-source software and calibrations were conducted. The participants performed 3 regular walking trials, 3 walking trials carrying a 1.5lb biomechanics book in their right hand, followed by 3 walking trials with a 1.5 lb wrist weight on the same wrist. Right arm flexion was captured and processed using OpenCap's open-source software, ensuring accurate measurement and we analyzed peak arm flexion. A 1-way repeated measures ANOVA was conducted in SPSS to determine if there were any significant differences in peak arm flexion angle between conditions with $\alpha < 0.05$. Pairwise comparisons were conducted between each of the conditions with $\alpha < 0.05$. Peak arm flexion was significantly reduced in individuals carrying a book compared to regular walking (17.54 ± 7.58 vs. 26.12 ± 10.69, $p = .03$) but no significant differences compared to individuals walking with a wrist weight (17.54 ± 7.58 vs. 28.37 ± 12.40, $p = .07$). There was no significant difference in peak arm flexion between regular walking and walking with a wrist weight (26.12 ± 10.69 vs. 28.37 ± 12.40, $p = .40$). The results from this study demonstrate that grasping an object interrupts the CPG coordination and reduces arm swing amplitude. This effect was not due to the weight of the object dampening the arm flexion response as arm flexion returned with a wrist weight of equal weight to the object grasped. Considering prior studies that link arm movements during slips to subcortical regions based on EMG timings, future research should explore how perturbations from carrying objects might disrupt natural motor control. Future studies can investigate the effects of perturbations while carrying objects as it may interrupt the natural motor control.

Disclosures: J. Lee-Confer: None. **M. helwig:** None. **C. Eggert:** None. **D. Garcia:** None. **R. Martin:** None. **A. Neff:** None. **C. Spiess:** None.

Poster

PSTR075: Kinematics, Muscle Activity, Exercise and Fatigue, and Biomechanics of Posture and Gait

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR075.08/F31

Topic: E.06. Posture and Gait

Support: McCamish Blue Sky Foundation
BWF CASI to JEM
David & Lucile Packard Foundation
Sloan Foundation

Title: Towards capturing musculoskeletal dynamics using injectable fluorescent nanoparticles

Authors: *E. ULUTAS[1], A. PRADHAN[2,3], D. KOVEAL[1], J. E. MARKOWITZ[1];
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Abstract: Recent technical advances in both recording hardware and machine learning have enabled the study of unrestrained, naturalistic movements with newfound precision (Biderman et al., 2023; Dunn et al., 2021; Mathis et al., 2018; Pereira et al., 2022). In mice, nearly all state-of-the-art methods image mice at a short distance from the outside using 2D or 3D sensors. Then, positions of key points on the body - e.g. joints, the snout, and the tail - are estimated using machine learning models trained on hand-labeled data. Despite the considerable progress in the development and deployment of these methods, many of these methods do not directly measure the primary part of the body controlled by the central nervous system - the skeleton. Since musculoskeletal dynamics are obscured by soft tissue and fur, it remains unclear if movement of the skeleton can be resolved from imaging movement from the outside (Monsees et al., 2022). Here, we describe a novel approach that leverages biocompatible, photostable, and bright injectable fluorescent nanoparticles. We present results demonstrating that our injectable markers are long-lasting, have high signal-to-noise, and are suitable for non-invasive in vivo measurements in freely moving mice. In addition to providing a path for directly measuring musculoskeletal dynamics, our method can also be used to collect large ground-truth datasets for the development of foundation models for markerless pose estimation.

Disclosures: E. Ulutas: E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Invention disclosure filed. **A. Pradhan:** None. **D. Koveal:** None. **J.E. Markowitz:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Invention disclosure filed.

Poster

PSTR075: Kinematics, Muscle Activity, Exercise and Fatigue, and Biomechanics of Posture and Gait

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR075.09/F32

Topic: E.06. Posture and Gait

Support: NSF NeuroNex 2015317
DFG DI 2907/1-1 (Project number 500615768)

Title: Investigating six leg campaniform sensilla discharge in freely walking Drosophila using a biomimetic robotic model

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Abstract: Investigating six leg campaniform sensilla discharge in freely walking *Drosophila* using a biomimetic robotic modelAuthors: *C. A. Goldsmith[1], G. F. Dinges[1] N. S. Szczecinski[1]**; [1]**Mechanical, Materials and Aerospace Engineering, West Virginia Univ., Morgantown, WV
Disclosures C. A. Goldsmith: None. G.F. Dinges: None **N.S. Szczecinski:** None.**Abstract**
Sensory feedback plays an important role in how the nervous system controls dynamic walking; feedback from sense organs influences activity throughout the nervous system which subsequently shapes leg motions. One such type of sensory organ in insects are campaniform sensilla (CS). CS are load-sensitive receptors located in high stress areas of the exoskeleton that transduce strain into neural activity. In several species of insect, leg CS have been found to encode both the magnitude of a load as well as the rate of loading. This sensory information is believed to affect interleg coordination during walking by influencing legs to transition between stance and swing phases. However, many of these experiments were conducted with fixed animals, and electrophysiological recording from CS in free-walking animals can pose technical challenges. These hurdles are magnified in smaller insects like the fruit fly, *Drosophila melanogaster*. Biomimetic robots modeled after insects can circumvent these constraints by facilitating strain recordings during biomimetic stepping. The data produced by strain gauges in leg CS locations increases our understanding of the load feedback signaled by CS in freely moving animals. We have previously developed Drosophibot II, a 140:1 robotic model of an adult fruit fly with similar kinematics and dynamics as the animal. The robot includes strain gauge rosettes on each leg in locations corresponding to the trochanteral and femoral CS fields in *Drosophila*, allowing for biomimetic strain recordings during walking. Six leg strain data from Drosophibot II can be collected for forward and backward walking on flat ground in a variety of directions, as well as straight line walking on an incline. Inputting this strain through our previously developed model to transform strain into plausible CS discharge allows us to directly hypothesize what load sensory feedback is available to the nervous system in these scenarios. In particular, we are interested in investigating how the sensory discharge in each leg pair may differ depending on their role in stepping, and how this discharge may change with walking direction.
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Poster

PSTR075: Kinematics, Muscle Activity, Exercise and Fatigue, and Biomechanics of Posture and Gait

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR075.10/F33

Topic: E.06. Posture and Gait

Title: Neural Control of Running in Animals

Authors: *A. OZTURK[1], O. MORGUL[1], I. UYANIK[2];
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Abstract: Legged locomotion is essential for understanding the mechanisms and strategies of the animals that traverse diverse and challenging terrains. To mimic the natural running behavior, legged locomotion models often utilize spring systems mirroring the functions of the animal locomotor systems' tendons, ligaments, and muscles. Leg springs are widely studied in robotics and involve several morphologies, such as monopod, biped, and multiped designs. While using a monopod is counterintuitive as the direct natural counterparts are limited, the monopods offer an inspiring platform to understand the core dynamics of legged locomotion as they present a general template for running. As the locomotion mode of the monopod robots is via consecutive jumps without any static phases, we can purely focus on the dynamic stability of the movement, which is a vital feature of the animal movement capabilities. The control methods developed for the legged locomotion span a broad spectrum and include numerical, model-based, and data-driven solutions. Data-driven solutions include neural networks, which present the opportunity to mimic the control strategy of the animal locomotor system on top of the locomotion mechanism. While the use of neural networks is well analyzed in the state-of-the-art studies for legged locomotion, most focus on the biped or multiped morphologies where the joint actuation and leg coordination schemes drive the priority away from the primary running behavior. Our study focuses on the neural control of the core running behavior using a spring-mass running template, which utilizes a monopod morphology. We generated and trained our neural control models in a realistic running simulation based on previous studies that showed successful resemblances between the simulation model and the animal locomotor system. After training, we tested our neural controllers against multiple scenarios, including the single-step control and multi-step trajectory tracking experiments. In our trajectory tracking experiments, we designed a goal trajectory that spans 1000 steps, covering smooth and sharp changes in the desired positions and velocities. Our neural controllers showed great potential in dynamic stability, energy monitoring, and resilience against these varying goals, showing the effectiveness of our methods for the neural control of the core running behavior. Using bioinspired control models, we analyzed the core aspects of animal locomotion, and this analysis allowed us to understand animal locomotion more thoroughly and develop more dexterous bioinspired robots to overcome the problems of nature.

Disclosures: A. Ozturk: None. **O. Morgul:** None. **I. Uyanik:** None.

Poster

PSTR075: Kinematics, Muscle Activity, Exercise and Fatigue, and Biomechanics of Posture and Gait

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR075.11/F34

Topic: E.06. Posture and Gait

Support: HD084672-03
NS110953

Title: Exploring the role of the 5-HT_{2C} receptor in motor function using behavioral assessments

Authors: *M. SIM[1], C. HECKMAN[2], D. BIRCH[3], V. M. TYSSELING[4];
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Abstract: The serotonin (5-HT) receptors are complex neuromodulators found throughout the central nervous system. A subtype of the 5-HT2 receptor family, the 5-HT_{2C} receptor (5-HT_{2C}R), has been suggested to be involved in the modulation of motor function. The 5-HT_{2C}R has been implicated in various movement parameters such as locomotion, gait, coordination, and muscle contraction. Although the 5-HT_{2C}R has been described to be involved in motor function, the precise mechanism as to how specific movement and gait patterning are altered by this receptor is not well understood. In this study, we have investigated the motor function and gait pattern of knock-out (KO) mice that lack the 5-HT_{2C}R by comparing these genetically manipulated mice to typical-functioning wildtype (WT) mice. The horizontal ladder test, a behavioral assessment designed to evaluate coordination and locomotion, revealed no significant disparities between the 5-HT_{2C}R KO mice and WT mice. In contrast to this, while using the grip strength test, a behavioral assessment used to determine the maximal muscle contraction, we found a significant difference between the 5-HT_{2C}R KO mice and WT mice, specifically in regard to maximal hindlimb strength. The imaging system, DigiGait — comprehensive ventral plane treadmill instrumentation and software used to assess subtle gait pattern differences between strains — revealed a combination of significant and insignificant variation between the 5-HT_{2C}R KO mice and WT mice. Although no explicit coordination deficits were observed in the horizontal ladder analysis, the specific alterations observed in the grip strength and DigiGait treadmill analyses suggest a distinct difference between the two mouse groups. Overall, our comprehensive behavioral assessment provides noteworthy and supporting evidence that the 5-HT_{2C}R has a significant effect on the motor function and gait pattern of mice.

Disclosures: M. Sim: None. **C. Heckman:** None. **D. Birch:** None. **V.M. Tysseling:** None.

Poster

PSTR075: Kinematics, Muscle Activity, Exercise and Fatigue, and Biomechanics of Posture and Gait

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR075.12/F35

Topic: E.06. Posture and Gait

Title: Changes in kinematic and spatiotemporal gait parameters with a biarticular lower limb exosuit for adolescents with crouch gait

Authors: *C. BASLA[1,2], P. WOLF[1], R. RIENER[1,3], H. J. VAN HEDEL[4];
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Abstract: Crouch gait represents the most common gait abnormality in children with cerebral palsy. Excessive knee and hip flexion during walking forces these children to typically walk at a slower speed, with reduced stability, and with increased fatigue and effort compared to neurotypical peers. Children who walk with a crouch gait considerably diminish their engagement in routine physical activities and participation in everyday life. Over the past decade, exoskeletons have been developed to assist children when walking. However, the currently available solutions for the pediatric population only target the knee joint and are either tethered or excessively bulky, making their integration into everyday life impractical. For the first time, we deployed a biarticular, cable-driven, and portable exosuit for adolescents walking in a crouch gait. The exosuit has been developed for the adult population, weighs 5 kg, and provides active support to knee and hip joint extension during the stance phase of gait. We designed a cross-sectional study to assess improvements in the gait pattern induced by the mechanical assistance of the exosuit. Each participant repeatedly walked a distance of approximately six meters (i) without the exosuit, (ii) with the exosuit worn but inactive (transparency), and (iii) with the exosuit worn and active. We used a gold standard 3D motion capture system to measure changes in spatiotemporal and kinematic gait metrics between the three conditions.

Five participants with moderate cerebral palsy completed the study. Compared to walking normally, the average knee and hip extension during stance showed a statistically significant increase by a mean of 7° and 14°, respectively, when the assistance of the exosuit was provided. There were no statistically significant differences between no exosuit and transparency mode. A statistically significant reduction in stride length by 15 and 18 cm was measured in the transparency and active mode, respectively.

Our study findings underscore the potential of the exosuit’s working principle to improve extension deficits due to crouch gait. However, the exosuit’s weight, particularly, might have restricted the children from maximally benefiting from its assistance. These insights have encouraged the development of a new, lighter version of the exosuit, tailored explicitly for the pediatric population. This advancement aims to enlarge the population that can benefit from the exosuit and maximize improvements in walking efficiency.

Disclosures: C. Basla: None. **P. Wolf:** None. **R. Riener:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Myoswiss AG. **H.J. van Hedel:** None.

Poster

PSTR075: Kinematics, Muscle Activity, Exercise and Fatigue, and Biomechanics of Posture and Gait

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR075.13/Web Only

Topic: E.06. Posture and Gait

Support: University of New Mexico RAC Grant

Title: Upright trunk position in gait after a self-mobilization exercise program

Authors: *D. SHIBATA[1], Y. YOSHIDA[2];
[1]Health, Exercise and Sports Sci., Univ. of New Mexico, Albuquerque, NM; [2]Dept. of Orthopaedic and Rehabil., Univ. of New Mexico, Albuquerque, NM

Abstract: The integration of sensory signals is essential for maintaining postural stability and should be optimally adapted to peripheral stimuli such as postural changes. A self-mobilization exercise program was developed to realign spinal curvature and can effectively reduce postural sway in static standing. However, mechanisms of the adapted stability in dynamic motor tasks such as gait are unknown. Thus, this study aims to examine ground reaction force (GRF) and kinematic parameters in gait before and after the self-mobilization exercise program. Thirty-two healthy young adults were randomly allocated to either the Exercise group (Ex: n=16) or the Control group (Ctrl: n=16). The Ex group performed three warm-up positions and seven small movements while lying on a cylindrical tube (98 cm length, 15 cm diameter). The duration of self-mobilization exercises program was 15 min. The Ctrl group laid supine on a flat surface with their legs flexed for 15 min. Before and immediately after their respective interventions, subjects walked on an 11.8m path for 8 trials at a comfortable speed. A 10-camera 3D motion analysis system (VICON Ltd.) with embedded force plates (AMTI. Inc.) was used to capture and compute a) the joint angle of trunk, hips, knees, and ankles, b) the joint velocity of hips, knees, and ankles, and c) peak GRF in 3 dimensions. Repeated measures ANCOVAs, with pretest measures as the covariate, were used to examine the gait parameters between the groups after the interventions. The statistical analysis showed that, after the self-mobilization exercise, the Ex group showed decreased hip flexion during the initial contact and increased hip extension during the terminal stance-pre-swing while maintaining their trunk to become a more upright position ($p < 0.05$). In the Ctrl group, the hip or trunk motion after the intervention remained the same ($p > 0.05$). No significant change in GRF or joint peak velocity between the interventions in either group was found ($p > 0.05$). A previous study showed that increased trunk flexion in gait is associated with substantial changes in joint kinematics and kinetics at the hips, knees, and ankles, resulting in greater activity in trunk extensors to counteract the anteriorly shifted center

of mass. Thus, it is speculated the upright trunk position found in the present study would reduce the load from the muscles and preserve energy used in gait. Our results provide insight into how the subjects initially change their trunk-hip motion in gait to adapt to the new center of mass displacement after the self-mobilization exercises while preserving the energy of gait.

Disclosures: D. Shibata: None. **Y. Yoshida:** None.

Poster

PSTR075: Kinematics, Muscle Activity, Exercise and Fatigue, and Biomechanics of Posture and Gait

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR075.14/F36

Topic: E.06. Posture and Gait

Support: NIH Grant R01NS102333
Searle Scholar Award
Klingenstein-Simons Fellowship
Pew Biomedical Scholar Award
McKnight Scholar Award
Sloan Research Fellowship
New York Stem Cell Foundation Award

Title: A low-dimensional control architecture for coordination of 3D joint kinematics in walking Drosophila

Authors: *G. M. CHOU[1], S. WALLING-BELL[1], L. KARASHCHUK[2], B. W. BRUNTON[3], J. C. TUTHILL[1];
[1]Physiol. and Biophysics, [2]Grad. Program in Neurosci., [3]Biol., Univ. of Washington, Seattle, WA

Abstract: To traverse complex and unpredictable environments, animals must flexibly adjust limb coordination patterns. For example, changes in speed and walking direction require coordinated changes in joint angle kinematics within and across limbs. However, the specific local control mechanisms used to achieve this robust multi-joint coordination of walking remain unknown. Here, we recorded high speed video of tethered flies walking on a spherical treadmill and tracked all of their 30 leg joints in 3D. We first identified correlations of individual joint angle dynamics with both speed and direction. We then quantified the dynamics of multi-joint coordination using principal components analysis and found a low-dimensional representation of distinct, interpretable kinematic synergies for walking. Specifically, variability due to inter-leg step coordination patterns, joint flexion dynamics driving forward walking, and kinematic asymmetries driving turning were all captured by the first five principal components.These results suggest that flies use a low-dimensional control architecture to coordinate many joints during changes in walking speed and turning direction. Finally, we demonstrate that optogenetic

manipulations to leg proprioceptors alter joint kinematics and locomotor output, suggesting that specific control dimensions are refined by specific proprioceptive feedback pathways.

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Poster

PSTR075: Kinematics, Muscle Activity, Exercise and Fatigue, and Biomechanics of Posture and Gait

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR075.15/F37

Topic: E.06. Posture and Gait

Support: NSF DBI 2015317

Title: Biologically Inspired Design and Control of a Robotic Rat.

Authors: *H. PHAM[1], B. ARMSTEAD[1], C. JACKSON[2], W. NOURSE[3], R. D. QUINN[4]; [1]Mechanical and Aerospace Engin., Case Western Reserve Univ., Cleveland, OH; [2]Mechanical and Aerospace Engin., Case Western Reserve Univ., Lyndhurst, OH; [3]Electrical Engin., Case Western Reserve Univ., Cleveland, OH; [4]Mechanical Engin., Case Western Reserve Univ., Cleveland, OH

Abstract: This interdisciplinary research presents the design and development of a biologically inspired rat robot. The robot is scaled up to 2.5 times the size of a female Sprague-Dawley rat. The hindlimbs are each equipped with four motors to control the hip, knee, and ankle rotation in the sagittal plane, andinternal/external hip rotation. The forelimbs are equipped with five motors to control the scapula, shoulder, elbow, and wrist rotation in the sagittal plane, as well as abduction/adduction of the scapula. Additionally, the hands and feet of the robot are comprised of two sections, connected with a pin andtorsional springs. This allows the feet to have passive compliance and better conform to the ground while walking. The leg segments are based on a scanned rat bones model with shapes modified for ease of assembly and 3D printing. Parts are printed using micro carbon fiber filled nylon, strengthened by various amounts of continuously inlaid carbon fiber. The scapula, shoulder, and hip joints are directly driven by motors, while the lower joints are driven by motors using a pulley-belt transmission system. This allows the motors to be mounted higher up on the leg, reducing the legs inertia. In addition to the biologically inspired mechanics, the robot is controlled with a synthetic nervous system (SNS), a computational model of neurons with a structure intended to mimic that of the animal. The controller consists of higher-level pattern generators to drive the rhythmic locomotor activity, as well as lower-level motor circuits which directly drive the joint activity. We are able to incorporate position, velocity, and torque feedback from the motors, akin to types II, Ia, and Ib afferent feedback, respectively. The integration of these two biologically inspired systems will

allow us to test and make predictions about the control system and how the animal may interact with the environment in a more realistic way than in simulations alone.

Disclosures: H. Pham: None. **B. Armstead:** None. **C. Jackson:** None. **W. Nourse:** None. **R.D. Quinn:** None.

Poster

PSTR075: Kinematics, Muscle Activity, Exercise and Fatigue, and Biomechanics of Posture and Gait

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR075.16/G1

Topic: E.06. Posture and Gait

Support: NSF Grant 2015317

Title: Biomimetic actuation of compliant robot joints using feedforward neuromorphic control

Authors: *F. HOLMQUIST, N. S. SZCZECINSKI;
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Abstract: Animal movement is dictated by the mechanics of an organism. While an animal walks, mechanical energy is continuously injected by muscles and transformed by the body. Body movement increases kinetic energy, raising the body against gravity and stretching muscles, tendons, and other tissues stores potential energy. These transform into heat by the body's viscous and structural damping, which resists vibrations and movement. The proportions of these energies make up an animal's dynamic scale and vary with its physical scale and speed. The nervous system's control over movement is likewise affected by dynamic scale. Prior modeling work has suggested that the phase lag between actuation force and limb displacement quantifies dynamic scale in periodic movements, in that motions with the same phase lag are dynamically similar.

The motion of small animals such as insects is dominated by the viscoelasticity within their joints. For a meso-scale robotic arm actuated by a DC motor, its larger mass contains more kinetic energy than an insect, producing a different dynamic scale. To balance the scale, a proportional viscoelastic torsional spring was integrated into the robotic joint. We hypothesize that modifying a meso-scale robotic limb by introducing a viscoelastic torsional spring, mimicking the elastic properties of insect muscles, apodemes, and joint membranes, would produce an insect-like dynamic scale.

Furthermore, we hypothesize that this change in dynamic scale would change the control pattern required to drive the robotic arm without proprioceptive feedback. To emulate neural activity sent to an antagonistic pair of muscles, a controller using a network of integrate-and-fire neural models dictates the amount and direction of current supplied to the motor. One advantage of a robotic model is the ability to investigate the plausibility of isolated explanations for behavior. In this instance, we test the limit of feedforward position control as the robot receives no

proprioceptive information. A robotic limb with insect-like dynamic scale, able to control position without the use of feedback may increase understanding in how the small scale of insects affect the nervous systems control strategies.

Disclosures: F. Holmquist: None. **N.S. Szczecinski:** None.

Poster

PSTR075: Kinematics, Muscle Activity, Exercise and Fatigue, and Biomechanics of Posture and Gait

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR075.17/G2

Topic: E.06. Posture and Gait

Support: US Army, Award Number: W911NF2120230

Title: Heart rate complexity-based gait optimization for soft exosuits may improve adaptation outcomes

Authors: S. RAMADURAI[1], J. C. BRADFORD[3], *M. KIM[2];
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Abstract: Recent studies revealed the importance of training individuals to use exoskeletons to reduce user's physical effort and benefit from the assistance offered by the device. We found that heart rate complexity (Effort-to-Compress; ETC) derived from ECG (Electrocardiogram), an index of the autonomic nervous system, could be an indicator of human adaptation to assistive devices such as exosuits [1]. An increase in complexity was indicative of decreased mental load as participants adapted and developed an efficient motor strategy for walking with the exosuit. In this study, we performed a pilot study to investigate the outcomes of using ETC as an objective function for human-in-the-loop gait optimization for a passive hip exosuit. Two subjects walked on a treadmill wearing a passive soft hip exosuit, which consisted of a pair of elastic bands attached between the hip and knee joints, assisting with hip flexion during gait. A wearable heart rate sensor (Polar H10) was used to measure their ECG data in real time and calculate the objective function, heart rate complexity or ETC. Their step frequency was optimized for ETC using the Bayesian Optimisation framework based on Gaussian Process as a surrogate model. The outcomes such as perceived effort, comfort and kinematic parameters were compared between normal step frequency, optimal frequency, and no-band conditions. We found trends towards improved comfort and reduced perceived effort and step width variability (7.5%), an indicator of balance, for the optimal step frequency compared to normal step frequency, but not compared to the no-band condition. As heart rate complexity could be an indicator of adaptation to the device, ETC-based step frequency optimization for exosuits could potentially improve comfort, effort and balance compared to the normal gait frequency. The findings imply the potential benefits of using complexity cost functions in optimization algorithms to drive users

towards better human-device co-adaptation.
[1] S. Ramadurai, C. Bradford, and M. Kim, “Insights into human acclimation to wearable devices could be derived from electrocardiogram data,” in Progress in Clinical Motor Control II: Movement and Rehabilitation Sciences, 2023.

Disclosures: S. Ramadurai: None. **J.C. Bradford:** None. **M. Kim:** None.

Poster

PSTR076: Posture and Gait: Reflexes and Reflex Modulation

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR076.01/G3

Topic: E.06. Posture and Gait

Support: NSERC Grant 326910

Title: The effects of postural constraints on the frequency characteristics of the stretch reflex pathway during standing

Authors: *K. SUTHERLAND, G. ESCHELMULLER, J. INGLIS, M. G. CARPENTER; Univ. of British Columbia, Vancouver, BC, Canada

Abstract: Postural control is maintained through the integration of multiple sources of sensory input from our visual, vestibular, and somatosensory systems. Proprioceptive input via muscle spindles within the ankle muscles is critical in maintaining standing balance. Muscle spindles code for static length and velocity of skeletal muscle stretch, and through the monosynaptic stretch reflex circuit can produce rapid corrections to changes in muscle length. Noisy tendon vibration (NTV) allows for the characterization of the frequency characteristics of the stretch reflex pathway in posturally engaged muscles during quiet stance (Mildren et al. 2017). The amplitude of the stretch reflex response is unchanged when posture is constrained through visual feedback (Mildren et al. 2016) or by holding an external support (Schieppati & Nardone 1995), however, it is unknown how the frequency characteristics of the stretch reflex pathway may change when posture is constrained. The aim of this study was to examine the frequency characteristics of the motor response to muscle spindle input when postural control was constrained through focus of attention (standing “relaxed” vs “as still as possible”) and when holding an external handrail, with and without vision. The NTV stimuli (white noise filtered between 20-100Hz) was applied to the right Achilles tendon during various postural conditions in healthy young adults. A force plate was used to measure COP displacements and surface EMG was recorded from the right soleus, medial gastrocnemius, and tibialis anterior muscles. To estimate the frequency characteristics and amplitude of response, coherence and cumulant density values were calculated between the acceleration of the tendon probe and rectified soleus EMG activity. To compare the strength of responses across conditions, peak to peak (P2P) cumulant density values were extracted. A 3x2 (postural condition, vision) repeated measures ANOVA indicated no significant effects on the overall P2P amplitudes. Pairwise difference of

coherence (DOC) test was used to assess changes in the frequency characteristics between the different postural constraint conditions. Findings reveal that focus of attention or the use of a physical support had no effect on the muscular response to NTV. The DOC revealed a significant difference of frequency in the bandwidth of ~30-60Hz between eyes open and eyes closed, when the participant was asked to reduce their postural sway. This suggests that the stretch reflex may depend on the sensory information available and assist in the maintenance of postural control through frequency-based changes of the reflex response.

Disclosures: K. Sutherland: None. **G. Eschelmuller:** None. **J. Inglis:** None. **M.G. Carpenter:** None.

Poster

PSTR076: Posture and Gait: Reflexes and Reflex Modulation

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR076.02/G4

Topic: E.06. Posture and Gait

Title: Modulation of cutaneous reflexes during forward and backward locomotion in cats

Authors: *R. AL ARAB, J. HARNIE, S. YASSINE, S. MARI, J. AUDET, O. EDDAOUI, P. JEHANNIN, C. NADEAU, A. FRIGON;
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Abstract: During locomotion, cutaneous afferents send inputs to spinal and supraspinal circuits to coordinate limb movements in response to external perturbations. In cats and humans, cutaneous reflexes are modulated with task and phase to generate functionally appropriate responses. A few studies have shown modulation of cutaneous reflexes during forward (FW) and backward (BW) locomotion with electrical stimulation of the foot dorsum in cats (Buford & Smith,1993) and of the sural nerve in humans (Duysens et al., 1996; Hoogkamer et al., 2012). Here, we describe cutaneous reflexes evoked by stimulating the superficial peroneal nerve, which supplies the foot dorsum, during FW and BW in four intact adult cats, which will serve as a baseline for comparison in future studies after spinal cord injury. We evoked cutaneous reflexes in six ipsilateral and four contralateral hindlimb muscles during FW and BW hindlimb-only locomotion on a treadmill (with forelimbs standing on stationary platform). The most noticeable difference between conditions was the appearance of long-latency inhibitory responses in ipsilateral ankle and hip extensors, such as soleus (SOL) and biceps femoris anterior (BFA), respectively, during BW locomotion in the stance phase. In addition, long-latency excitatory responses occurred more frequently in all ipsilateral extensors, including SOL, BFA, and vastus lateralis (VL), during BW locomotion. Although long-latency excitatory responses were more frequent in the ipsilateral semitendinosus during BW, their amplitude was reduced compared to FW. For contralateral muscles, short-latency inhibitory and mid- and long-latency excitatory responses were only present in contralateral BFA during BW. On the other hand, mid-latency excitatory and long-latency inhibitory responses were only found in the contralateral

sartorius during FW. Short-, mid, and long-latency excitatory or inhibitory responses, when present, were significantly modulated with phase in both FW and BW locomotion. These results extend previous findings in cats and humans showing changes in cutaneous reflexes as a function of task, highlighting the role of sensorimotor circuits in generating contextually appropriate responses.

Disclosures: R. Al Arab: None. **J. Harnie:** None. **S. Yassine:** None. **S. Mari:** None. **J. Audet:** None. **O. Eddaoui:** None. **P. Jehannin:** None. **C. Nadeau:** None. **A. Frigon:** None.

Poster

PSTR076: Posture and Gait: Reflexes and Reflex Modulation

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR076.03/G5

Topic: E.06. Posture and Gait

Support: NSERC RGPIN-2017-04175

Title: Soleus H-reflexes are influenced by the reliability of a light touch reference during standing

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Abstract: Light touch of a stable reference reduces sway during standing. Unexpected displacement of this light touch reference induces short-latency reactions in ankle muscles consistent with a balance reaction. However, such responses are only observed after the first unexpected displacement, replaced by responses in arm muscles on subsequent trials. This suggests that the integration of tactile cues from the finger with postural control is dependent in part on the relevance of the cues to balance control. We anticipated that a sensorimotor path involved in regulation of ankle muscle activity would reflect these changes in behavior. In this study, we tested the soleus H-reflex while participants touched a stable reference and after the touch reference became unreliable. We hypothesized that H-reflexes would be facilitated when the touch reference was stable, but reduced when the touch reference became unreliable. Soleus H-reflexes were recorded from 10 participants (6 female; aged 20-29 yrs) during each of five conditions while standing on foam: a) eyes open, b) eyes open with touch (< 1 N vertical load of the index finger), c) eyes closed, d) eyes closed with touch, and e) eyes closed touching a reference that has been unexpectedly and repeatedly displaced. Soleus H-reflexes were evoked with a 1-ms square-wave pulse delivered to the tibial nerve at the popliteal fossa with an intensity that evoked a small, but stable M-wave. Peak-to-peak H-reflex amplitudes, normalized to the maximum evoked M-wave, were significantly ($p<0.05$) smaller when standing eyes closed (mean ± SD %Mmax; 50.1 ± 23.8) than standing eyes open (61.4 ± 26.6) or eyes open with

touch (61.5 ± 26.3). Providing a stable touch when standing eyes closed resulted in larger H-reflexes (54.8 ± 23.6), compared to eyes closed without touch. However, H-reflexes were not different from eyes closed without touch when the touch reference became unreliable (49.4 ± 22.5). These findings indicate that the amplitude of the soleus H-reflex varies with the expected reliability and relevance of a touch reference, mirroring changes in sway reported previously. Moreover, the soleus H-reflex was smallest during the eyes closed and eyes closed with unreliable touch conditions, suggesting that the contribution of this spinal reflex to balance control is reduced when the task is most challenging. In addition, these findings indicate that the integration of tactile feedback in balance control is context-dependent and is rapidly reweighted based on recent history.

Disclosures: J.E. Misiaszek: None. **B.E. Davis:** None. **S.G. Hemakumara:** None. **J. Forero:** None.

Poster

PSTR076: Posture and Gait: Reflexes and Reflex Modulation

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR076.04/G6

Topic: E.06. Posture and Gait

Support: Research Foundation of the University of Saint Augustine

Title: The interaction of the reticulospinal tract with Presynaptic inhibition at the level of final common pathway

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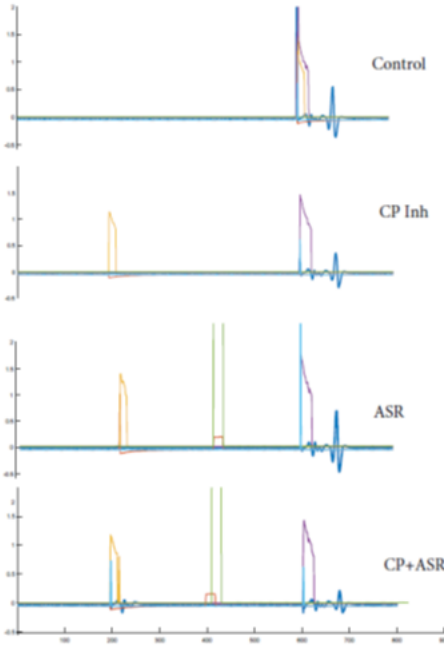
Abstract: The reticulospinal tract (RST) has long been investigated for its role in normal and pathologic movements. Recently the role of this motor pathway on spasticity has been reexamined and its significance has been reevaluated. In this experiment, we aimed to examine if there is an interaction between the RST and presynaptic control of spinal reflexes in healthy individuals. Five young healthy individuals (age=24.2±2.4) participated in this study. H-reflex recruitment curve was examined first and an H equal to 30% of H-max was selected as the control H-reflex. To examine the effect of RST, a 700 Hz, 90 dB auditory stimulation (AS) was given to subjects through custom-made headphones. Presynaptic inhibition was examined by stimulating the Common Peroneal (CP) nerve at 1.3 x motor threshold. The interstimulus interval was set to 200 ms. To examine the interaction of RST on presynaptic circuits, the auditory stimulation was applied 100 ms prior to H-reflex which was conditioned by a 200 ms preceding CP inhibition. We observed that AS increases H-reflex to 120%, CP inhibition decreases the control H to 57.5 and CP with AS decreases the control H to 67.4. Our results suggest the existence of an interaction between RST and the presynaptic inhibitory pathway from the

common peroneal to soleus H-reflex. We are in the process of examining this protocol and interaction on stroke survivors with spasticity. References: Tahayori, Behdad, Bahman Tahayori, and David Koceja. "Characteristics of preceding Ia activity on postactivation depression in health and disease." *Journal of neurophysiology* 113.10 (2015): 3751-3758.



Disclosures: B. Tahayori: None. **M. Perez:** None. **B. Tahayori:** None. **P. Jooya:** None.

Poster

PSTR076: Posture and Gait: Reflexes and Reflex Modulation

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR076.05/G7

Topic: E.06. Posture and Gait

Support: NIH Grant R01 NS-064964
Swedish Research Council Grant 2020-02502

Title: Role of CaMKIIα reticular neurons in control of posture in rabbits

Authors: L.-J. HSU[1], P. V. ZELENIN[2], V. F. LYALKA[3], *T. DELIAGINA[3];
[1]Neurosci., Karolinska Inst., Stockholm, Sweden; [2]Dept. of Neurosci., Karolinska Institutet, Stockholm, Sweden; [3]Karolinska Inst., Stockholm, Sweden

Abstract: Terrestrial quadrupeds actively stabilize the basic body orientation in space due to activity of the postural control system. Also, they can specifically change the body configuration in context of different motor behaviors. Supraspinal influences play a crucial role in control of

posture. The aim of the present study was to reveal the role of CaMKIIα reticular neurons (CaMKIIα-RNs) located in medullary reticular nucleus ventral part (MdV) in control of posture. For this purpose, effects of unilateral chemogenetic activation/inactivation of CaMKIIα-RNs (with excitatory/inhibitory DREADDs delivered with AAV-vectors) on different aspects of postural control were studied in intact rabbits. Then, the animals were decerebrated and effects of unilateral activation/inactivation of CaMKIIα-RNs on postural limb reflexes (PLRs) were studied. The side where CaMKIIα-RN activity was higher (ipsilateral to excitatory DREADDs and contralateral to inhibitory DREADDs), was termed "the dominant side". We found that in animals quietly standing on a horizontal surface, unilateral activation/inactivation of CaMKIIα-RNs evoked bending of the head and trunk toward the dominant side. The bending was accompanied by adduction/flexion of the ipsilateral and abduction/extension of the contralateral forelimb. The size of the infected area affected the strength of the effect. The animals with a smaller infected area exhibited the following periodical movements: slowly increased body bending toward the dominant side followed by quick body straightening. Rabbits with a larger infected area performed lateral corrective steps by the forelimbs leading to circling toward the body bending. Thus, left-right asymmetry in activity of CaMKIIα-RNs in MdV evoked changes in the body configuration typical for the lateral turn. However, during locomotion in open field, the asymmetry of posture disappeared. The animals were able to perform turns in either direction, although the animals with a larger infected area exhibited a significant bias in turning toward the dominant side. The bent body configuration was actively stabilized on a laterally tilting platform and the efficacy of the postural corrections was not affected. After decerebration, unilateral activation/inactivation of CaMKIIα-RNs led to a significant asymmetry in PLRs. They were decreased on the dominant side and enhanced on the opposite side. The increase and decrease of PLRs were caused by an increase in activity of extensors and by distortion of EMG pattern, respectively. Thus, unilateral activation/inactivation of CaMKIIα-RNs in MdV strongly affects the brainstem-cerebellar-spinal network generating PLRs.

Disclosures: L. Hsu: None. **P.V. Zelenin:** None. **V.F. Lyalka:** None. **T. Deliagina:** None.

Poster

PSTR076: Posture and Gait: Reflexes and Reflex Modulation

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR076.06/G8

Topic: E.06. Posture and Gait

Title: Role of environmental condition on auditory input to the soleus H-reflex in humans

Authors: *K. KITANO[1,2], D. M. KOCEJA[3];
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[3]Kinesiology, Indiana Univ., Bloomington, IN

Abstract: There have been numerous studies which addressed the relationship between human postural control and spinal neural mechanisms. It is known that auditory inputs have facilitatory

effects on the soleus H-reflex. The purpose of this study was to investigate the effects of different postural tasks on auditory facilitation of the soleus H-reflex in young adults. Five subjects participated in the study. Electromyography was recorded from the soleus muscle. The H-reflex was evoked by stimulating the tibial nerve (1 msec pulse) at the popliteal fossa. The H-reflex was conditioned with an auditory stimulus. The conditioning sound was a 700Hz square wave pulse with a duration of 30 msec and was delivered through a headset with the sound level at 75dB. Some trials included H-reflex only whereas other trials were H-reflex conditioned by the preceding auditory stimulus. In the conditioned trials, the interval between the initiation of the auditory stimulus and tibial nerve stimulation was 60 msec. Subjects were instructed to stand quietly during testing on a carpeted floor or on a foam pad. Reflex gain values were calculated for each floor condition with and without the auditory conditioning. The auditory conditioning significantly facilitated the H-reflex when standing on the floor ($p = 0.04$) but not on foam ($p = 0.22$). Mean gain values were 1.31 for carpeted floor which significantly differed from 1.07 for foam pad ($p = 0.04$). Results indicate less facilitation produced with auditory input when standing in more challenging environment. This suggests that the facilitatory effect of auditory input on soleus H-reflex in humans is environmentally dependent.

Disclosures: K. Kitano: None. **D.M. Koceja:** None.

Poster

PSTR076: Posture and Gait: Reflexes and Reflex Modulation

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR076.07/G9

Topic: E.06. Posture and Gait

Support: Japan KAKENHI Grant JP23K19413
Japan KAKENHI Grant JP24K18163
Japan KAKENHI Grant JP24KJ0242

Title: Biomechanics and neural circuits for the pitch control in larval zebrafish

Authors: *T. SUGIOKA, M. TANIMOTO, S.-I. HIGASHIJIMA;
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Abstract: Postural maintenance is important for many animals. Biomechanics and neural mechanism for the postural control are, however, not fully understood. To unveil the mechanisms of the postural control in fish, we used larval zebrafish, which have many advantages in neural circuit analysis. Fish correct body pitch angle by forward swimming (Ehrlich and Schoppik, 2017). Through close observation of freely swimming fish, we noticed that they swam with dorsal/ventral deflection of tail tip depending on the pitch angle change. The tail tip deflected dorsally when fish swam upward, while it deflected ventrally when fish swam downward. In a simplified mechanical model of swimming, fish receive two forces that pitches body; 1) swimming with the deflected tail tip pushes water diagonally backward, which

generates propulsive force; 2) fish body in the deflected side receives water flow, which generates lift force. To examine whether propulsive force contributes to the postural control, we held fish by restricting the fish's body movement. In this situation, fish receive propulsive force but not lift force by swimming. The fish recovered from severely pitch-tilted posture by swimming with the tail tip deflection. This result suggests that propulsive force plays an important role in the pitch angle change, although contribution of the lift-based mechanism is not completely excluded. We also found that fish exhibited a slight flexion of the rostral body in a pitch angle-dependent manner. The rostral body flexed dorsally or ventrally when the head tilted downward or upward, respectively. In a mechanical model, the body increases rotational torque during swimming by slightly changing the direction of propulsive force. Thus, the rostral body flexion likely contributes to recovering the horizontal posture. We next investigated the neural circuits for the rostral body flexion. By Ca^{2+} imaging during tilt and cell ablation, we revealed that neurons in a vestibular nucleus, reticulospinal neurons, and specialized muscles in the trunk are involved in the flexion. We are trying to unveil whole picture of the neural pathways that control the behaviors.

Disclosures: T. Sugioka: None. **M. Tanimoto:** None. **S. Higashijima:** None.

Poster

PSTR076: Posture and Gait: Reflexes and Reflex Modulation

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR076.08/G10

Topic: E.06. Posture and Gait

Support: CNOMK AAP 2022
APPARA GIRCI Grand Est 2022

Title: Spasticity treatment by local vibrations in subacute stroke: a controlled single-blind randomized trial.

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[1]INSERM CAPS U1093, DIJON, France; [2]Pit, CHU Dijon Bourgogne, Dijon, France; [3]Neuro Rehabil., CHU Dijon Bourgogne, DIJON, France; [4]SSR BOUCICAUT, CHALON SUR SAONE, France; [5]Rehabil. Sci., Univ. of Burgundy, Dijon, France

Abstract: Stroke is a worldwide leading cause of disability. Within the first months post-stroke, about 50% of patients with arm paresis develop spasticity, causing pain and functional limitations (Doussoulin et al., 2020). Among therapeutics, local muscle vibration (LMV) has emerged as a non-pharmacological approach to overcome spasticity, demonstrating efficacy during the chronic phase (> 6 months) (Zeng et al., 2023). However, its effects during the subacute phase (< 3 months) post-stroke, which offers the optimal window for promoting neuroplasticity, remain underexplored. Additionally, the neurophysiological mechanisms

underlying the beneficial effects of LMV on spasticity are not well understood. This study aims to evaluate the impact of a 6-weeks LMV program on spasticity incidence in the affected upper limb of patients in the subacute phase of stroke recovery. A secondary goal is to analyze the neurophysiological mechanisms associated with LMV effects on spasticity development. Eighteen LMV sessions were delivered (three per week) on a relaxed and hidden limb, targeting wrist and elbow flexors of the affected arm. Participants in the control group (SHAM) received 40Hz-0.5mm vibrations via a foam band between the vibrator and skin, while those in the intervention group (INT) received 80Hz-0.5mm vibrations directly applied on the skin. Evaluations occur before, at 3 weeks, at 6 weeks, and 6 months post-intervention. Spasticity was assessed using the modified Ashworth scale (MAS), an isokinetic ergometer, and electromyograms. Spinal excitability was measured via the H-reflex/M-wave ratio and H-reflex post-activation depression (H-PAD) at the flexor carpi radialis (FCR). Inclusion is still ongoing but preliminary results of 24 participants (12 in each group; mean age: 70.2 ± 10.5 years old; days post-stroke: 28.2 ± 8.9) are already acquired. Both groups felt vibrations, 100.0% and 95.0% of the time for SHAM and INT, respectively. The illusion of arm and/or wrist movements was perceived 4.0% of the time for SHAM and 33.8% for INT ($p < 0.01$). INT showed a tendency to develop less spasticity of the entire upper limb than SHAM between the beginning and the end of the intervention (MAS scores ratio: + 108.0% SHAM and +12.2% INT, $p = 0.07$, Cohen's $d = -0.61$). The H/M ratio decreased for INT and increased for SHAM ($p = 0.02$, Cohen's $d = -1.66$), while no difference was observed for the H-PAD. To date, this study shows that 6 weeks of LMV would reduce incidence of spasticity in the upper limb for subacute post-stroke patients, accompanied by a reduction of spinal excitability (H/M ratio).

Disclosures: S.I.S. Julliand: None. **N. Amiez:** None. **J. Gaveau:** None. **A. Mock:** None. **M. Raumel:** None. **D. Laroche:** None. **C. Papaxanthis:** None.

Poster

PSTR076: Posture and Gait: Reflexes and Reflex Modulation

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR076.09/G11

Topic: E.06. Posture and Gait

Title: The internal model for long-latency reflexes appropriately changes its directional tuning with a change in limb posture, even within a movement

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Abstract: The long-latency reflex (LLR, 50-100 ms) is a stretch-evoked response which helps stabilize our limbs against unexpected mechanical perturbations. These fast feedback responses integrate multi-joint motion in a manner consistent with an "internal model" of limb dynamics as they suitably counter the underlying torque. Further evidence of an internal model for LLRs is their dependence on the arm's joint configuration and concomitant mass distribution. However,

those studies only employed a single perturbation direction and could not test between a global change in sensitivity (equally to all perturbation directions) or a sculpted change in sensitivity (more for some perturbation directions than others). A change in directional tuning would point to a more sophisticated “internal model” which separately re-weights shoulder and elbow inputs for the LLR.
30 healthy individuals interacted with a programmable robot (BKIN Technologies) while surface EMG (Bortec AMT-8) was obtained from their shoulder extensor muscle. In Exp 1, 15 participants maintained their arm at an elbow-flexed posture (120 deg) or at an elbow-extended posture (45 deg); shoulder angle of 45 deg. Randomly occurring torques pulses displaced the arm in eight equally spaced directions at each location. In Exp 2, 15 different participants reached from an elbow-extended posture to an elbow-flexed posture; shoulder angle of 45 deg. Torque pulses were randomly applied when the elbow exceeded either 45 or 120 deg and induced displacements of either pure-elbow flexion or equal shoulder flexion-elbow extension. During postural maintenance (Exp 1) the shoulder extensor’s LLR exhibited a change in directional tuning with arm posture ($p < 0.001$). The plane-fit of LLR responses to joint displacement was more oriented to elbow flexion when participants maintained the elbow-extended posture than the elbow-flexed posture. During reaching (Exp 2), the ratio of LLR activity for elbow flexion vs shoulder flexion-elbow extension was greater when the elbow passed through the extended than flexed angle (t-test of log ratio, $p < .05$); that is, the LLR’s directional tuning was updated within a movement. These changes in multi-joint feedback are appropriate for the greater change in inertial resistance for pure elbow flexion (and extension) displacement than other directions. Sculpted changes in arm LLRs with arm posture point to an “internal model” which separately re-weights the shoulder and elbow inputs, even within a movement. Accordingly, detailed information about the arm’s mechanical properties is used for fast feedback control.

Disclosures: I. Kurtzer: None.

Poster

PSTR076: Posture and Gait: Reflexes and Reflex Modulation

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR076.10/G12

Topic: E.06. Posture and Gait

Support: NINDS 1ZIA NS003153

Title: Characterizing the neuronal circuit of the fast nociceptive hindlimb withdrawal reflex in mice

Authors: *P. J. MEKDARA[1], L. N. WIMALASENA[2], C. WASHINGTON[2], N. GOVINDARAJAN[2], C. PANDARINATH[2], A. J. LEVINE[1];
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Abstract: Potential harmful stimuli are detected at the skin where cutaneous nociceptive sensory neurons activate spinal reflex arcs to drive a withdrawal of an affected limb away from the potential harmful source. While the spinal cord plays a key role in this behavior, the intraspinal mechanisms that underlie the sensorimotor integration and the resultant motor programs that are produced to coordinate muscle firing patterns have yet to be understood. Using optogenetics and multi-electrode array electrophysiology in awake behaving mice, we investigate the neural population dynamics that underlie the patterns of neural activity in the lumbar spinal cord during a stimulus-driven limb withdrawal reflex. Here, we first established methods for high-density *in vivo* electrophysiology recordings from single units in the spinal cords of vertebrally-fixed, awake, and behaving mice. Mice in this preparation can produce clear, repeatable behaviors including self-driven locomotion, grooming, optogenetically-cued limb withdrawal reflexes, and clear responses to different naturalistic stimulations of the hindlimb receptive field. Next, we characterized single unit firing parameters across multiple animals as a function of laminar distribution in the deep dorsal and ventral horns. We are currently exploring patterns of single unit and population activity across the full dorsal-ventral axis of the spinal cord in the context of limb withdrawal behaviors. We hypothesize that (1) activity from a limb withdrawal response in the ventral horn will be strongly correlated with activity in the deep dorsal horn and (2) that perturbing specific interneuron populations optogenetically will allow us to investigate the function of those neurons involved in limb withdrawal reflexes.

Disclosures: P.J. Mekdara: None. **L.N. Wimalasena:** None. **C. Washington:** None. **N. Govindarajan:** None. **C. Pandarinath:** None. **A.J. Levine:** None.

Poster

PSTR076: Posture and Gait: Reflexes and Reflex Modulation

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR076.11/G13

Topic: E.06. Posture and Gait

Title: The Effect of Post-Stroke Increase in Reciprocal Control of the Stretch Reflex on Movement

Authors: *M. MCDONOUGH[1,3], D. LUDVIG[1,3], E. J. PERREAULT[1,3,2];
[1]Biomed. Engin., Northwestern Univ., Evanston, IL; [2]Physical Med. and Rehabil., Northwestern Univ., Chicago, IL; [3]Shirley Ryan AbilityLab, Chicago, IL

Abstract: Stroke can cause many changes to the motor system that drastically impair activities of daily living. Many impairments have been attributed to spasticity, caused by a heightened stretch reflex. However, the stretch reflex is not a constant response; it scales with task and muscle activation among other factors. Reciprocal control of the reflex, defined by agonistic muscle facilitation and antagonistic muscle inhibition, is a fundamental mechanism contributing to task-appropriate reflex behavior. While the influence of stroke on agonist modulation has been assessed during postural control, the effects of antagonistic inhibition have not. The goal of this

work was to fill this gap, testing the hypothesis that stroke alters reciprocal control mediated by both agonist and antagonist muscle activation. Any observed changes could have significant implications for movement, since the relative weighting of agonist-antagonist modulation of the reflex is nearly balanced during movement.
24 individuals with chronic stroke and 20 healthy controls participated. Electromyographic (EMG) signals were measured from the biceps brachii and the triceps long head of the dominant arm. Subjects produced different combinations of biceps and triceps background activity. Reflexes were elicited by applying a series of 0.03 rad perturbations at the elbow. Background and reflex activity were computed as the average EMG activity during the 10 - 40 ms before the perturbations and the 20 - 50 ms after the perturbations, respectively. We quantified reciprocal control of the stretch reflex by fitting a mixed effects model for reflex activity with agonist and antagonist muscle activities as fixed effects. Individuals with stroke also performed the Fugl-Meyer upper extremity assessment.
In the stroke group, agonist gains, or slopes, were approximately 2x higher than that of controls ($p = .01$), indicating that the stretch reflex was more sensitive to changes in agonist activity. In addition, antagonist gains were significantly different from zero in the stroke group ($p = .0025$) and not in the control group ($p = .83$), but the difference between groups was modest and did not reach statistical significance ($p = .08$). Antagonist gains were moderately correlated with impairment, as determined by the Fugl-Meyer assessment, but the results did not reach statistical significance ($p = .10$, $R = 0.34$).
Reciprocal control increases post-stroke, and the weak correlation between antagonist inhibition and movement ability suggests that reciprocal control may contribute to movement ability. Exploring post-stroke reciprocal control during movement is required to test this possibility more directly.

Disclosures: M. McDonough: None. **D. Ludvig:** None. **E.J. Perreault:** None.

Poster

PSTR076: Posture and Gait: Reflexes and Reflex Modulation

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR076.12/G14

Topic: E.06. Posture and Gait

Support: National Science Foundation Graduate Research Fellowship under Grant No. 1937968
National Institute of Health NICHD R01HD100416

Title: Assessing spinal reflex modulation during gait post-stroke

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Reserve University, Cleveland, OH; [4]MetroHealth Ctr. for Rehabil. Res., The MetroHealth Med. Syst., Cleveland, OH; [5]Biomed. Engin., Case Western Reserve Univ., Cleveland, OH

Abstract: Introduction: The prominent theory on post-stroke spasticity associates up-regulated descending input as the root cause. However, there remains a significant gap regarding the spinal cord's role in linking this supraspinal input to motoneurons. Our overall goal is to help bridge this gap by examining how spinal interneurons contribute to spasticity. Stiff-Knee gait (SKG) is an impairment post-stroke defined by a reduced swing phase knee flexion angle. SKG is often attributed to quadriceps hyperreflexia, a component of spasticity. In this study, we use SKG as a model for investigating the role of spinal primary afferent depolarization interneurons in lower limb hyperreflexia. We hypothesize an increased facilitation of the monosynaptic muscle reflex (meaning a depression of pre-synaptic spinal inhibition) during the pre-swing phase of gait in both the paretic and non-paretic legs of people with post-stroke SKG, compared to able-bodied age-similar individuals. Results presented in this abstract reflect a single chronic case (19y post-stroke). Methods: Spinal interneuron modulation was evaluated through two experiments conducted during gait. Heteronymous facilitation (1) examines tonic inhibition by interneurons to the tibial nerve motoneurons when facilitated by femoral nerve afferents. D1 inhibition (2) examines phase-specific inhibition by interneurons to the tibial nerve when inhibited by the common peroneal nerve. Following optimization of inter-nerve stimulation timing while in supine position, participants walked on a treadmill at a self-selected speed. H-reflexes used to innervate nerve fibers were elicited during the pre-swing (PS) and loading response (LR) phases of gait. Modulation was quantified by normalizing the peak-peak amplitude of the soleus H-reflex from conditioned over control responses. Results were shown as the ratio of the modulation PS to LR. Results: Current results of heteronymous facilitation post-stroke SKG (n=1) revealed a normalized modulation of 0.67±0.24 while modulation during D1 inhibition was 1.47±2.39. These results suggest a varying inhibition by interneurons which decreases at specific points in the gait cycle. Further validation of these results is necessary, including comparison with able-bodied individuals. Conclusion: In this study we aim to evaluate the contributions of spinal interneurons in post-stroke spasticity. Initial results demonstrate modulation which fluctuates across gait. Future work will involve a larger cohort of individuals with post-stroke SKG to help clarify the phase-dependent spinal contributions to quadriceps spasticity during gait.

Disclosures: J. Correa: None. **R. Siu:** None. **D. Lorenz:** None. **S. Ramani:** None. **D. Cunningham:** None. **J. Sulzer:** None.

Poster

PSTR076: Posture and Gait: Reflexes and Reflex Modulation

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR076.13/G15

Topic: E.06. Posture and Gait

Support: NIH NRSA Fellowship F31-DC020390
NIH Grant R01-DC002390

Title: The vestibular nuclei distinguish perturbations from active postural adjustments during support surface tilts

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Abstract: The vestibular system plays a vital role in postural control. As a result, patients with bilateral vestibular loss experience significant postural instability even after rehabilitation. Notably, vestibular afferents encode head motion in a context-independent manner, while neurons in the vestibular nuclei (VN) that generate vestibulo-spinal reflexes exhibit reafference suppression, attenuating their response to self-generated motion.
Generating an appropriate postural response to maintain stability requires distinguishing unexpected self-motion arising from an external perturbation, from intended self-motion arising from active behavior. We hypothesize that initial head motion elicited by postural perturbations is encoded by the VN in order to drive postural responses. However, once the postural response is initiated this motion is due to a combination of an externally-applied perturbation and the ongoing self-generated postural response itself, and thus neuronal responses will be attenuated. To test this, we utilized a rhesus monkey model of postural control to determine whether reafference suppression occurs during postural responses to support surface motion. Specifically, we recorded behavioral and neural responses to transient tilts. Monkeys were trained to adopt a standard posture on a force plate mounted to a hexapod motion platform while wearing a head-mounted IMU. While normal animals were able to compensate, monkeys with bilateral vestibular loss showed a maladaptive response that was hypermetric and in the reverse direction of normal. This response had a shorter latency than normal, indicating behaviorally that vestibular feedback is required at every phase of the response.
To understand how vestibular input drives these normal responses, we recorded neurons in VN using a 32-channel probe and neural logger. Neural responses in the normal animal occurred at significantly shorter latency than the onset of head motion, at a similar latency to head motion in the absence of vestibular input. In agreement with previous recordings during active head turns, a negative image of the motor commands driving postural responses is represented in the VN. Because the goal is to stabilize the head by driving the limbs opposite body motion, the signal is in the on-direction of the VO cells. After the first 100ms, head motion arising from active postural adjustments are cancelled and neurons are primarily modulated by deceleration of the platform. Taken together, these results underscore the essential role of vestibular feedback in distinguishing perturbations from active postural adjustments, which is crucial for driving appropriate responses.

Disclosures: O.M.E. Leavitt Brown: None. **B. Ramadan:** None. **K.E. Cullen:** None.

Poster

PSTR076: Posture and Gait: Reflexes and Reflex Modulation

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR076.14/G16

Topic: E.06. Posture and Gait

Title: Evidence of Causal Relationship between Spinal Reflex Gain Modulation and Gait Asymmetry During Active Locomotion in Humans

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Abstract: According to Sherrington, the spinal reflex is the fundamental mode of action of the nervous system [1]. In his views, the 'simple reflex' is an idealization that can rarely be isolated, and is rather part of a harmony of circuitry that utilizes, modifies and, sometimes, overrides it. Spinal reflexes have been shown to play a significant role in gait control in different species. The dynamics of interaction between spinal (that encodes the 'simple reflex') and supraspinal circuits during locomotion, to this day, however, remain vaguely understood [2]. In recent work, we showed that the short latency reflex is dynamically modulated during gait adaptation in healthy humans, but had not established a causal relationship between reflex modulation and gait adaptation (as measured by changes in gait asymmetry) [3]. In this work, we show in 10 healthy individuals that suppressing the short latency reflex on one side only using randomly-timed rate-dependent depression during stance phase results in robust and reproducible gait asymmetry that persists for one or more strides following stimulation. We further show that, in all participants, reflex suppression temporally precedes gait asymmetry, and that the magnitude of gait asymmetry is proportional to the degree to which the reflex is suppressed. Applying the same stimulation parameters, but stimulating off-nerve and thereby not suppressing the reflex (i.e. sham condition), results in no noticeable changes in gait asymmetry. We further show that instructing participants to walk asymmetrically using visual guides on a tied-belt results in asymmetric reflex gains. Together, we argue, these studies constitute strong evidence that changes in the gain of the short latency reflex are causally linked, or at least on the causal chain of events that lead to changes in gait asymmetry: the first demonstration we know of in the active locomoting human. Given that supraspinal centers also influence motor output via other mechanisms (e.g. directly controlling motoneuronal output) [2], the conceptual picture that emerges is that tuning of spinal reflexes to modify gait is one of multiple mechanisms by which the motor system can adjust gait as needed.
References:
[1] Charles Sherrington (1906), The integrative action of the nervous system.[2] Jens Bo Nielsen (2016), Human Spinal Motor Control, Annu. Rev. Neurosci. 39:81-101.[3] Refy et al. (2023), Dynamic spinal reflex adaptation during locomotor adaptation, Journal of Neurophysiology 2023 130:4, 1008-1014

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Poster

PSTR077: Parental Behaviors

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR077.01/G17

Topic: F.02. Neuroendrocrine Processes and Behavior

Support: NIH F31HD114466
HHMI
NIH 1S10OD023587-01

Title: Brain-wide neural activity enhancing auditory-guided maternal behavior

Authors: *B. R. MCRAE[1], D.-L. FERGUSON[2], A. LAWEN[3], H. IBARRA AVILA[4], L. A. HAMMOND[4,6], I. KAHN[2], B. J. MARLIN[5];
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Abstract: From the moment of giving birth, a mother must quickly adapt to the new demands of motherhood, attending to signals from her offspring and using them to inform her behavior. Research in rodents has begun to disentangle innate and learned features of the neural circuitry underlying maternal responses to infant cues. For example, distress vocalizations emitted by isolated mouse pups, termed pup calls, elicit maternal behavior and time-locked neural activity in the left primary auditory cortex (A1) in mothers and virgins with maternal care experience, but not pup-naïve virgin females. However, naïve virgins are primed with innate neuronal tuning to a narrow range of pup calls, which broadens with pup care experience to allow for more reliable caregiving and evoked A1 responses. Given the complexity of the pup call-evoked behaviors we observe, we hypothesize that pup calls engage different neural circuitry in experienced versus naïve animals, beyond the known differences in auditory areas. We conducted a Y-maze behavioral assay and revealed that mothers, but not experienced nor naïve virgins, exhibit a preference for pup calls. We then used whole-brain activity mapping via immediate early genes to characterize the experience-dependent representation of pup calls throughout the brain. We implemented the iDISCO+ and ClearMap pipelines to assess c-Fos expression associated with pup call perception in mothers, experienced virgins, and naïve virgins, and our findings revealed partially overlapping combinations of activated regions. Future work will investigate the temporal coordination of these brain regions via functional magnetic resonance imaging (fMRI) in awake animals. Altogether, this work takes advantage of whole-brain imaging methods to identify brain regions that exhibit experience-dependent representations of pup calls, a stimulus that is crucial to mother-child communication and maternal behavior.

Disclosures: B.R. McRae: None. **D. Ferguson:** None. **A. Lawen:** None. **H. Ibarra Avila:** None. **L.A. Hammond:** None. **I. Kahn:** None. **B.J. Marlin:** None.

Poster

PSTR077: Parental Behaviors

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR077.02/G18

Topic: F.02. Neuroendrocrine Processes and Behavior

Support: The Boehringer Ingelheim Fonds
HHMI

Title: Mechanisms underlying olfactory-guided maternal behavior

Authors: *V. ANDREU[1,2], N. MIMOUNI[2], R. LEE[4], B. R. MCRAE[2], B. J. MARLIN[5,2,1,3]; [2]Neurosci., [3]Hhmi, [1]Columbia Univ., New York, NY; [4]Barnard Col., New York, NY; [5]Columbia Univ. Zuckerman Inst., New York, NY

Abstract: Motherhood is a period of immense plasticity. During pregnancy and after birth, the reproductive, endocrine, and nervous systems undergo changes so that an individual can support the growth and maintenance of its offspring. In mice, the olfactory system plays an essential role for maternal behavior, but how the olfactory system changes with motherhood is still unknown. Here, we have shown that mothers display a significant preference toward pup odor. Moreover, this preference is not observed in pregnant females, naïve virgin females, pup-exposed virgin females, and pup-odor-only-exposed virgin female mice. Additionally, we have demonstrated that this preference is specific to pup odor and is not observed with other social odors (female urine) or neutral odors (acetophenone). Using LCMS and GCMS analysis as well as selective manipulation of the olfactory system, we now aim to characterize the exact mechanism behind pup odor preference and its potential impact on olfactory-guided maternal behaviors.

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Poster

PSTR077: Parental Behaviors

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR077.03/G19

Topic: F.02. Neuroendrocrine Processes and Behavior

Support: HHMI- Howard Hughes Medical Institute

Title: Unveiling molecular signatures in the main olfactory epithelium during the transition to motherhood

Authors: *N. MIMOUNI[1], V. ANDREU[1], R. LEE[1], S. L. FULTON[2], D.-L. K. FERGUSON[3], B. R. MCRAE[4], I. ABDUS-SABOOR[5], B. J. MARLIN[6];
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Abstract: Transition to motherhood represents a remarkable period of plasticity, wherein the reproductive, endocrine, and nervous systems undergo profound changes to support the growth and care of offspring. Among these, the olfactory system plays a crucial role in facilitating maternal behaviors across species, including humans. However, the specific molecular changes occurring within the olfactory system, particularly the main olfactory epithelium (MOE), during the transition to motherhood remain elusive. This study aims to characterize the global molecular changes in the MOE in peripartum female mice and across estrus cycles and their potential impact on olfactory-guided maternal behaviors.To investigate the molecular dynamics associated with the transition to motherhood, we conducted Bulk RNA sequencing on MOE tissues collected from virgin mice (in Diestrus and Poestrus), pregnant mice at Embryonic day E18.5, and postpartum mothers at postpartum day 5 (PPD5). This time point was chosen to coincide with robust pup retrieval behavior and an enhanced olfactory response to pup chemosensory cues based on findings from our laboratory. To understand the interplay between hormonal shifts, olfactory system and maternal behavior in these groups, we concurrently measured hormonal fluctuations in estrus stages, pregnancy and postpartum across groups including estradiol and progesterone and evaluated maternal caregiving behaviors using pup retrieval tests. Moreover, we employed the iDISCO+ technique to perform whole-MOE clearing and staining phospho 6, to accurately map MOE-wide activity after pup exposure in mothers compared to virgin females.Our bulk RNA sequencing analysis revealed distinctive gene expression patterns between virgin females and postpartum mothers (at PPD5), with a total of 840 genes identified as differentially expressed. Notably, 507 genes exhibited significant differential expression between mothers and virgin females. Subsequent gene enrichment analysis highlighted pathways associated with hormone fluctuations and stress responses, with Nuclear Receptor Subfamily 1, Group D, Member 1 (Nr1d1) emerging as a candidate gene implicated in the molecular changes underlying changes in maternal behavior.Altogether, these findings provide deeper insights into molecular changes during the transition to motherhood, unveiling novel molecular signatures within the MOE. This highlights the MOE's remarkable adaptability and responsiveness to both internal changes, such as hormonal variations, and external stimuli, including pup olfactory chemosensory cues, thereby facilitating maternal adjustment and behavior.

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Poster

PSTR077: Parental Behaviors

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR077.04/G20

Topic: F.02. Neuroendrocrine Processes and Behavior

Support: HHMI
NIH F31HD114466
NIH 1S10OD023587-01

Title: Motherhood on the brain: characterizing oxytocinergic circuitry using whole-brain clearing

Authors: *D. K. FERGUSON[1], B. R. MCRAE[2], N. MIMOUNI[2], T. ARZUA[1], H. IBARRA AVILA[1,3], B. J. MARLIN[1,4,2,5];
[1]Zuckerman Inst., [2]Neurosci., [3]Cell. Imaging Platform, [4]Psychology, [5]Hhmi, Columbia Univ., New York, NY

Abstract: Numerous phenotypic changes characterize an individual's transition into motherhood. The processes of gestation, parturition, and parenting are marked by modifications in endocrinology, neural activity, and behavior. Our goal is to elucidate the circuitry underpinning these changes. In particular, we seek to parse out how child-bearing and child-rearing may differentially and similarly impact oxytocinergic circuitry. The neuropeptide oxytocin has been shown to be vital for the transition from the virgin to the maternal brain, thus examining oxytocinergic circuitry across different maternal experiences will garner greater insight into the mechanisms supporting maternal care (Marlin et al, 2015). We hypothesized that oxytocinergic circuitry will be upregulated in mice that exhibit maternal care behaviors. To that end, we have implemented the iDISCO+ pipeline to carry out whole-brain clearing and staining of the distribution of murine oxytocinergic neurons. To precisely map the brain-wide oxytocinergic projections, we used light sheet microscopy, the Imaris visualization software, and FIJI analysis tools. With these tools, we characterized the differences in oxytocinergic projections across maternal experience as represented by virgin, surrogate, and maternal female mice. Altogether, our findings will provide a clearer picture of how hormonal circuitry may be altered with maternal experience, thus identifying key brain regions involved in the transition to motherhood. This will have far-reaching implications for understanding the circuitry underlying maladaptive maternal behaviors, such as in the case of postpartum depression.

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Poster

PSTR077: Parental Behaviors

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR077.05/G21

Topic: F.02. Neuroendrocrine Processes and Behavior

Support: NIH R01 DA 052386

Title: Exploring the Impact of Oxytocin Dose and Administration Route on Enhancing Maternal-Infant Interactions and Offspring Outcomes Following Gestational Buprenorphine Exposure: A Pilot Study

Authors: *L. M. RICHARDSON, J. DURAN, D. PATEL, E. WALSH, A. KHAN, S. E. BOWEN, S. BRUMMELTE;
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Abstract: Over the past two decades, the United States has experienced an ongoing crisis of opioid abuse, which has reached epidemic proportions. Notably, from 2010 to 2017 opioid-related diagnoses have increased by 131% among pregnant women. Opioid dependent women are commonly prescribed Medication for Opioid Use Disorder (MOUD), such as buprenorphine (BUP), given that more favorable outcomes for infants have been demonstrated as compared to methadone or continuation of illicit opioids. Despite this, the neurological effects of BUP on mothers and the implications for maternal behavior remain poorly understood, but our lab has previously demonstrated that gestational BUP exposure can impair maternal care behaviors and offspring survival in a translational rodent model. This pilot study used the same translational rat model to test whether oxytocin administration could improve maternal behavior in BUP-exposed dams. For this, we investigated postpartum oxytocin administration (I.P and Intranasal) at varying doses following prenatal BUP exposure (1.0 mg/kg), beginning on gestational day 5 throughout postnatal day (PN) 2. Adult female rodents (N=14 total, n=2-3/group) were assigned to one of 5 experimental groups; BUP (BUP) + mock handling, BUP + I.P oxytocin low dose (BUP-IPL, 60 IU/kg), BUP + I.P oxytocin high dose (BUP-IPH, 180 IU/kg), BUP + intranasal oxytocin low dose (BUP-INL, 0.8 IU/kg) and BUP + intranasal oxytocin high dose (BUP-INH, 4 IU/kg). Oxytocin was administered once following parturition on PN0. Dams were assessed for nesting quality, maternal caregiving behaviors (nursing, licking/grooming, time spent on/off nest), and maternal motivation (pup-retrieval task). Offspring were assessed for presence of milk bands, and developmental milestones. Results from this pilot study indicate that postpartum oxytocin administration, specifically intranasal oxytocin at the higher dose, may increase pup-directed maternal caregiving behaviors, nesting quality, and maternal motivation in BUP treated dams. As well, results indicated oxytocin administration improved offspring outcomes, with a higher percent of milk bands present within the litter, as well as improved developmental milestones compared to offspring exposed to only BUP. This pilot data suggests that a single oxytocin administration shortly after birth may partly rescue the maternal brain network from the adverse impact of BUP. However, more research is needed to further illuminate the effects of BUP and oxytocin on the maternal brain and subsequent offspring outcomes.

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Poster

PSTR077: Parental Behaviors

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Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR077.06/G22

Topic: F.02. Neuroendrocrine Processes and Behavior

Support: R15 HD110963-01

Title: Embryonic disruption of oxytocin receptor or vasopressin 1a receptor signaling does not impact maternal care

Authors: *A. HAUPT[1], H. K. CALDWELL[2];
[1]Kent State Univ., Kent, OH; [2]Dept. of Biol. Sci., Kent State Univ. - Biol. Sci., Kent, OH

Abstract: The neuropeptides oxytocin (Oxt) and arginine vasopressin (Avp) are known neural modulators of both social and maternal behaviors. Specifically, in rodents, Oxt is important for the initiation of maternal care while Avp is associated with maternal aggression. Our lab is interested in how disruption of Oxt receptor (Oxtr) or Avp receptor 1a (Avpr1a) signaling during embryonic development affects behavior throughout the lifespan. We have found that injection with either an Oxtr antagonist (OxtrA) or Avpr1a antagonist (Avpr1aA) at embryonic (E) day 16.5—a critical timepoint in development for both systems in the mouse brain—appears to alter the trajectory of brain development such that there are measurable changes in adult social behavior. Specifically, OxtrA-treated males display increased social investigation, agonistic, and depressive-like behaviors while OxtrA-treated females display impaired social recognition memory. Avpr1aA-treated males have measurable changes in affiliative behavior and both Avpr1aA-treated males and females have impairments in the preference for social novelty. Based on these data, we hypothesized that in offspring that received an injection of either an OxtrA or an Avpr1aA at E16.5 that there would be changes in maternal care. Specifically, we predicted that maternal care would be impaired in OxtrA-treated dams and only mildly affected in Avpr1aA-treated dams, as compared to controls. To test our hypothesis, we injected an OxtrA, an Avpr1aA, or saline at E16.5. Once female offspring reached 2 months of age they were paired with an experienced male and observed for pregnancy. After parturition, maternal behavior was tested from postnatal day 0-9. Pup abandonment, nest building, and direct maternal behaviors including pup retrieval, time on the nest, licking the pups, nursing, and maternal aggression were measured. Anxiety-like and depression-like behaviors were also evaluated. We found that there were no significant treatment-specific effects for any of the behaviors tested. These results suggest that while embryonic disruption of Oxtr or Avpr1a signaling results in changes in adult social behaviors, there are no obvious effects on maternal behavior. We speculate that the neural circuitry that regulates maternal behavior may not be vulnerable to our disruption at this timepoint. Rather, it is the social behavior neural network that is specifically impacted. These data are the first to suggest that Oxtr and Avpr1a signaling during embryonic life does not globally affect all behaviors, which is critical to understanding their neurodevelopmental role.

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Poster

PSTR077: Parental Behaviors

Location: MCP Hall A

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Program #/Poster #: PSTR077.07/G23

Topic: F.02. Neuroendrocrine Processes and Behavior

Support: KAKENHI 23K05858

Title: Oxytocin-dependent parental behavior contributed by melanin-concentrating hormone neurons

Authors: *T. XIONG[1], L. TSUCHIDA[1], A. INUTSUKA[2], T. ONAKA[2], K. YAMADA[1], C. ORIKASA[3];
[1]Univ. of Tsukuba, Tsukuba, Japan; [2]Jichi Med. Univ., Shimotsuke, Japan; [3]Nippon Med. Sch., Tokyo, Japan

Abstract: Parental behavior is performed in the presence of multiple sequential responses and a rationale for protecting the offspring. The paraventricular hypothalamic nucleus (PVN) oxytocin neurons contribute to maternal behavior in mice. We previously demonstrated the importance of the association between the lateral hypothalamus area (LHA) melanin-concentrating hormone (MCH) neurons and PVN oxytocin neurons in the regulation of parenting nursing behavior. Animals with congenitally ablated MCH neurons under the control of the Tet-off system exhibited reduced parental behavior. However, virgin male mice lacking MCH neurons showed more aggression toward pups, often committing infanticide. Moreover, a recent study suggested that excitatory inputs from MCH neurons to PVN-oxytocin neurons are enhanced after mice become fathers. These data implicate in regarding parental behaviors, the finer modulation of oxytocin neurons contributed by MCH neurons. Further studies are warranted to understand the underlying mechanisms. This study used a double transgenic mice model expressing Cre recombinase in MCH and oxytocin neurons to determine the relationship between LHA-MCH and PVN-oxytocin neurons associated with maternal behaviors. Optogenetic stimulation of channelrhodopsin-2 (ChR2)-expressing PVN-oxytocin neurons induced typical pup retrieval and crouching behaviors in virgin male mice with intact LHA-MCH neurons. Conversely, on LHA-MCH neurons ablation even optogenetic stimulation of PVN-oxytocin neurons failed to induce pup retrieval and crouching behaviors in male mice, resulting in neglect rather than maternal behavior. Moreover, approximately half of the subjects exhibited burying behavior toward pups, which suggested that pups became aversive stimuli, and male mice actively performed burying behavior to avoid these aversive stimuli. This study highlights novel aspect of oxytocin ―often dubbed the ‘trust hormone’―which could promote neglect behavior in the absence of LHA-MCH regulation. These insights could advance our understanding of child abandonment in humans.

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Poster

PSTR077: Parental Behaviors

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR077.08/

Topic: F.02. Neuroendrocrine Processes and Behavior

Title: State-dependent prioritization of feeding and parenting behaviors

Authors: *I. C. ALCANTARA[1], C. LI[1], L. E. MICKELSEN[1], C. M. MAZZONE[2], E. O. KAROLCZAK[1], A. I. GOLDSCHMIDT[1], M. L. REITMAN[1], M. J. KRASHES[1];
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Abstract: Across mammalian species, new mothers undergo considerable behavioral changes to nurture their offspring and meet the increased caloric demands of milk production. Since these two drives are both high postpartum, mothers must carefully switch between prioritizing maternal care and procuring food. While many neural circuits underlying feeding and parenting behaviors are well characterized, their interplay and modification during lactation remain less clear. Here, we measured feeding behavior in female mice across different stages of motherhood and found that mothers consume nearly five times more calories during lactation. This increase in appetite was accompanied by an increase in activity of hunger-promoting agouti-related peptide (AgRP) neurons in the arcuate nucleus (ARC^{AgRP}) of the hypothalamus. To assess the strength of hunger versus maternal drives during lactation, we designed a choice assay in which mice chose between a food source or a chamber containing pups and nesting material. Although food-deprived lactating mothers prioritized parenting over feeding, hunger reduced and disrupted sequences of parenting behaviors in both lactating and virgin females. This effect was mimicked by stimulating inhibitory ARC^{AgRP} axonal projections to the medial preoptic area (MPOA), a parenting node in the hypothalamus. Inhibiting parenting-responsive MPOA neurons also reduced parenting and shifted an animal's priority toward feeding. Using optogenetics and electrophysiology, we found that ARC^{AgRP} neurons monosynaptically inhibit MPOA bombesin receptor subtype-3 ($MPOA^{Brs3}$) neurons, a population that we discovered to govern both parenting and satiety. This ARC^{AgRP} to $MPOA^{Brs3}$ circuit may therefore explain how hunger can shift an animal's behaviors from parenting to food-seeking. Furthermore, single-cell RNA sequencing of the ARC and MPOA in fed and food-deprived lactating and virgin females revealed that $AgRP^{+}$ and $Brs3^{+}$ neuronal clusters are transcriptionally sensitive to hunger and reproductive states. Thus, hypothalamic networks are modulated by various internal states and work antagonistically during the prioritization of competing motivational drives.

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Poster

PSTR077: Parental Behaviors

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Program #/Poster #: PSTR077.09/G24

Topic: F.02. Neuroendrocrine Processes and Behavior

Support: NIH Grant MH109302
NIH Grant MH122622
NIH Grant MH110212

Title: Female Syrian hamsters with genetic deletion of arginine-vasopressin 1a receptors exhibit impaired sexual behavior and maternal care

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Abstract: Arginine-vasopressin V1a receptors (Avpr1a) within the social behavior neural network are critical for regulating social behaviors. Our lab utilized CRISPR- Cas9 to knockout (KO) the gene for Avpr1a in Syrian hamsters to investigate the role of this receptor in social behaviors in comparison to wild type (WT) and heterozygous (Het) animals. Previous findings have demonstrated increased social communication and aggression towards a same sex conspecific in Avpr1a KO hamsters in comparison to WT and Het groups. Besides their role in social and aggressive behaviors, AVP and Avpr1a are also known to participate in modulating sexual and maternal behaviors. Thus, we aimed to investigate if Avpr1a KO alters sexual and maternal behaviors in female hamsters. To evaluate changes in reproductive behavior, we placed a male hamster in the cage of a virgin female in estrus and observed sexual behavior for 30 minutes. Once pups were born, maternal behavior was videorecorded for analysis from postpartum day (PPD) 0 to PPD3 for 5 minutes at four separate timepoints: 0 and 8 hours after lights on; then 2 and 10 hours after lights off. To analyze both mating and maternal care; latency, total duration, and number of times that each behavior occurred were measured. For maternal care, a paradigm was created to identify various behaviors and each behavior was averaged per PPD per animal. Our results revealed alterations of both sexual and maternal behaviors in Avpr1a KO female hamsters. Both Avpr1a KO and Het females received significantly fewer and shorter mounting attempts by the male in comparison to WT animals. This finding indicates a possible deterrent for the male to mount and/or decreased receptive behaviors in the female such as time spent in lordosis. Interestingly, even though Avpr1a KO females spent a similar amount of time as the other groups (WT and Het) in the nest, they engaged in significantly less pup-care related behaviors, such as decreased time spent building a nest, licking and sniffing the pups, and crouching over them. Instead, Avpr1a KO female hamsters occupied their time with behaviors unrelated to pup care such as self-grooming, burying, and digging. The impaired care of the pups in Avpr1a KO females was also demonstrated by the fact that this group of animals was the only one to show infanticide among all the groups. Our findings reveal the importance of Avpr1a in regulating sexual and maternal behaviors in female hamsters. These data emphasize the importance of Avpr1as within the social neural network in contributing to the regulation of sexual and maternal behaviors.

Disclosures: E.A. Sambor: None. **D. Aspesi:** None. **N.S. Campbell:** None. **M.C. Stoehr:** None. **J.H. Taylor:** None. **Z.A. Grieb:** None. **K.L. Huhman:** None. **H. Albers:** None.

Poster

PSTR077: Parental Behaviors

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR077.10/G25

Topic: F.02. Neuroendrocrine Processes and Behavior

Support: NIH Grant P30 DA018310

Title: Neuropeptide underpinnings of parental care in three-spined stickleback

Authors: *A. M. JOGLEKAR[1], M. F. MACIEJEWSKI[2], C. XU[3], E. SHEN[3], S. SHEN[3], Y. CHEN[3], A. BELL[2], E. ROMANOVA[1], J. V. SWEEDLER[1];
[1]Chem., [2]Evolution, Ecology, and Behavior, [3]Statistics, Univ. of Illinois Urbana-Champaign, Urbana, IL

Abstract: The three-spine stickleback *(Gasterosteus aculeatus)* showcases diverse parental care behaviors where the father assumes sole responsibility for offspring care. Our previous studies have illuminated the potential role of neuropeptide genes in parental care. To investigate the role of neuropeptides and their dynamics associated with heritable paternal behavior, this study focused on directly measuring the neuropeptide profile change at different stages of breeding behavior, including nesting, spawning, and parenting, using liquid chromatography tandem mass spectrometry. With the aid of bioinformatics for de novo interpretation of tandem spectra, we identified the neuropeptide complement of the pituitary gland from the three breeding stages of behaving fish, n=9 for each stage. Over 6000 identified peptides were mapped to 436 unique proteins from the stickleback proteome available in the Uniprot database; secreted proteins comprised 21% of the unique proteins. We analyzed proteolytic processing of several major prohormones and compiled a library of characterized mature peptides for future functional studies. Next, we statistically quantified proteins across breeding stages, considering those backed by multiple peptides and present in >50% of samples per group/stage. Initially, ANOVA was conducted across stages followed by pairwise comparisons and fold change calculations. A small subset of secreted proteins showed significant changes. Specifically, proopiomelanocortin (POMC), prohormone convertase 1 (PC1), secretogranin II, and corticotropin releasing hormone b (CRHb) differentiated the nesting and spawning groups. Altered levels of chromogranin A, CRHb, PC1 and several enzymes critical for neuropeptide signaling marked the transition from spawning to parenting behavior. CRH is a hypothalamic neuropeptide from the urocortin family in vertebrates. It has been shown to regulate satiety and elicits anxiety-like behavior in other fish and rodents. Importantly in vertebrates, CRH regulates processing of POMC through changes in prohormone PC1 expression levels in the pituitary. These results suggest that the neuroendocrine stress response plays an important role in coordinating stickleback breeding behavior where overall homeostasis might be at risk.

Disclosures: A.M. Joglekar: None. **M.F. Maciejewski:** None. **C. Xu:** None. **E. Shen:** None. **S. Shen:** None. **Y. Chen:** None. **A. Bell:** None. **E. Romanova:** None. **J.V. Sweedler:** None.

Poster

PSTR077: Parental Behaviors

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR077.11/G26

Topic: F.02. Neuroendrocrine Processes and Behavior

Support: F31HD102163

Title: Corticotropin releasing factor receptor-2 expressing neurons in the medial amygdala facilitate infant-directed aggression in both sexes

Authors: *V. M. SEDWICK, A. AUTRY;
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Abstract: Caregiving behavior is highly conserved in animals, particularly mammals. While the phenotypic expression of caregiving may differ across species, the goal of this behavior is to increase the likelihood of infant survival. In laboratory mice, a range of infant-directed responses can be observed including caregiving, neglect, or infant-directed aggression and attack. However, around 2-3 weeks after mating, these aggressive tendencies decrease, giving way to parental behaviors such as pup retrieval and grooming. This shift offers a valuable framework for studying the neural mechanisms regulating infant care in males and females. We recently found that projections from urocortin-3 (Ucn3) neurons to the posterior amygdala, including the posterodorsal medial amydgala (MeApd) and the amygdalohippocampal area, promoted infant-directed aggression in females. Ucn3 binds with high affinity to corticotropin releasing factor receptor-2 (CRFR-2), and Ucn3 to CRFR-2 signaling in the MeA has been shown to mediate social preference. Here, we set out to dissect the role of CRFR-2 expressing neurons in the MeApd in infant-directed behavior and aggression in males and females as a function of social/sexual experience. We hypothesized that these neurons would be selectively active during infant-directed aggression in males, and that their activity would promote infant-directed aggression, but not adult aggression, in both sexes. Immediate early gene studies reveal that MeApd CRFR-2 neurons respond to pup exposure regardless of infant-directed phenotype, but MeApd CRFR-2 neurons are less active in mated animals compared to virgin animals. Using fiber photometry recordings, we confirm that infant odors activate MeApd CRFR-2 neurons across behavioral states and sex, but these neurons also strongly respond during infant-directed aggression in virgin males. Chemogenetic activation of these neurons elicits infant-directed aggression in virgin males and females and mated males, while this effect is blunted in mated females. Anatomical tracing uncovers strong projections of MeApd CRFR-2 neurons to the bed nucleus of stria terminalis (BNST), nigrostriatal tract, and the bed nucleus of the olfactory tract. Optogenetic inhibition of MeApd CRFR-2 projections to the BNST reduces pup approach and pup grooming in non-aggressive virgin males. With chemogenetically-induced infant-directed

aggression, optogenetic inhibition of the MeApd CRFR-2 projections to BNST reduces infant-directed aggression. Altogether, these results reveal a role for MeApd CRFR-2 neurons in regulating expression of infant-directed behaviors in both sexes.

Disclosures: V.M. Sedwick: None. **A. Autry:** None.

Poster

PSTR077: Parental Behaviors

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR077.12/G27

Topic: F.02. Neuroendrocrine Processes and Behavior

Support: NICHD HD088411 to R.C.F
BRAIN Initiative NS107616 to R.C.F
NSF GRFP to L.P.S

Title: Neural Basis of Cooperative Co-Parenting in Mice

Authors: *V. J. IVAN[1], L. PINEROS SCHUSTER[2], R. C. FROEMKE[3];
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[3]Otolaryngology, NYU Med., New York, NY

Abstract: The cohesion of family units is integral to survival in many social species, as cooperative co-parenting helps ensure the welfare of initially helpless offspring. Caregivers must learn how to coordinate and delegate responsibilities, detecting and recognizing infant distress cues and differentiating infant calls from adult calls. Caregiving behavior is exhibited by biological parents as well as alloparents (Dulac et al. 2014). Previously, we showed how virgin female mice acquire alloparental skills following visual observation and social interactions with a dam; this transference of caregiving skills is facilitated by oxytocin to enhance salience of sensory cues and promote prosocial behavior (Marlin et al. 2015, Carcea et al. 2021, Froemke and Young 2021).
Oxytocin from the hypothalamic periventricular nucleus (PVN) positively regulates the dopaminergic mesolimbic pathway, and this has been implicated in motivated and rewarding aspects of pup- and adult-directed social behaviors. Recent findings from our lab reveal that pup interactions trigger oxytocin release from the PVN to the VTA, signaling infant needs and enabling maternal pup retrieval (Valtcheva, Issa et al. 2023). VTA dopamine neurons are differentially activated by adult social interactions, with their activity levels predicting social reward (Hung et al. 2017, Solie et al. 2022).
Here we aimed to understand how the oxytocin and dopamine systems interact when adult females cooperate to ensure maternal-infant survival. We built low-cost open-source systems for months-long 24/7 behavioral monitoring (Schuster et al. 2023). We found that dams with low litter survival rates did not show improved outcomes across litters. However, cohousing these animals with dams with high litter survival rates led to enduring increases in litter survival by the

initially low-pup-survival dams. We quantified how dams encourage or demonstrate co-parenting to naïve virgin females, by physically guiding ('shepherding') the female to the nest until she stays with the newborns. We performed photometry of GRAB-DA signals in the NAc or GCaMP7s signals from VTA dopaminergic neurons of experienced DAT-Cre maternal mice. These animals were cohoused for several days peripartum with naïve females to characterize the emergence of communal caregiving behaviors. We found that shepherding or other forms of 'teaching' behaviors activated the dopaminergic reward system in the experienced mother. We conclude that multiple modulatory systems are required to coordinate brain activity and cooperative behavior for co-parenting and helping inexperienced adults become effective caregivers.

Disclosures: V.J. Ivan: None. **L. Pineros Schuster:** None. **R.C. Froemke:** None.

Poster

PSTR077: Parental Behaviors

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR077.13/G28

Topic: F.02. Neuroendrocrine Processes and Behavior

Title: Preoptic neuronal remodelling drives the onset of alloparenting in mice

Authors: *B. B. JAMIESON, M. X. CHEN, L. EL RASHEED, G. M. CHATTEY, J. KOHL; The Francis Crick Inst., London, United Kingdom

Abstract: Parental behaviour is controlled by brain-wide circuits, the functional organisation of which is increasingly well understood in mice. However, the relevance and function of these circuits in early life remains unknown. Here, we uncover the onset of alloparenting in juvenile mice and how changes in the functional neuronal architecture of parental circuits control alloparental social interactions at this age. We have observed that juvenile mice start to display spontaneous alloparental behaviour between postnatal day (P) 14 and 15, at levels similar to adult virgin females. Immediate early gene mapping revealed that this behaviour recruits galanin-expressing neurons in the medial preoptic area ($MPOA^{Gal}$ neurons). We confirm that these neurons start exhibiting pup-evoked activity at P15, using *in vivo* calcium imaging. While anterograde viral tracing from $MPOA^{Gal}$ neurons in juveniles shows adult-like projection patterns, retrograde trans-synaptic tracing uncovers a more extensive input pattern in juveniles. We find that $MPOA^{Gal}$neurons undergo extensive morphological remodeling between P14 and P15, accompanied by an increased frequency of spontaneous postsynaptic currents. This suggests that maturation of parenting-relevant synaptic inputs drives the onset of alloparental behaviour in juveniles. We are currently investigating the mechanisms underlying this cellular remodeling. Our results indicate that morphological and biophysical alterations in juvenile $MPOA^{Gal}$ neurons underlie the onset of alloparental behaviour. This work provides valuable insights into the neurodevelopmental processes that drive expression of caregiving behaviour in early life.

Disclosures: B.B. Jamieson: None. **M.X. Chen:** None. **L. El Rasheed:** None. **G.M. Chattey:** None. **J. Kohl:** None.

Poster

PSTR077: Parental Behaviors

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR077.14/G29

Topic: F.02. Neuroendrocrine Processes and Behavior

Title: Effect of the paternal exposure on memory and anxiety responses in male rats

Authors: *A. T. PALOMINO, J. M. IBARRA-HERNÁNDEZ, A. E. GONZÁLEZ, A. M. GARCIA, A. DAMIÁN LÓPEZ;
Dept. de Fisiología, Facultad de Medicina. UANL, Monterrey, Nuevo León, Mexico

Abstract: Maternal behavior is defined as the actions performed by the mother to ensure the survival of her offspring. It is considered that maternity benefits only the offspring; however, it is now known that the mother also benefits, likely due to hormonal changes during gestation and lactation, which improve her memory and reduce her response to stressors. The effects of paternal behavior in male rats are still unknown. Our main was to evaluate memory and anxiety in male rats cohabiting with their pups and the female.We used male Wistar rats aged 45 to 50 days. The rats were divided into four groups (n=5 per group). The first group had no exposure to pups. The second was exposed to two of their litters with the same partner, while the third was exposed to three of their litters. At the end of the lactation period according to the group, anxiety was assessed using the elevated plus maze test, and the rats were subjected to four days of training in the Barnes maze, followed by an evaluation of short-term memory (STM) the next day and long-term memory (LTM) on the seventh day. The time spent in open and closed arms, as well as the latency to find the escape box, the number of correct choices, and errors were analyzed using an ANOVA test. A *P* less of 0.05 was considered statistically significant.Exposure to litters significantly decreased the time spent in open arms in the elevated plus maze for the males. Additionally, it decreased the latency time to find the escape box during training sessions and in the evaluation of STM (up to a 92% reduction) and LTM (up to an 82% reduction) compared to Group 1. In this same context, the group exposed to two litters had a lower number of errors (2 ± 1 errors) compared to Group 1 and 3 (10 ± 1.5 errors) during both STM and LTM assessments.Paternal behavior in male rats increases anxiety-related behaviors, which likely improves memory consolidation according to the experience acquired with the number of litters.

Disclosures: A.T. Palomino: None. **J.M. Ibarra-Hernández:** None. **A.E. González:** None. **A.M. Garcia:** None. **A. Damián López:** None.

Poster

PSTR077: Parental Behaviors

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR077.15/G30

Topic: F.02. Neuroendrocrine Processes and Behavior

Support: NSF AAH5162
ABS Research Grant

Title: Division of labor in California mice: predictors of efficiency and the impact of oxytocin manipulation

Authors: *C. MALONE[1], C. A. MARLER[2];
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Abstract: Oxytocin (OXT) signaling is known to impact coordinated, close-range behaviors (e.g. following, contact, huddling) in rodents. However, it is unknown if OXT impacts spatially-separated coordinated behaviors. The biparental, monogamous California mouse (Peromyscus californicus) coordinates spatially-separated tasks to accomplish spatially-separated goals such as resource acquisition, territorial defense, and parental care. Using this unique species, we investigated how division of labor changes across the social life span and whether OXT can alter division of labor in the primiparous stage. We manipulated OXT systems via intranasal or intraperitoneal injections of an agonist, antagonist, or vehicle after the first litter of pups were born. Behavioral analyses of the pairs during their pre-pair, post-pair, and primiparous stages in a nonsocial (foraging) and social (territory intrusion) challenge were conducted. Our results indicate that during social challenges, mice use more sex-delineated roles, with males spending time near the intruder and females spending time at the nest. In contrast, nonsocial challenges are divided more equitably between the sexes. Division of labor also increases as time demands increase, such as during the primiparous life stage. Under the influence of OXT antagonists, division of labor tactics were disrupted, as evidenced by an increase in time spent foraging together with neglect of the nest. These results indicate a new role of OXT signaling in the coordination of spatially-separated tasks, not just proximal synchrony.

Disclosures: C. Malone: None. **C.A. Marler:** None.

Poster

PSTR077: Parental Behaviors

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR077.16/G31

Topic: F.02. Neuroendrocrine Processes and Behavior

Support: NIH K99HD108801-01A1
NIH 2R01HD082131

Title: Molecular Basis of Parental Care: Cell-Type Specific Insights into Behavioral Circuits

Authors: *B. L. LOGEMAN, P. M. HORVATH, C. G. DULAC;
Harvard Univ., Cambridge, MA

Abstract: Parental care is composed of multiple infant-directed behaviors that promote offspring survival and is influenced by the sex and physiological state of the caregiver. Previous work in mice has identified the medial preoptic area of the hypothalamus as a key brain area implicated in parental behaviors. However, numerous naturalistic behaviors and homeostatic processes are controlled by this area, hindering mechanistic investigation of the circuits underlying parental care. To overcome this challenge, here we employ cell-type specific sequencing and ATACseq analysis, recording, tracing, and perturbation to gain access into molecular, biophysical, and circuit-based causality of behavioral control. We find that various neuronal types involved in parenting behavior are each distinctively influenced by the sex and physiological status of an individual and we uncover how cell-type specific regulatory programs alter gene expression, connectivity, and neural activity underlying behavior control. These results demonstrate how cell-type specific transcriptional responses to internal physiological cues mediate circuit specific alterations to neural activity and ultimately influence animal behavior.

Disclosures: B.L. Logeman: None. **P.M. Horvath:** None. **C.G. Dulac:** None.

Poster

PSTR077: Parental Behaviors

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR077.17/G32

Topic: F.02. Neuroendrocrine Processes and Behavior

Support: Princeton University New Ideas in the Natural Sciences (Dean for Research Innovation Fund)
NIH Grant F32HD110180

Title: The neural architecture of paternal care in African striped mice

Authors: *F. D. ROGERS[1], R. MALLARINO[2], C. J. PENA[3];
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Abstract: While we know much about the neural mechanisms of maternal behavior, the absence of naturally occurring paternal care among traditional model species has prevented a thorough understanding of the neural substrates that promote active parental behavior in males. The African striped mouse (Rhabdomys pumilio) is a murine rodent in which parental care among males is naturally occurring and common, both before and after sexual experience. Here, we leverage substantial natural variation of paternal behavior in African striped mice in parallel with immunohistochemistry (IHC) for an immediate early gene, cFos, to reveal the putative neural

architecture of paternal care. We applied brain-wide cFos mapping to uncover regions with high neural activity during bouts of exposure to novel infant stimuli (N = 24 males). We juxtaposed these maps of correlated activity with those generated from individuals exposed to an empty cage (N = 20 males). Unsurprisingly, cFos in the medial preoptic area (MPOA) distinguished paternal phenotypes in sexually naïve male striped mice; i.e., we find a significant positive correlation ($p < .005$) between cFOS+ cells in the MPOA and paternal phenotypes (vs. infanticidal and ambivalent phenotypes). From there, we have built out a map of the putative neural network underlying male parental care in African striped mice (or a "paternal network") by correlating MPOA activity with activity across brain regions. These findings lay the groundwork for better defining subsequent specific molecular and cellular mechanisms driving individual differences in paternal care.

Disclosures: F.D. Rogers: None. **R. Mallarino:** None. **C.J. Pena:** None.

Poster

PSTR077: Parental Behaviors

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR077.18/G33

Topic: F.02. Neuroendrocrine Processes and Behavior

Support: NIH
HHMI

Title: Molecular and functional dissection of medial preoptic area circuit regulating parenting behavior

Authors: *M. RAHMAN[1], D. CIFTCI[1], A. H. SONG[2], R. FANG[3], M. TALAY[4], D. E. BA[1], X. ZHUANG[5], C. G. DULAC[1];
[1]Harvard Univ., Cambridge, MA; [2]MIT, Cambridge, MA; [3]Dept. of Chem. and Chem. Biol., Howard Hugh Med. Inst. / Harvard Univ., Cambridge, MA; [4]MCB, Brown Univ., Cambridge, MA; [5]Depts. of Chem. & Chem. Biol. & Physics, HHMI / Harvard Univ., Cambridge, MA

Abstract: Parenting is a conserved naturalistic social behavior displayed in a semi rigid sequence of stereotyped motor actions. The implementation of parenting behaviors is sexually dimorphic, and parenting motor actions and sequences vary depending on the internal state of the animal and the presence of another conspecific. The hypothalamus (specifically MPOA) is a key brain region that controls internal states and drives associated with social behaviors and physiological states. While previous studies have shown that several molecularly distinct neuronal populations in the MPOA are active during parenting, the mechanism and dynamics of this activity is not well understood. It is also known that the MPOA is heavily involved in neuroendocrine regulation hormonal states and associated behaviors in the brain. Can functionally distinct MPOA neurons be distinguished based on their activity dynamics displayed during various steps of parenting? What features in parenting behavior do these neurons encode?

What is the relation between the temporally precise activity of neurons and their underlying gene expression patterns? We developed a novel experimental approach to combine deep brain calcium imaging from MPOA neurons and concurrent spatial transcriptomics (MERFISH) from the same neurons to address these questions. We identified multiple clusters of neurons with distinct activity profiles associated with several features of parenting behavior. Many of these neurons displayed persistent activity lasting more than 100 seconds. Finally, we discovered that these neuronal clusters based on activity profiles belonged to molecularly distinct neuronal clusters. This provides one of the first evidence linking molecular properties of neurons with their distinct circuit activity. Thus, parenting circuits emerge as a complex local microcircuit consisting of multiple functional modules with characteristic molecular properties.

Disclosures: M. Rahman: None. **D. Ciftci:** None. **A.H. Song:** None. **R. Fang:** None. **M. Talay:** None. **D.E. Ba:** None. **X. Zhuang:** None. **C.G. Dulac:** None.

Poster

PSTR078: Stress-Modulated Pathways: Cognition, Learning, and Memory Circuits

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR078.01/G34

Topic: F.03. Stress and the Brain

Title: Neuromodulatory effect of enriched environment and Tribulus terrestris in restoring cognitive deficits

Authors: *B. BARAKA[1], T. KRISHNAMURTHY[2], R. VASUDEV[2], V. BHAGYA[3]; [1]Pharmacol., KLE Col. of Pharm., BANGALURU, India; [2]Pharmacol., KLE Col. of Pharm., Bengaluru, India; [3]Pharmacol., KLE Col. of Pharm., Bangalore, India

Abstract: Major depressive disorder is a mental health condition that causes a persistently low or depressed mood and a loss of interest in pleasurable activities. Chronic stress causes a harmful effect on hippocampus and prefrontal cortex functioning which is associated with cognitive deficits, depression and anxiety. Enriched Environment (EE) stimulates the brain by physical and social interaction, sensory and cognitive stimulation. EE enhances neuronal functioning, boost hippocampal neurogenesis, improve memory and cognitive performance. Phyto therapeutic approaches have been widely proposed to improve mental health. *Tribulus terrestris* (TT) and EE are combined to reduce the impacts of anxiety and behavioral changes brought on by stress. The main objective of this work is to address the behavioural and neurobiological effects of EE along with herbal plant TT on chronic immobilization stress (CIS) induced depression, anxiety and cognitive deficits in rats. The findings showed that CIS increased anxiety and depression, impaired cognitive functions. Chronic treatment with TT with EE improved CIS induced cognitive deficits and reduced anxiety and depression. Also, the expression of biomarkers improved followed by the combined treatment of TT and EE. This study shows that the enriched environment enhances the beneficial effect of *Tribulus terrestris* in restoring stress induced cognitive deficits

Disclosures: B. Baraka: Other; kle college of pharmacy, bengaluru. **T. Krishnamurthy:** None. **R. Vasudev:** None. **V. Bhagya:** None.

Poster

PSTR078: Stress-Modulated Pathways: Cognition, Learning, and Memory Circuits

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR078.02/G35

Topic: F.03. Stress and the Brain

Support: DoD W81XWH-20-1-0066

Title: Female gonadal hormones on the day of trauma and outcome

Authors: *C. V. CHEN;
Texas A&M Univ., Bryan, TX

Abstract: Post-traumatic stress disorder (PTSD) is the fourth most common mental disorder. Interestingly, women are twice as likely as men to develop (PTSD) after a traumatic event. To determine whether female gonadal hormones on the day of trauma might play a role on outcome, we used the widely accepted rodent model of PTSD, Single Prolonged Stress (SPS). Intact adult female Sprague Dawley rats were ovariectomized, injected with estradiol benzoate, progesterone, both or vehicle and exposed to SPS (or not), and later tested on fear learning tests to determine severity of extinction recall deficits, as this is a cardinal symptom in PTSD patients.

Disclosures: C.V. Chen: None.

Poster

PSTR078: Stress-Modulated Pathways: Cognition, Learning, and Memory Circuits

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR078.03/G36

Topic: F.03. Stress and the Brain

Title: Exposure to Indian classical Mohana raga along with Tephrosia purpurea leaves extract restored spatial working memory, recognition memory, anxiety and depression in stressed rats

Authors: *T. KRISHNAMURTHY[1], R. VASUDEV[2], B. BARAKA[3], V. BHAGYA[4,5];
[1]Pharmacol., KLE Col. of Pharm., Bengaluru, India; [2]Pharmacol., KLE Collge of Pharm., Bengaluru, India; [3]Pharmacol., KLE Col. of Pharm., BANGALURU, India; [4]Neurophysiology, Natl. Inst. Mentl Hlth. & Neuro Sci., Bangalore, India; [5]KLE Collge of Pharmacy, Bangalore, India

Abstract: Chronic stress leads to psychiatric disorders, causes damage to the brain regions responsible for cognitive functions and induces anxiety and depression-like behaviour. Exposure to chronic stress increases neurodegeneration and also impairs learning and memory. Cognitive-behavioural stress management (CBSM) including yoga, meditation, mindful-based interventions, and music therapy relieves stress. Listening to music reduces anxiety, improves mood and provides a calming effect, especially listening to raga Bhupali (Mohana) improved learning and memory. Herbal drug therapy offers a holistic approach to promote physical and emotional well-being. The methanolic extract of *Tephrosia purpurea* (TP) leaves has higher antioxidant activity. This research work involves the study of the effect of TP and Indian classical music on chronic unpredictable mild stress-induced learning and memory impairment. Stressed animals demonstrated increased anxiety, anhedonia, behavioural despair, impaired recognition and spatial memory. The animals treated with TP for 14 days showed complete restoration of cognitive deficits. Treated animals showed less anxiety, depression, and improved recognition and working memory. Interestingly, stressed animals exposed to Indian classical music for 1 h per day for a period of 21 days helped in the restoration of cognitive deficits. Also, the combination of music and TP treatment had a synergistic effect in alleviating chronic stress-induced compromised cognitive functions.To conclude, the animals exposed to music and treated with *Tephrosia purpurea* had a beneficial effect in improving cognitive impairment. The combination of *Tephrosia purpurea* and Indian classical music can be used as a therapeutic approach for chronic stress related neuropsychiatric issues and cognitive deficits.

Disclosures: T. Krishnamurthy: Other; KLE COLLEGE OF PHARMACY, BENGALURU; KAHER. **R. Vasudev:** None. **B. Baraka:** None. **V. Bhagya:** None.

Poster

PSTR078: Stress-Modulated Pathways: Cognition, Learning, and Memory Circuits

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR078.04/G37

Topic: F.03. Stress and the Brain

Title: Interactive influence of alcohol and stress on learning and intrusive memories

Authors: *J. L. KIRKLAND[1], K. N. SUZELIS[1], C. M. GURGANUS[1], A. J. FARRELL[1], K. M. SIEREVELD[1], J. R. YUEN[1], J. I. C. IFEAKANWA[1], K. R. FLEETHAM[1], M. L. STANEK[1], M. S. RISNER[1], J. G. BLASCO[1], B. R. RORABAUGH[2], P. R. ZOLADZ[1];
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Abstract: Stressful, often traumatic, events, such as sexual (or other physical) assaults and motor vehicle accidents, frequently involve individuals who are under the influence of alcohol. Some research suggests that peri-traumatic alcohol ingestion increases the risk for PTSD symptomatology, such as intrusive memories. Indeed, experimental work in neurotypicals has shown that alcohol increases the number of intrusive memories that result from watching an

emotionally arousing film. However, no studies have examined the impact of alcohol on what participants remember about a laboratory-controlled stressful event or the number of intrusive memories that result from such an event. We aimed to address this gap in the present study. Undergraduate students ingested 0.4 g/kg ethanol or a placebo over a period of 30 min. They were then exposed to a modified version of the Trier Social Stress Test (TSST) or the friendly-TSST (f-TSST), both of which were designed to enable participant memory for the experiences to be quantified. The TSST required participants to deliver a ten-minute speech in front of two lab panel members as part of a mock job interview; the f-TSST required participants to casually converse with panel members about their interests and hobbies. In both conditions, the panel members interacted with (central) or did not interact with (peripheral) several objects sitting on a desk in front of them. Participants' BrAC, subjective intoxication, heart rate, and anxiety levels were assessed before, during, and after the TSST or f-TSST, and saliva samples were collected to assay for cortisol and alpha-amylase. The next day, participants' memory for the objects that were present on Day 1 was assessed with recall and recognition tests. We also quantified participants' intrusive memories on Days 2, 4, 6, and 8. Alcohol led to increased BrAC and subjective intoxication ratings, and TSST exposure resulted in greater subjective anxiety. Participants exposed to the TSST exhibited greater recall of central and peripheral objects and fewer falsely recalled objects than participants exposed to the f-TSST. Participants who ingested alcohol demonstrated greater recognition of central, relative to peripheral objects, an effect that was absent in participants who ingested placebo. Importantly, on Days 2 and 4, participants exposed to the TSST reported a greater number of intrusive memories related to the speech task, and this effect was augmented by alcohol. Our findings suggest that memory for a stressful event is enhanced, relative to memory for a non-stressful event, and that alcohol may increase the development of intrusive memories related to a stressful experience.

Disclosures: J.L. Kirkland: None. **K.N. Suzelis:** None. **C.M. Gurganus:** None. **A.J. Farrell:** None. **K.M. Siereveld:** None. **J.R. Yuen:** None. **J.I.C. Ifeakanwa:** None. **K.R. Fleetham:** None. **M.L. Stanek:** None. **M.S. Risner:** None. **J.G. Blasco:** None. **B.R. Rorabaugh:** None. **P.R. Zoladz:** None.

Poster

PSTR078: Stress-Modulated Pathways: Cognition, Learning, and Memory Circuits

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR078.05/H1

Topic: F.03. Stress and the Brain

Support: Scialog grant #29105 from the Research Corporation for Science Advancement and Frederick Gardner Cottrell Foundation

Title: The Effects of Early Life Stress on Developmental Stress Markers, Thigmotaxis, and Associative Recognition Memory in Juvenile Rats

Authors: *G. NIGAM[1,2], R. NYGREN[1], A. ABRAMENKO[3], N. ALY[1], A. DEFINA[1], A. MAY[1], L. ROKITA[4], A. MACKEY[5], S. M. TRASK[6], P. A. ROBINSON-DRUMMER[1,7]; [1]Neurosci., Haverford Col., Haverford, PA; [2]Neuroscience, Bryn Mawr College, Bryn Mawr, PA; [3]Biol., Haverford Col., Haverford, PA; [4]Psychology, Haverford Col., Haverford, PA; [5]Neurosci., Univ. of Pennsylvania, Philadelphia, PA; [6]Neurosci., Purdue Univ., West Lafayette, IN; [7]Psychology, Haverford College, Haverford, PA

Abstract: Exposure to early-life stress (ELS) has been shown to accelerate the emergence of aversively-reinforced contextual memory in rodents. Regions like the hippocampus show accelerated neuronal maturation associated with early emergence of these learning behaviors. However, whether ELS also accelerates the development of non-reinforced behaviors like spatial-associative recognition memory is unclear. Further, it is unknown whether changes in prefrontal cortex (PFC) activity would be associated with these changes. The current project explored the effects of ELS on development of spatial-associative memory using the Object-in-Place (OiP) recognition task and by measuring behavioral and neurobiological markers of stress and learning in juvenile rats. Following postnatal day (PD)8-12 low-bedding/nesting ELS, in addition to stress-related alternations in maternal behavior and activity, we found a trending negative correlation between PD12 cyclin D1 (a cell cycle regulator) expression in the dorsal hippocampus and corticosterone levels suggesting decreased cell proliferation processing in stressed pups. During open field exploration, both control (CON) and ELS rats between PD22-24 showed similar amounts of thigmotactic behavior and a preference to remain in areas with a distinct landmark. Simple recognition memory was similar between CON and ELS animals at PD24 and 25, however at PD26 ELS animals showed a stronger, adult-like novelty preference not observed in CON pups that subsequently changed to a slight deficit in ELS NOR preference by adulthood. For the spatial-associative OiP task, both groups demonstrated irregular learning between PD24-26. Because this task typically emerges by PD26, these results suggest PD24-26 is a transition period for this behavior. Sixty minutes after PD26 training, CORT levels remained elevated in ELS animals relative to CON further demonstrating a prolonged effect of early stress on subsequent stress responding. When examining cortical changes after learning, for simple NOR, prefrontal activity did not differ between groups, however following spatial-associative OiP training, ELS animals showed reduced prefrontal activity. Together, these results reveal ELS-related long-term dysfunction in stress systems that may interact with developing learning systems to both accelerate maturation of simple recognition memory only to cause premature decline in memory in adulthood.

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Poster

PSTR078: Stress-Modulated Pathways: Cognition, Learning, and Memory Circuits

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR078.06/H2

Topic: F.03. Stress and the Brain

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Title: Neural dynamics predicting individual differences in human psychological resilience using a machine learning approach.

Authors: *N. WATANABE[1,2], S. YOSHIDA[3,4], R. KEERATIVITTAYAYUT[3,5], M. TAKEDA[3,6];
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Abstract: Neurophysiological mechanisms underlying psychological resilience, the ability to overcome adversity have been extensively studied in animals. However, in comparison with animals, human resilience is unique in that it is underpinned by higher cognitive functions, such as self-confidence and a positive attitude to challenges. Given these discrepancies, the neurophysiological mechanisms underlying human resilience remain unclear. To address this issue, we recorded non-invasive multimodal responses driven by acute stress exposure over 1.5 hours using functional brain imaging (resting-state fMRI and EEG) and peripheral physiological measurements (pupil size, heart and respiratory rates, and cortisol density). Data were collected from 90 participants (68 males and 22 females, mean age 20.13 years). Here we showed that the degree of individual resilience is indexed by multiple changes in neural dynamics 1 hour after acute stress. Both fMRI and EEG show that activity in the cortical salience network and power in high-beta and gamma oscillations increase in less resilient individuals. Contrastingly, activity in the cortical default mode network and spontaneous activity in the posterior hippocampus increase in more resilient individuals (statistical thresholds: $P < 0.05$ *FDR corrected*). Furthermore, machine learning analysis using ElasticNet confirmed that, 1 hour after stress exposure, the functional connectivity in the salience network was the most influential, followed by that in the default mode network, gamma power, high-beta power, and hippocampal activity. The neurophysiological dynamics for resilience do not occur as previously thought, but rather in a time-lagged manner against stress exposure. Our findings shed light on a new approach to recovery from stress-induced deficits such as delayed neuromodulation after a stressful event.

Disclosures: N. Watanabe: None. **S. Yoshida:** None. **R. Keerativittayayut:** None. **M. Takeda:** None.

Poster

PSTR078: Stress-Modulated Pathways: Cognition, Learning, and Memory Circuits

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR078.07/H3

Topic: F.03. Stress and the Brain

Title: The Effects of Mindfulness Practice on Student Burnout Rates: Use of Salivary Alpha-Amylase and Salivary Cortisol as Metrics of Burnout

Authors: H. M. HUGHES, L. R. AUNE, *T. E. BLACK;
Psychological Sci., Weber State Univ., Ogden, UT

Abstract: Research on the human stress response has focused on two distinct systems: the hypothalamic-pituitary-adrenal axis and the sympathetic nervous system. Cortisol is a glucocorticoid hormone produced in the adrenal glands that suppresses inflammation, controls metabolism, and plays a crucial role in the circadian rhythm. It is associated with the sleep-wake cycle being highest just after waking and lowest in preparation for sleep. Cortisol is involved in most organs and systems in the body (Tomlinson & Stewart, 2001). Thus, it can be measured in a variety of ways, such as blood draws and saliva. The metabolization of cortisol into other forms makes it hard to get an accurate measure. One enzyme that plays a role in the inactivation of cortisol is 11β-hydroxysteroid dehydrogenase (11β-HSD) (Tomlinson & Stewart, 2001), converting cortisol to cortisone. Using cortisol as an indicator of stress is difficult due to the temporal fluctuations related to its involvement in the sleep-wake cycle. Salivary alpha-amylase is an enzyme in saliva responsible for the breakdown of carbohydrates into simpler sugars (Ali & Pruessner, 2012). It is activated by the presence of food in the mouth and or during a stress response, as there is a heightened need for simple sugars during mass activation. This establishes salivary alpha-amylase as a dependable physiological metric for assessing stress and burnout (Aguilar-Raab, et al., 2021). Mindfulness techniques are a set of coping strategies to better manage stress (Aguilar-Raab, et al., 2021). They aim to draw attention to the here and now, combined with a non-judgmental attitude towards what is being experienced. Mindfulness techniques have been shown to decrease stress levels in both cortisol and salivary alpha-amylase (Aguilar-Raab, et al., 2021). Compassion-based mindfulness allows for events to be seen through compassion rather than empathy, allowing a person to reframe the distinction between their own emotions and the emotions of others (Jazaieri et. al., 2012) while practicing general principles of mindfulness. The current study aims to further explore the effectiveness of compassion-based mindfulness techniques. Physiological stress levels will be measured using salivary alpha-amylase and cortisol.

Disclosures: H.M. Hughes: None. **L.R. Aune:** None. **T.E. Black:** None.

Poster

PSTR078: Stress-Modulated Pathways: Cognition, Learning, and Memory Circuits

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR078.08/H4

Topic: F.03. Stress and the Brain

Support: NIH Grant MH104602

Title: Ventral hippocampal CA2 enables social discrimination after acute defeat

Authors: *W. SHENG[1], L. M. BOYLE[2], S. A. SIEGELBAUM[3];
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Abstract: The hippocampus, a brain region critical for episodic memory, is composed of distinct anatomical subregions. Along its transverse axis, hippocampus is divided into the dentate gyrus, CA3, CA2 and CA1 regions. Along its longitudinal axis, hippocampus has been divided into a dorsal portion, which is important for cognitive aspects of memory, and a ventral portion, which has been implicated in emotional behaviors. Recent studies from our laboratory have focused on the importance of the dorsal CA2 region in social memory behaviors that test the ability of a mouse to distinguish a novel from familiar conspecific. However, the behavioral role of ventral CA2 is unclear. Using chemogenetic silencing approaches, we found that ventral CA2 is not required for social novelty discrimination, in contrast to the importance of dorsal CA2. Here we report that home cage levels of cFos expression are significantly higher in ventral than in dorsal CA2. Moreover, whereas social exploration caused only a modest increase in cFos levels in ventral CA2, a 10-min episode of acute social defeat caused a marked increase in ventral CA2 cFos expression that was significantly greater than the increase following social exploration. Of particular note, chemogenetic silencing of ventral CA2 silencing during either acute social defeat or during an acute defeat memory recall session impaired the normal ability of the defeated mouse to distinguish the aggressor from a non-aggressor stimulus mouse when tested 24 h after interactions with both stimulus mice. Thus, ventral CA2 is required for valence-associated social discrimination but not for the discrimination of social novelty.

Disclosures: W. Sheng: None. **L.M. Boyle:** None. **S.A. Siegelbaum:** None.

Poster

PSTR078: Stress-Modulated Pathways: Cognition, Learning, and Memory Circuits

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR078.09/H5

Topic: F.03. Stress and the Brain

Support: EndoCARE

Title: Fear Conditioning and Extinction in the rat: A Gender and Strain Comparison

Authors: *E. ESNEAULT[1], K. R. WALKER[2], C. FROGER-COLLEAUX[1], E. CAMPEROS[1], A. HERNIER[1];
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Abstract: Post-Traumatic Stress Disorder (PTSD) is a stress-related mental disorder characterized by recurrent and intrusive memories from a traumatic experience and considered as a maladaptation to traumatic stressors, with altered fear learning and extinction. Although women are less exposed to traumatic events in their lifetime than men, they have a higher risk of PTSD. In the rodent, strain and sex differences related to anxiety-like behavior are also known. The aim of this study was to compare the susceptibility of four different strains of rats in both genders to a Fear Conditioning and Extinction procedure. In this protocol rodents associate a tone (conditioned stimulus, CS) with electrical shocks previously received (unconditioned stimulus, US). Following re-exposure to the same stimulus (tone) freezing behavior is observed as an indicator of fear. Repeated exposure to the cue in the absence of electrical shocks leads to a progressive suppression of the fearful reaction evoked by the cue through an extinction process, which represents a key process in exposure-based therapies for PTSD at the clinical level. Long-Evans, Sprague-Dawley, Wistar and Wistar Kyoto rats all displayed freezing behavior during the conditioning and extinction sessions. The highest fear response was observed in Long-Evans rats while Wistar-Kyoto rats showed lowest performances. Long Evans rats demonstrated the slowest rate of extinction, Wistar Kyoto rats generally exhibited a lower and relatively constant degree of freezing over extinction sessions. During acquisition and the first extinction session similar levels of freezing behavior were observed in both genders. However, the extinction process appeared faster and more pronounced in females compared to males, particularly in the Wistar strain. While no clear differences were observed in fear response to stressors such as electric foot shocks, these results highlight some strain and sex differences in fear learning and extinction. Long Evans rats demonstrate the highest fear response and lowest extinction, suggesting this strain may be more appropriate for evaluating new drug candidates relevant to PTSD disorders in the Fear conditioning and Extinction protocol.

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Poster

PSTR078: Stress-Modulated Pathways: Cognition, Learning, and Memory Circuits

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Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR078.10/H6

Topic: F.03. Stress and the Brain

Support: Grant support MH127835

Title: Activation of Corticolimbic Parvalbumin Interneurons in an Animal Model of PTSD

Authors: *S. TALAGADADEEVI;
Neurobio., Univ. of Cincinnati, Cincinnati, OH

Abstract: Post-Traumatic Stress Disorder (PTSD) can develop after a traumatic experience and can greatly impair quality of life in numerous ways. Two brain regions have been identified as key actors in fear responses: the basolateral amygdala (BLA) and prefrontal cortex (PFC). The PFC is subdivided into the prelimbic cortex (PL) and the infralimbic cortex (IL). The PL and IL have robust projections to the BLA), which can then mitigate the expression of fear. Recent studies suggest that involvement of parvalbumin interneurons (PV) and perineuronal nets (PNNs) in mediating fear behavior in the prefrontal cortex and BLA This study aims to further explore their contribution to PTSD symptomology. PV are GABAergic inhibitory neurons intrinsic to IL, PL and BLA, while PNNs are extracellular structures that stabilize brain plasticity. PV neurons are frequently contacted by PNNS, which is thought to limit plasticity of inputs. Reduced expression of PNNs can facilitate hyperactivity. Previously, we observed decreases in PV and PV with PNNs in the BLA of Sprague Dawley rats after exposure to single-prolonged stress (SPS) relative to unstressed controls. SPS is used as a method to recapitulate PTSD-related behaviors in rats. Given this data, we hypothesized that SPS will cause a decrease in PV activity in the BLA and PL, and a decrease in activity in the IL. consistent with changes in inhibitory control of fear circuitry. To test this hypothesis, neuron activity was measured in the BLA, PL, and IL, using FOS protein as a marker of neuron activity. Immunohistochemistry was performed to visualize the PV, PNNs, and c-FOS. SPS appeared to decrease the number of PV with PNNs and PV, FOS, and PNN co-labeled neurons in the PL. No significant changes were observed in the BLA or IL. The decrease in PL PV FOS activation may be related to reduced investment of PNNs, reducing inhibition of PL circuitry that may promote fear learning following SPS. Our results are consistent with a role for PNNs in maintaining PL PV neuron control of PFC output, which is disrupted by SPS.

Disclosures: S. Talagadadeevi: Other; Grant support MH127835.

Poster

PSTR078: Stress-Modulated Pathways: Cognition, Learning, and Memory Circuits

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR078.11/H7

Topic: F.03. Stress and the Brain

Support: R21AG079025

Title: An open-source trace fear conditioning system for head-restrained mice

Authors: *Y. SHI[1], C. PAYNE-ROGERS[2], A. SCHAEFER[2], C. LACEFIELD[1], M. S. AHMED[1], R. HEN[3], G. F. TURI[4,5];
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Univ., New York State Psychiatric Inst., New York, NY; [4]Systems Neurosci., New York State Psychiatric Inst., New York, NY; [5]Columbia University, New York, NY

Abstract: Temporal binding capacity, which enables the relational association of discontiguous stimuli and events, diminishes with normal aging and select neuropsychiatric disorders. An improved understanding of changes in neural functions that contribute to degraded temporal binding capacity could greatly facilitate the long-term objective of alleviating cognitive and affective impairments in normative aging and aging-associated neuropsychiatric disorders.
“Trace” fear conditioning (tFC) has long been a reliable experimental paradigm for studying the temporal binding of emotionally salient stimuli and events in subjects, which learn to associate a neutral auditory cue (conditioned stimulus, CS) with an aversive unconditioned stimulus (US), despite their separation by a stimulus-free gap.
Currently available tFC paradigms perform the task on freely moving subjects, which is not compatible with recording techniques that require head-restraining the subject, such as electrophysiological and optical imaging tools. In order to investigate the changes in circuit and network functioning contributing to diminished temporal binding capacity, we have developed an open-source head-restrained apparatus for ‘‘trace’’ fear conditioning.
Operated by a range of microcontrollers, custom-designed hardware, and software interfaces utilizing an open-source electronics prototyping platform, the system provides measurement of behavioral parameters and adaptable stimulus delivery to mice head-fixed on the rig. Behavioral data, including licking behavior, whisker movement, pupil dilation, and facial expressions, are collected using lick-sensors and an infrared video camera. Water solenoids and LEDs are integrated for delivering timed auditory and visual stimuli, while lick ports serve dual purposes of delivering rewards and detecting lick suppression behavior based on lick counts. The provided scripts are designed for running the system and collecting data in JSON files. Moreover, a graphical user interface (GUI) has been developed to simplify system operation, ensuring that researchers with varying levels of coding experience can utilize the apparatus effectively. Additionally, the repository includes a basic analysis pipeline for rapid assessment of behavior through data cleaning, visualization, and numerical analysis.
Using this paradigm with multiple cohorts of mice we demonstrated effective conditioning. Our innovative, modular, and open-source system allows researchers to design flexible, modular systems to measure trace fear conditioning in head fixed mice in order to dissect neuronal circuits required for this behavior.

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Poster

PSTR078: Stress-Modulated Pathways: Cognition, Learning, and Memory Circuits

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR078.12/H8

Topic: F.03. Stress and the Brain

Title: The Effects of an Acidic Environment on the Nervous System of C. elegans

Authors: *J. R. RAINVILLE, A. GARRASTEGUI SEGARRA;
Sch. of Neurosci., Virginia Technol., Blacksburg, VA

Abstract: Climate change has resulted in changes to the incidence and intensity of heat waves. These have been linked to neurological and neurodegenerative pathologies, including Alzheimer's, Parkinson's, and Motor Neuron Diseases. While there does seem to be a pattern between global warming and the prevalence of neurodegenerative diseases in literature reports, the direct link between them is yet to be established. We hypothesize that long-term exposure to varied levels of acidic pH in water reduces associative learning in *C. elegans*. We test this by exposing *C. elegans* to three pH levels (7, 4.3, and 3.5) for 7 consecutive days. We use an associative learning paradigm to test the learning ability and feeding behavior of the test group against the control. We anticipate as the acidity increases, the associative learning in *C. elegans* will decrease. The results of the experiment would provide meaningful applications in understanding environmental impacts on the nervous system and encourage further inquisition toward strategies to combat resultant effects.

Disclosures: J.R. Rainville: None. **A. Garrastegui Segarra:** None.

Poster

PSTR078: Stress-Modulated Pathways: Cognition, Learning, and Memory Circuits

Location: MCP Hall A

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Program #/Poster #: PSTR078.13/H9

Topic: F.03. Stress and the Brain

Support: VA Grant #BX005923

Title: Traumatic stress-induced glucocorticoid signaling and rat behavior

Authors: *E. A. DEVINE[1], J. B. CHAMBERS[2], B. A. PACKARD[3], J. P. HERMAN[4];
[1]Pharmacol. and Systems Physiol., Univ. of Cincinnati, Cincinnati, OH; [2]Pharmacol. & Systems Physiol., Univ. of Cincinnati, Independence, KY; [3]Neurosci, Univ. Cincinnati, Cincinnati, OH; [4]Dept Pharmacol. and Systems Physiol., Univ. of Cincinnati, Cincinnati, OH

Abstract: It is estimated that 3.6% of the world population is affected by post-traumatic stress disorder (PTSD). Experiencing severe or traumatic stress impacts the brain by altering emotional processing, leading to hyperarousal, anxiety, hypervigilance, and deficits in impulse control and fear memory extinction. This hyperarousal is thought to occur via dysfunctional glucocorticoid receptor (GR) signaling upon exposure to trauma. Previously, we found increased plasma corticosterone (CORT) in male rats 24 hours post- exposure to a single-prolonged stress (SPS) exposure relative to unstressed controls. SPS is used as a method to recapitulate PTSD-related behaviors in rats. Using this method, we previously described enhanced threat assessment behaviors in rats in an open field test, impaired novel object discrimination and increased threat

avoidance in rats previously exposed to SPS. Other studies indicate that administration of GR antagonists after SPS exposure block SPS-induced deficits in extinction of fear memory. Given these data, we hypothesize that GR signaling drives the development of behavioral pathologies associated with SPS.To test this hypothesis, male rats received bilateral implantation of cannulas into the infralimbic cortex (IL), a brain region important for fear memory extinction and emotional regulation. Two weeks after implantation, rats were either briefly removed from their home cage (control) or exposed to SPS. All rats then immediately received infusion of either vehicle or CORT113176, a GR antagonist, and received additional doses for the two days following. One week later, rats completed fear/anxiety-related behavioral testing, including novel object recognition (NOR), elevated plus maze, and threat generalization, using a threat imminence task.In this paradigm SPS appears to reduce familiar object interaction and shows a tendency to enhance NOR. Infusions of CORT113176 do not affect SPS-related effects on NOR but may attenuate distance traveled and movement velocity in the open field of SPS exposed animals during pre-object habituation trials, reflecting an impact on stress-induced locomotor behavior. There were no effects of SPS or drug on EPM behaviors. Notably, SPS enhances fear generalization in a CORT113176-dependent manner, with drug appearing to enhance generalization in non-SPS animals. The data indicate that infusions of GR antagonist tend to promote expression of fear related behaviors, even when administered several days prior to testing. These studies suggest that the glucocorticoid response to SPS may be required for appropriate processing of fear memories.

Disclosures: E.A. Devine: None. **J.B. Chambers:** None. **B.A. Packard:** None. **J.P. Herman:** None.

Poster

PSTR078: Stress-Modulated Pathways: Cognition, Learning, and Memory Circuits

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Program #/Poster #: PSTR078.14/H10

Topic: F.03. Stress and the Brain

Support: ONR grant N0014-24-1-2014

Title: Deficits in episodic memory and hippocampal circuit function occur following early life adversity.

Authors: M. T. BIRNIE[1], B. PRUESS[2], G. LYNCH[4], ***B. GUNN**[3];
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Abstract: Adverse experiences early in life (ELA) are associated with increased vulnerability to neuropsychiatric disorders including depression and anxiety. Many such conditions show a high comorbidity with impaired memory function, with episodic or “every day’ memory being particularly sensitive. The hippocampus, a brain structure critical for episodic memory, has long

been associated with clinical depression and related conditions. However, the specific circuits and mechanisms underlying this relationship remain poorly understood. In the present study we demonstrate that episodic memory is impaired in young adult male and female mice exposed to ELA (P2-P9). We then tested for ELA-related disturbances in the operation of the hippocampal networks that are critical to the acquisition and retrieval of episodes. Using a slice preparation that enables recording of CA1 spike output following lateral perforant path (LPP) activation we characterized the manner in which ELA alters frequency-dependent signal transformations across the entire hippocampal circuit. The resultant data indicate that signal throughput observed following LPP activation at theta frequency (5Hz) is unaffected by ELA, while the pronounced filtering of signals evident in response to activation at beta frequencies (20Hz) and above is significantly impaired. A more detailed interrogation of the individual links and nodes of the hippocampal circuit suggest that perturbations within field CA3 is likely to be the 'weak link' affected by ELA. The findings from these studies provide a novel description of how ELA influences episodic memory and suggest a specific hypothesis about the underlying causes. We are currently attempting to pinpoint the particular filtering element(s) within CA3 that are rendered ineffective by ELA and exploring potential routes for normalizing processing within the subfield.

Disclosures: M.T. Birnie: None. **B. Pruess:** None. **G. Lynch:** None. **B. Gunn:** None.

Poster

PSTR078: Stress-Modulated Pathways: Cognition, Learning, and Memory Circuits

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Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR078.15/H11

Topic: F.03. Stress and the Brain

Title: Investigating gilz and its role in stress-related behavior

Authors: *F. FANAEI;
Neurobio. and Memory, Univ. of California, Irvine, Tustin, CA

Abstract: Stress, often triggered as a physiological response, is crucial to both short and long-term memory consolidation, recall, and involves the induction of glucocorticoid activity. Gilz, an X-chromosome linked glucocorticoid-induced leucine zipper gene plays a significant role in the pathways responsible for stress response and has been well studied for its anti-inflammatory effects. However, its role in the formation of stress-associated memories remains elusive. Only one study to date has shown lower Gilz expression to be associated with increased methylation in its promoter and increased trauma exposure in males only, suggesting it may be epigenetically regulated. To explore the potential sex-dependent role of Gilz in stressful memories, we utilized Gilz female heterozygous and male hemizygous knockouts, contextual fear conditioning (CFC) and repeated exposure to multiple concurrent stressors (RMS) as a means to investigate how Gilz expression varies during stressful behaviors. We found Gilz expression levels to be strongly induced during the memory consolidation period 1 hour after behavior and return back to

homecage levels within 24 hours after behavior in wildtype mice. However, we found no significant behavioral differences in both male and female Gilz knockout mice. Lastly, additional preliminary data from our lab has shown that Gilz deletion in males but not females significantly impairs long-term potentiation and may decrease synaptic connectivity after RMS. These results suggest Gilz may be acting as an important modulator of synaptic plasticity and stress feedback pathways rather than influencing related gene expression.

Disclosures: F. Fanaei: None.

Poster

PSTR078: Stress-Modulated Pathways: Cognition, Learning, and Memory Circuits

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR078.16/H12

Topic: F.03. Stress and the Brain

Support: R01MH136381

Title: Stress disrupts outcome updates to impair flexible decision making

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Abstract: Cognitive flexibility is the ability to change the current strategies to adapt behaviors to dynamic environment. It is associated with positive life outcomes, such as academic achievement and success in adulthood. Stress, intrinsic or extrinsic stimuli that evokes biological responses, can cause various functional changes in the brain. It affects cognitive flexibility, prevents people from making informed decisions and increases rigidity. However, how stress affects the brain to impair cognitive flexibility is largely unknown.Studies have shown that the medial prefrontal cortex (mPFC) is responsible for cognitive flexibility in rodents. The mPFC plays important roles in working memory, rule learning and selective attention, which are necessary for cognitive flexibility. However, the mechanism that enables switch or shift in the mPFC is not clear. Our brain supports adaptive behavior by learning from previous outcomes and updating this information to incorporate new situations. Studies suggest that mPFC also represents prior trial outcomes, but from where does it receive the information? The anterior insular cortex (aIC) is known to encode bodily states, mediate interoceptive attention and project to the mPFC, making it a perfect candidate. Here we show, the aIC plays a crucial role in flexible decision making by conveying previous outcomes to the mPFC, and stress disrupts the outcome updates to impair cognitive flexibility. We found that stress affects the attentional set-shifting task (AST), a mouse behavior that assesses cognitive flexibility, as well as neuron activity in mPFC and aIC. Furthermore, optogenetic activation or inhibition of aIC to mPFC projection (aIC-mPFC) mimic the stress effects of AST. In vivo calcium (Ca) recordings from aIC-mPFC neurons by fiber photometry reveal a significant difference between correct and incorrect outcome, that is retained

to the next trial, with higher activity following incorrect outcomes. Optogenetic decrease the difference disrupts behavior. To investigate the cellular mechanism of how aIC-mPFC signal affects decision making, we performed the miniature fluorescence microscopic Ca recording in the mPFC and found that optogenetic stimulation of aIC-mPFC disrupts the neuronal decoding of previous choice outcome. Indeed, the difference in Ca activity between correct and incorrect outcome disappears in stressed animals. Finally, optogenetic activation of aIC-mPFC after incorrect trials rescues the stress induced behavioral deficits. Our results not only elucidate a novel mechanism of aIC-mPFC in flexible decision making but also provide understanding of how stress affects cognitive flexibility.

Disclosures: S. Ma: None. **K.H. Wang:** None. **Y. Zuo:** None.

Poster

PSTR078: Stress-Modulated Pathways: Cognition, Learning, and Memory Circuits

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR078.17/H13

Topic: F.03. Stress and the Brain

Support: NIH R01AG083841

Title: Impact of chronic stress on PV neurons and perineuronal nets in the entorhinal cortex

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Abstract: Parvalbumin (PV)-expressing GABAergic interneurons, characterized by fast-spiking activity, play an important role in controlling the output of the entorhinal cortex to various brain regions, including the hippocampus. Mature PV neurons are surrounded by perineuronal nets (PNNs), a mesh-like extracellular matrix structure that shields neurons from oxidative stress and is vital for maintaining their high-frequency firing. This study aimed to investigate the effects of chronic unpredictable stress (CUS) on PV neurons and PNNs in the entorhinal cortex. Male C57BL/6 mice were subjected to various types of stressors for 10 consecutive days. Brain sections were immunostained with anti-PV antibody to visualize PV neurons and Lectin from Wisteria floribunda (WFA) to label PNNs. The total number of PV neurons and the number of PNN-positive PV neurons were quantified using unbiased stereology. Given that PNN degradation may manifest as changes in intensity or integrity without a reduction in PNN-positive PV neurons, further analysis of density and integrity of PNNs is being conducted using high-magnification single-plane confocal images. Additionally, the role of entorhinal PV neurons and PNNs in modulating behavioral responses to stress is being explored.

Disclosures: N. Rajanala: None. **F. Patel:** None. **Y. Bai:** None. **X. Lu:** None. **Y. Lei:** None.

Poster

PSTR078: Stress-Modulated Pathways: Cognition, Learning, and Memory Circuits

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR078.18/H14

Topic: F.03. Stress and the Brain

Support: NIH R21MH134158

Title: Differential Synaptic Enhancement in Basolateral Amygdala Following a Stress-Enhanced Fear Learning Protocol

Authors: *C.-W. CHANG[1], M. S. FANSELOW[2];
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Abstract: Animal models that replicate certain aspects of PTSD symptoms serve as valuable tools for investigating the underlying mechanisms of this disorder. One hallmark of PTSD is an exaggerated response to minor stressors, resulting in inappropriate fear reactions. Inappropriately heightened arousal and avoidance of trauma-related cues can lead to exhaustion, sleep disturbances, and a restricted lifestyle. We developed a rodent model called stress-enhanced fear learning (SEFL), which mimics this heightened fear response. In the SEFL model, animals undergo a traumatic experience followed by mild conditioning in a different context, resulting in an exaggerated fear response to the mild conditioning context. During fear conditioning, synaptic strengthening in the basolateral amygdala (BLA) occurs via long-term potentiation (LTP), mediated by NMDA receptors. Notably, the BLA is implicated not only in basic fear conditioning but also in SEFL, with increased amygdala activity predicting heightened fear responses. Furthermore, following SEFL-inducing stress, there is prolonged upregulation of GluA1 AMPA receptors, which may contribute to altered synaptic plasticity in the BLA. GluA1, along GluA2 or GluA3, cluster as heteromers to form functional AMPA receptors (AMPARs).The GluA2 subunit renders the receptor impermeable to calcium influx, but increased levels of GluA1 relative to GluA2 can lead to the formation of GluA1 homomeric receptors, allowing for calcium entry and an alternative form of long-term potentiation (LTP). Previous studies have shown that mice lacking the GluA2 subunit within certain regions of the hippocampus exhibit a unique NMDAR-independent form of synaptic plasticity that depends on GluA1 only, calcium-permeable AMPARs (CP-AMPARs). Taken together, these findings suggest that stress may increase CP-AMPARs. To address the effect of SEFL-inducing stress in BLA excitatory synaptic transmission, we utilized BLA slice electrophysiology. We found that the SEFL-inducing stress augments excitatory synaptic input onto BLA, and the augmented BLA excitatory input comes along with an increased presence of Calcium permeable AMPARs. Moreover, the augmentation occurs largely in the medial prefrontal cortex (mPFC) to BLA projections, rather than other examined BLA-targeting projections. Further, CP-AMPAR-medicated LTP was examined on each BLA-targeting projection. Overall, these findings suggest that stress-induced alterations in AMPA receptor composition and BLA plasticity may underlie the enhanced fear learning observed in SEFL, providing insights into the mechanisms of PTSD-like behaviors in rodents.

Disclosures: C. Chang: None. **M.S. Fanselow:** None.

Poster

PSTR078: Stress-Modulated Pathways: Cognition, Learning, and Memory Circuits

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR078.19/H15

Topic: F.03. Stress and the Brain

Title: Prolonged social isolation but not prenatal stress reduces social acquisition learning in aged male c57bl/6j mice

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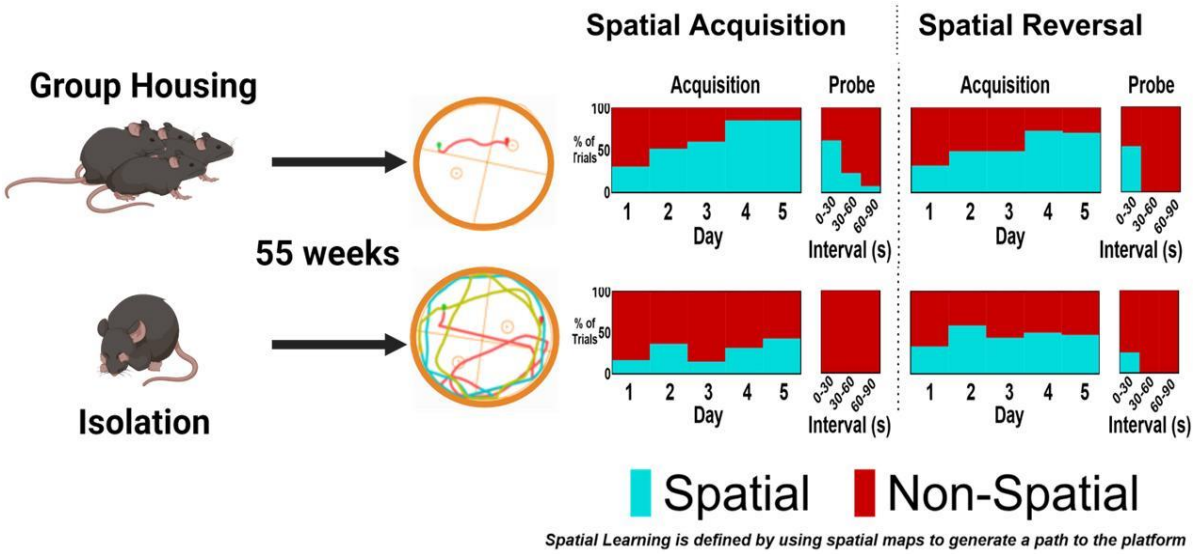
Abstract: Prenatal stress and postnatal social isolation may compound the aging process increasing the risks for cognitive decline and metabolic dysfunction. Older males are at increased risk for social isolation, therefore, we have tested the effects of prenatal stress and social isolation on spatial cognition in male mice. We restrained pregnant mice three times daily for 45 minutes, during weeks 2 and 3 of gestation. Prenatally stressed (PRS) male offspring (n=15) were tested for behavioral deficits and metabolic activity in comparison with non-stressed (NS) controls (n=13) at 60 weeks of age. A subgroup of PRS and NS mice were exposed to 55 weeks of social isolation (n=12). Mice were assessed in the open field test, the light-dark box, and the Morris water maze (MWM) test of spatial learning and memory. We also used the Phenomaster TSE system to record activity, and measure indirect calorimetry for 72 hours. No stress group showed altered behavior in the open-field or light-dark box. Socially isolated mice had decreased MWM spatial acquisition performance ($F_{2, 31} = 7.841$, $p = 0.002$). This may be due to increased thigmotactic and non-spatial search strategy behavior (day 5 spatial acquisition: $\chi^2 = 19.72$, $p < 0.0001$). The latter was observed previously in Alzheimer's mouse models. Performance in MWM probe trials revealed no significant differences between the PRS, socially isolated and NS groups. Similarly there were no differences in metabolic measures between the groups. These data suggest that prolonged social isolation impairs spatial search strategy and spatial acquisition learning, but not spatial memory in C57BL/6J mice. These data also indicate that this inbred strain is less sensitive to the behavioral deficits induced by prenatal stress. Understanding the molecular basis of the relatively reduced sensitivity to prenatal stress in C57BL/6J mice, and the detrimental effects of social isolation could improve our understanding of the pathology of stress in the neural circuits regulating spatial cognition.



Disclosures: M. McCarthy: None. **T. Buck:** None. **M. Sodhi:** None.

Poster

PSTR078: Stress-Modulated Pathways: Cognition, Learning, and Memory Circuits

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR078.20/H16

Topic: F.03. Stress and the Brain

Support: NIH Grant MH108837
NIH Grant MH078064

Title: The Integration of Social Information into the Episodic Memory System

Authors: *T. BASSETT[1], A. CICVARIC[2], Z. PETROVIC[2], H. ZHANG[3], E. WOOD[3], J. M. RADULOVIC[2];
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Abstract: Abnormal processing of social interactions, including the formation of social memories, has a lasting negative impact on mental health and it is found many psychiatric illnesses, ranging from post-traumatic stress disorder to social anxiety disorder and depression. Therefore, uncovering the underlying neurobiological mechanisms behind the processing of social information is critical to understanding the development of these harmful and persistent affective states. The hippocampus plays a well-known role in the formation and integration of memories, particularly for the relational, temporal, and contextual components of a memory representation. More recently, its role was expanded to include social memory, with CA2 projections into the vCA1 being proven necessary for social recognition, a key component of

social memory. Given the functional segregation of other hippocampal subfields across the longitudinal axis, we sought to determine whether dorsal, intermediate, and ventral subregions of the CA2 similarly or distinctively contribute to social memory formation and recall. Additionally, we studied the intra- and extra-hippocampal connectivity of these subfields. To begin answering these questions we have employed an array of circuit tracing techniques and circuit manipulations to examined their effects on social fear conditioning (SFC) and social recognition memory. Our findings demonstrate that SFC induces robust freezing to social stimuli that can be readily differentiated from the contextual and cue-related freezing acquired in the same episode. Ongoing experiments are interrogating how manipulations of CA2 activity relate to the formation and recall of social memory.

Disclosures: T. Bassett: None. **A. Cicvaric:** None. **Z. Petrovic:** None. **H. Zhang:** None. **E. Wood:** None. **J.M. Radulovic:** None.

Poster

PSTR078: Stress-Modulated Pathways: Cognition, Learning, and Memory Circuits

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR078.21/H17

Topic: F.03. Stress and the Brain

Support: NIMH MH108837
NIMH MH078064

Title: Cortical reorganization from adolescence to early adulthood

Authors: *H. ZHANG, Z. PETROVIC, E. M. WOOD, A. CICVARIC, T. E. BASSETT, K. PARKER, J. M. RADULOVIC;
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Abstract: The early postnatal reorganization of cortical brain areas has been recognized as a critical neurodevelopmental step, which is essential for the maturation of memory circuits. It is generally believed that memory circuits are fully mature around adolescence, however, human studies show pronounced cortical changes in the post adolescent period. We sought to determine whether such changes can be modelled in mice and what is their cellular and molecular basis. Based on their documented role in the stabilization of memory circuits, we investigated the expression and composition of perineuronal nets (PNN) in the dorsal hippocampus (DH) - retrosplenial cortex (RSP) memory circuit throughout adolescence and early-adulthood development. We found that in pre-adolescent development, the expression of PNN increased between p21 to p30 in both RSP and DH. In RSP, the number of PNN^{+} neurons underwent a temporary decline during adolescent and post-adolescent development (from p30 to p74). However, in DH, the PNN number showed linear increase during this time. The decrease of PNN number in RSP corresponded with the sex-dependent decrease of PNN constituents, including neurocan and aggrecan. In RSP, the build-up of PNN was restored and further increased during

early adulthood (p74 to 5-month-old). Our results demonstrate that, similar to human, the mouse cortex undergoes further reorganization during adolescence and early adulthood. The reorganization process includes fluctuations of the PNN numbers and composition, likely rooted in cell-specific changes of expression genes coding for different PNN constituents.

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Poster

PSTR078: Stress-Modulated Pathways: Cognition, Learning, and Memory Circuits

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR078.22/H18

Topic: F.03. Stress and the Brain

Support: DGAPA-PAPIIT IN 208722

Title: Differential effects of stress after exposure to different kinds of stress in the female rat

Authors: *Y. VIDAL-DE LA O[1], P. TORRES-CARRILLO[2], A. C. HERNÁNDEZ SÁNCHEZ[3], K. B. VALENCIA[4], D. B. PAZ-TREJO[5], H. SANCHEZ-CASTILLO[6];
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Abstract: Stress is considered the main predisposing factor for the development of multiple disorders (depression, anxiety, trauma, etc). The stress impact depends on different factors such as sex, age, stressor type, etc. In that sense, there are few reports where the stressor type is considered, nevertheless, distinct kinds of stressors have differential effects that were observed when they are compared. It is important to consider females in stress studies because the study of stress effects is more common in male subjects. For all this, the main goal of this research was to analyze the effects of different kinds of stress on animal models (Wistar female rats): chronic mild stress, social isolation, and predator scent stress. We used a chronic unpredictable stress battery (CUSB), a social isolation model (PWSI), and predator scent stress (PSS). We evaluated the depression-like behavior with the saccharin preference test (SPT) and free choice test (FCT) for the hedonic value, and anxiety-like behavior with open field test (OFT) and elevated zero maze test (EZM). We found that social isolation induced anhedonia. This was observed through decreased saccharine and evaporated milk consumption in SPT and MPT tests. Conversely, only the CUSB and PSS spent less time with open arms on the OFT and EZM tests. In conclusion, the presence of anxiety-like and depression-like behaviors is dependent on the stressor type. Those results demonstrate how important it is to consider the stressor type in depression models in rodents.

Disclosures: Y. Vidal-De La O: None. **P. Torres-Carrillo:** None. **A.C. Hernández Sánchez:** None. **K.B. Valencia:** None. **D.B. Paz-Trejo:** None. **H. Sanchez-Castillo:** None.

Poster

PSTR078: Stress-Modulated Pathways: Cognition, Learning, and Memory Circuits

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR078.23/H19

Topic: F.03. Stress and the Brain

Support: DGAPA-PAPIIT IN208722

Title: Sex differences on the mGluR5 modulation of depression-like, anxiety-like behavior and spatial memory induced by predator stress exposure

Authors: *P. TORRES-CARRILLO[1], A. C. HERNÁNDEZ SÁNCHEZ[2], Y. B. VIDAL-DE LA O[2], D. B. PAZ-TREJO[2], L. D. OCHOA-DE LA PAZ[2], H. SANCHEZ-CASTILLO[2]; [1]Univ. Nacional Autónoma de México, Ciudad de Mexico, Mexico; [2]Univ. Nacional Autónoma de México, Mexico City, Mexico

Abstract: Glutamatergic system has been one alternative in the explanation of the mechanisms that modulate the stress response. It has been reported that, the administration of MTEP, an inhibitor of mGluR5 receptors, has antidepressant and anxiolytic effects. Exposure to stress increases the expression of mGluR5 receptors in the prefrontal cortex, amygdala, and hippocampus, so these receptors may be associated with stress-induced depression-like, anxiety-like, and fear-like behavior. However, no studies have been conducted on the effects of MTEP administration under stress conditions in females. Exploration of biological systems related to stress-induced depression-like and anxiety-like behaviors in females is necessary for better understanding of the effects of stress, prevalence, symptomatology, prognosis, and treatment of stress-related disorders in females. Besides, findings on the underlying mechanisms as well as the evaluation of pharmacological treatments of stress-related disorders have been reported mostly in males. The main goal was to evaluate the intracerebroventricular administration of MTEP in females and males after exposure to predator stress. Female and male Wistar rats (12 weeks old) were used. Subjects were divided into a vehicle group and MTEP groups (1ug/ul and 10ug/ul), half of the subjects were stressed, and the other half were kept in non-stressed conditions (n=10 per group). After stress exposure, they were evaluated with the Barnes maze test, open field test and, forced swim test. The results found in the Barnes maze were stress decreases escape latency and the number of errors in the training phase in females and, males, however, in the reversal training phase stress increases escape latency and the number of errors in females but not in males. Female's latency and errors are improved with the administration of the highest concentration of MTEP (10 ug/ul) but not with the lowest concentration of MTEP (1ug/ul), while in males the administration of MTEP (10ug/ul) also decreases latency and errors. In the open field test stress decreased the time spent in the center of the arena and increased the time spent immobile in the forced swim test, while the stress-exposed group administered the

highest concentration of MTEP (10ug/ul) increased the time spent in the center and decreased the time spent immobile, but not with the lowest concentration of MTEP (1ug/ul) in females and males. The observed effects of MTEP administration can mitigate stress induced effects, indicating an important role of mGluR5 receptors in modulating stress in females and males, but not in the same way.

Disclosures: P. Torres-Carrillo: None. **A.C. Hernández Sánchez:** None. **Y.B. Vidal-De La O:** None. **D.B. Paz-Trejo:** None. **L.D. Ochoa-De La Paz:** None. **H. Sanchez-Castillo:** None.

Poster

PSTR078: Stress-Modulated Pathways: Cognition, Learning, and Memory Circuits

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR078.24/H20

Topic: G.01. Fear and Aversive Learning and Memory

Title: To Have or To Hold? Refined Methods in Mouse Handling

Authors: *J. STALLONE[1], S. CHURCHILL[2], L. R. WILSON[3], K. D. STEVANOVIC[3], D. GOULDING[1], T. YOUNG[1], D. WEBB[4], T. OLAGBAJU[5], A. KING-HERBERT[1], J. D. CUSHMAN[3];
[1]Natl. Inst. of Envrn. Hlth. Sciences(NIEHS), Research Triangle Park, NC; [2]Charles River Labs., Charleston, SC; [3]Neurobio. Lab., Natl. Inst. of Envrn. Hlth. Sci., Research Triangle Park, NC; [4]Vet. Med. Section, Natl. Inst. of Envrn. Hlth. Sci., Research Triangle Park, NC; [5]Dept. of Translational Toxicology, Natl. Inst. of Envrn. Hlth. Sciences(NIEHS), Research Triangle Park, NC

Abstract: Abstract: The standard practice of handling laboratory mice by their tail has a profound effect on their anxiety levels and other physiological stress responses. Variability in experimenter handling can influence performance in behavioral tests. Prior research has shown handling with tunnels to produce better behavioral outcomes, however this approach is still not widely used. The aim of the current study was to assess the use of tunnels in routine animal handling, as well as refine the overall performance of behavioral test outcomes. We used three different handling techniques in C57BL/6J mice: 1) Tail handled mice, which were handled by the tail for cage changes and behavioral tasks, 2) Transfer Tunnel mice, which were handled using a small tunnel and 3) Home-cage tunnel mice, which lived with tunnel in their home cage in addition to using it for handling. We ran a series of behavioral tests to determine the impact of handling on anxiety-like behavior, exploratory behavior and cognitive performance. The elevated plus maze and open field were used to measure anxiety-like behavior. Short-term spatial working memory was assessed using spontaneous alternation. Long term spatial learning and memory were measured with a spatial object recognition task. Contextual fear and non-associative sensitization were assessed in a fear conditioning paradigm. Overall, we found that tunnel handling reduced anxiety, increased exploration and improved spatial learning. Intriguingly, tunnel handling increased the baseline level of freezing in the novel tone-test context suggesting

that the tunnel may serve as a predictive transport cue. The Home-cage tunnel group showed the most improvements and the Tunnel handled group proved impractical as these mice took much longer to enter the tunnels for both behavioral tasks and cage changes. The impact of handling was highly sex-dependent with males showing increased exploratory behavior that eliminated the typical increase in locomotion in females. Females showed the most robust improvements in spatial learning due to handling, an effect that was mediated by increased exploration of the objects during the familiarization phase. Additionally, utilizing fiber photometry we are investigating the extent to which neuromodulators may mediate these sex-dependent impacts of handling on behavioral performance. Overall, our findings support the use of tunnel handling as it improves behavioral performance, reduces cross-experimenter variability and eliminates the need for extensive pre-handling.

Disclosures: J. Stallone: None. **S. Churchill:** None. **L.R. Wilson:** None. **K.D. Stevanovic:** None. **D. Goulding:** None. **T. young:** None. **D. Webb:** None. **T. Olagbaju:** None. **A. King-Herbert:** None. **J.D. Cushman:** None.

Poster

PSTR078: Stress-Modulated Pathways: Cognition, Learning, and Memory Circuits

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR078.25/H21

Topic: F.03. Stress and the Brain

Support: DGAPA-PAPIIT IN 208722

Title: Resocialization-effects in anhedonic-like behavior in females and male rats

Authors: *A. C. HERNÁNDEZ SÁNCHEZ[1], Y. B. VIDAL-DE LA O[2], P. TORRES-CARRILLO[3], D. B. PAZ-TREJO[1], H. SANCHEZ-CASTILLO[4];
[1]Univ. Nacional Autónoma de México, Mexico City, Mexico; [2]Univ. Nacional Autónoma de México, Ciudad de Mexico, Mexico; [3]Lab. de Neuropsicofarmacología, Univ. Nacional Autónoma de México, Mexico City, Mexico; [4]Psychobiology and Neurosciences, Univ. Nacional Autonoma de Mexico, Mexico City, Mexico

Abstract: After the COVID-19 pandemic, there has been significant interest in studying the effects of social isolation. Several studies have demonstrated that social isolation may predispose individuals to develop stress-related disorders, such as depression. Besides, the effects of social isolation could be influenced by the age and sex of the subjects. For example, female-isolated rats do not present anhedonic-like behavior while male isolated rat does. On the other hand, there is few evidence indicating the effects of resocialization in an animal model.Many studies show that resocialization may reverse the behavioral and cognitive effects of social isolation. Therefore, the main goal of this study was to explore the hedonic response of female and male rats exposed to resocialization after five weeks of social isolation. We evaluated male and female Wistar rats using the preference saccharine test (PST) and the free-choice test (FCT). We found

that social isolation groups exhibited preferences for saccharine and evaporated milk consumption similar to the control group. However, resocialization in male and female groups presented a decrease in palatable solution consumption and preference index, therefore an anhedonic effect was observed in PST and FCT. These findings shed light on the negative effects of resocialization after a social isolation period. Further research is necessary to elucidate the underlying mechanisms and potential interventions to mitigate the behavioral, cognitive, and physiological consequences of social isolation and resocialization.

Disclosures: A.C. Hernández Sánchez: None. **Y.B. Vidal-De La O:** None. **P. Torres-Carrillo:** None. **D.B. Paz-Trejo:** None. **H. Sanchez-Castillo:** None.

Poster

PSTR078: Stress-Modulated Pathways: Cognition, Learning, and Memory Circuits

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR078.26/H22

Topic: F.03. Stress and the Brain

Support: DGAPA-PAPIIT IN208722

Title: Effects of Acute Stress Exposure on Timing Behavior

Authors: *P. SAAVEDRA[1], D. B. PAZ-TREJO[2,3,1], H. SANCHEZ-CASTILLO[4,1,2];
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Abstract: Stress has been identified as the largest epidemic of the 21st century, with associations to various psychiatric disorders such as major depressive disorder and anxiety. Acute stress exposure has also been linked to conditions like post-traumatic stress disorder, anxiety, panic disorder, etc. It has been shown that stress exposure induce significant alterations in complex cognitive and behavioral mechanisms, however on timing behavior is not clear how this can modulate the time perception in organisms. The main goal of this research was to evaluate the effects of Predators Scent Exposure (PSE, acute stress exposure) on timing behavior. Fifteen male Wistar rats were trained on the immediate timing protocol Peak Procedure at 16 seconds interval. The subjects were distributed into two different groups; Stress exposure (n= 8) and non-exposure (n= 7)). The obtained data were analyzed with a three-parameter Gaussian bell-shaped function (f=aexp(-.5((x-x0)/b)^2)) to obtain the peak time, peak rate, spread and finally, the Weber fraction. An ANOVA analysis was conducted to identify statistically significant differences between groups. Our findings indicate that stress may modulate timing, suggesting an impact on temporal processing under stressful conditions.

Disclosures: P. Saavedra: None. **D.B. Paz-Trejo:** None. **H. Sanchez-Castillo:** None.

Poster

PSTR078: Stress-Modulated Pathways: Cognition, Learning, and Memory Circuits

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Topic: F.03. Stress and the Brain

Support: NIH R21 MH131980
NIH ROI DC020528
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DOD MS 220167

Title: A novel role of astrocyte FAK in promoting fear extinction, possibly by inhibiting CNTF

Authors: *K. TAYLOR-COX[1], D. COX[1], J. BULLEN[2], T. HAGG[2], J. T. GASS[2], C. JIA[2]; [1]East Tennessee State Univ., Johnson City, TN; [2]Biomed. Sci., East Tennessee State Univ., Johnson City, TN

Abstract: A novel role of astrocyte FAK in promoting fear extinction, possibly by inhibiting CNTF
Kaitlyn Taylor-Cox, Derek Cox, Joshua Bullen, Theo Hagg, Justin Gass, Cuihong Jia
Fear extinction deficit is a hallmark of post-traumatic stress disorder (PTSD) and linked to its persistence and resistance to treatment. Fear extinction learning in rodents serves as a preclinical model of exposure therapy in humans, i.e., reducing the impact of environmental cues. Thus, studying the mechanisms underlying fear extinction and exposure therapy has high clinical relevance. A history of chronic stress is a substantial risk factor for developing PTSD. Stress also induces fear extinction deficits in rodents. Our recent studies indicate that ciliary neurotrophic factor (CNTF) mediates stress responses. Using a fear conditioning paradigm, we found that chronic unpredicted stress (CUS) increased cue (tone)-induced freezing behavior in both female and male mice, suggesting that chronic stress impaired fear extinction learning. This deficit was rescued in CNTF KO mice, starting at extinction day 2 or 3. CNTF knockout also blocked CUS-induced contextual fear responses. The knockout effects were not due to locomotor deficits since neither CUS nor fear conditioning altered locomotor function tested in an open field test. Conditioned stimulus (electric shock)-induced freezing responses were higher at conditioning day 2 and 3 (around 80%) than day 1 and there were no differences among the groups on any day, indicating that neither CNTF knockout nor CUS affects conditioned fear acquisition. These results demonstrate that chronic stress induces deficits in fear extinction. Importantly, knockout of CNTF prevents this deficit, revealing a novel inhibiting and detrimental role of CNTF in fear extinction. These data are consistent with reports in human SNP allele and genotyping analyses that CNTF is associated with maintaining PTSD symptoms. In the brain, CNTF is only expressed in astrocytes and upregulated by inhibition of focal adhesion kinase (FAK). Here, inducible Cre-*lox* knockout of FAK in astrocytes increased deficits in the extinction of fear in both sexes, suggesting a novel role of astrocyte FAK in promoting fear extinction, possibly by inhibiting CNTF.

Disclosures: K. Taylor-Cox: None. **D. Cox:** None. **J. Bullen:** None. **T. Hagg:** None. **J.T. Gass:** None. **C. Jia:** None.

Poster

PSTR078: Stress-Modulated Pathways: Cognition, Learning, and Memory Circuits

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR078.28/H24

Topic: F.03. Stress and the Brain

Support: FONDECYT 1230471
FONDECYT 1211731
ANID Predoctoral Fellowship 21200834

Title: Sex-biased effects induced by chronic restraint stress on m^6A epitranscriptomics and neuroplasticity in the rat dorsal hippocampus

Authors: *W. A. CORRALES[1], J. P. SILVA[1], M. ALARCÓN[1], F. A. OLAVE[1], J. CATALÁN[1], A. D. CONEJEROS-SUAZO[1], J. T. LEE[3], V. MARACAJA-COUTINHO[2], J. L. FIEDLER[1];
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Abstract: The dorsal hippocampus is crucial for learning and memory and is highly sensitive to stress, reason enough to be a key structure in neuropsychiatric disorders. Recent interest has focused on the epitranscriptome, involving RNA modifications such as m^6A, which can have an extensive influence on the RNA metabolism and downstream cellular processes. Given that neuroplastic and behavioral responses to stress in the hippocampus may be influenced by sex and m^6A dynamics, our objective was to investigate the differential response of male and female rats after a chronic stressful stimulus. To explore this, we used a depressive-like paradigm (chronic restraint stress, 2.5 h per day for 14 days) on adult male and female Sprague-Dawley rats (n = 10 per condition and sex), aiming to evaluate changes in the levels or subcellular location of the m^6A modification machinery and m^6A profiles of the male and female dorsal hippocampus. RNA-seq analysis revealed several sex-biased and stress-sensitive genes in the dorsal hippocampus, including components of the m^6A machinery (*Mettl3*, *Alkbh5*, *Ythdf1-2*), involved in axonal guidance, glutamate signaling, RNA binding, and RNA metabolism in females, and axonal guidance, GABAergic and serotoninergic synapse in males. Interestingly, Sholl analysis performed on brain sections revealed a significant effect of sex, stress, and radial distance on the apical dendrites of CA1 region, where female control and male stressed rats have higher dendritic complexity at points closer to the soma. Under the light of these findings, we evaluated using *in silico* approaches whether the genes encoding the m^6A machinery have glucocorticoid response elements in their proximal promoters, identifying binding motifs in *Mettl3*, *Fto*, and *Ythdf1-3*. Additionally, Nanopore directRNA-seq data showed sex and stress-specific differences

in the number and distribution of m^6A sites in genes related to glutamate signaling and mitochondrial function. These findings suggest that chronic stress and sex may impact the m^6A modification landscape in the dorsal hippocampus, potentially explaining the reported morphological and behavioral changes by our research group and others in depressive-like animal models.

Disclosures: W.A. Corrales: None. **J.P. Silva:** None. **M. Alarcón:** None. **F.A. Olave:** None. **J. Catalán:** None. **A.D. Conejeros-Suazo:** None. **J.T. Lee:** None. **V. Maracaja-Coutinho:** None. **J.L. Fiedler:** None.

Poster

PSTR078: Stress-Modulated Pathways: Cognition, Learning, and Memory Circuits

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR078.29/H25

Topic: F.03. Stress and the Brain

Title: Reversal learning under 2-week bupropion or escitalopram treatment in mice

Authors: *T. SEDLINSKA[1], Y. KAJIHARA[1], Q. HUYS[2], K. DOYA[1];
[1]Okinawa Inst. of Sci. and Technol., Onna, Kunigami-Gun, Japan; [2]Max Planck UCL Ctr. for Computat. Psychiatry and Ageing Res., London, United Kingdom

Abstract: Background: Antidepressants (AD) share a paradigmatic delay in their clinical effect, potentially due to underlying learning processes that need time to fully unfold. Understanding differences and similarities in learning alterations between AD classes could help target AD therapy and better integrate it in broader psychotherapeutic context. Methods: In this pilot study, we assessed reversal learning in 8 wild-type mice (3 males and 3 females aged 8 weeks, and 2 females aged 30 weeks), treated with either 10mg/kg of serotonergic AD escitalopram (ESC), 10mg/kg dopaminergic/noradrenergic AD bupropion (BUP), or placebo (PLA) i.p. for 14 days. Thirty minutes after injection, the mice underwent a 60-minute testing session, where they could initiate an arbitrary number of trials and choose between two nose-poke sites with 80% and 20% probabilities of 5µl water reward. After 8 choices of the higher probability site, the reward contingencies were reversed. Results: Reversal learning was less efficient in both AD groups compared to the PLA group, as indicated by the increased number of trials needed for a reversal (Kruskal-Wallis test $H=18.18$, $p<0.001$; PLA mean $\mu=19$, $SD=3.5$; ESC $\mu=27$, $SD=10.2$, Cohen's $d=0.50$ in comparison to PLA; BUP $\mu=24$, $SD=7.5$, $d=0.47$), and reduced frequency of repeating a previous choice after a reward (win-stay probability: $H=25.9$, $p<0.001$; PLA $\mu=0.91$, $SD=0.2$; ESC $\mu=0.88$, $SD=0.1$, $d=-0.47$; BUP $\mu=0.91$, $SD=0.0$, $d=-0.54$). ESC-treated mice reached fewer reversals ($H=32.8$, $p<0.001$; PLA $\mu=20$, $SD=6.9$; ESC $\mu=12$, $SD=6.5$, $d=-0.46$) than PLA, while BUP was associated with more trials ($H=41.1$, $p<0.001$; PLA $\mu=370$, $SD=102$; BUP $\mu=463$, $SD=81$, $d=0.46$) and rewards ($H=42.5$, $p<0.001$; PLA $\mu=220$, $SD=67$; BUP $\mu=277$, $SD=55$, $d=0.44$) per session in comparison to PLA. Group-level differences remained significant after Bonferroni correction for 7 hypotheses. There were no group differences in lose-shift

probability and the number of rewards per trial and no sex differences in performance. Discussion: Both substances were associated with a shift from reward-driven to exploratory behavior in our sample. Mice treated with BUP compensated for learning inefficiency with increased vigor, whereas ESC-treated mice displayed no activating effect, resulting in worse performance. This could suggest that both substances help patients disregard maladaptive intrinsic rewards, encourage novelty seeking and thus gradually overcome counterproductive behavioral attractors. Further translational studies are needed to support this proposition.

Disclosures: T. Sedlinska: None. **Y. Kajihara:** None. **Q. Huys:** None. **K. Doya:** None.

Poster

PSTR079: Neurovasculature and Blood Brain Barrier

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR079.01/H26

Topic: F.05. Brain Blood Flow, Metabolism, and Homeostasis

Support: This study was funded by the Blue Brain Project, a research center of the École Polytechnique fédérale de Lausanne (EPFL), from the Swiss Government's ETH Board of the Swiss Federal Institutes of Technology.

Title: Modeling astrocyte-mediated blood flow dynamics in the rat somatosensory cortex

Authors: *S. BATTINI[1], N. CANTARUTTI[1], C. KOTSALOS[2], Y. ROUSSEL[1], A. ARNAUDON[1], C. FAVREAU[1], S. ANTONEL[1], H. MARKRAM[1], D. KELLER[1];
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Abstract: The cerebral vasculature plays a crucial role in supporting brain activity by supplying necessary nutrients and removing waste products of brain metabolism. This complex network of highly interconnected blood vessels is influenced by astrocytes, which release vasoactive substances in response to increased neuronal activity, leading to changes in blood vessel diameter. Our study aimed to simulate the coupling between blood flow variations and changes in blood vessel diameters driven by astrocytic activity in the rat somatosensory cortex. We developed a simulation framework consisting of three main components: coupling between vasculature and synthesized astrocytic morphologies, a fluid dynamics model for computing flow within each vasculature segment, and a stochastic process to approximate the effect of astrocytic endfeet activity on vessel radii. Our model was validated against experimental observations of flow values measured across cortical depth from the literature. We found that active astrocytes led to an increase in blood flow across the vasculature, particularly in capillaries, with a layer-specific response to astrocytic activity in deeper cortical layers. Furthermore, we observed that capillaries largely contribute to the variability in blood flow (67%), highlighting their pivotal role in regulating cerebral perfusion. Our results also suggest that the effect of astrocytic activity on blood flow dynamics is localized and clustered, with most vasculature segments influenced by

two to three neighboring endfeet. These findings could deepen our understanding of neurovascular coupling and inform future investigations into pathological models of blood flow-related diseases.

Disclosures: S. Battini: None. **N. Cantarutti:** None. **C. Kotsalos:** None. **Y. Roussel:** None. **A. Arnaudon:** None. **C. Favreau:** None. **S. Antonel:** None. **H. Markram:** None. **D. Keller:** None.

Poster

PSTR079: Neurovasculature and Blood Brain Barrier

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR079.02/H27

Topic: F.05. Brain Blood Flow, Metabolism, and Homeostasis

Support: NIH R01DC017470
NIH R21NS130508

Title: An auditory learning induces hemodynamics in the tail striatum.

Authors: *L. CHEN[1], H. SCHIFF[2], Q. XIONG[3];
[1]SBU Neurobio. & Behavior, Stony Brook, NY; [2]Neurobio. & Behavior, SUNY - Stony Brook, Stony Brook, NY; [3]Neurobio. & Behavior, SUNY Stony Brook, Stony Brook, NY

Abstract: Title: An auditory learning induces hemodynamics in the tail striatum **Abstract:** The tail striatum, the caudal tail portion of the dorsal striatum plays essential roles in driving auditory decision-making and learning. Despite accumulating knowledge focusing on the neuronal network, however, little is known about how learning modulates the local striatal network such as the microvasculature. Here we used an in vivo deep brain imaging approach in freely moving mice to examine the hemodynamics in the tail striatum during an auditory task learning. We found that task learning induced a non-linear increase of local blood flow. In vivo Ca2+ imaging in the learning mice revealed a similar activity dynamic in nNOS+ interneurons. Pharmacological inhibiting Nitric Oxide pathway delayed the learning process. Our findings demonstrate a local circuit mechanism underlying striatal neurovascular coupling during learning. This study provides foundation for research in understanding learning deficits in neurological disorders particularly those accompanied with vascular dysfunction.

Disclosures: L. Chen: None. **H. Schiff:** None. **Q. Xiong:** None.

Poster

PSTR079: Neurovasculature and Blood Brain Barrier

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR079.03/H28

Topic: F.05. Brain Blood Flow, Metabolism, and Homeostasis

Support: Grant-in-Aid for Scientific Research (KAKENHI) (26462156).

Title: Vasorelaxation induced by beta-adrenoreceptor agonist in cerebral arteries.

Authors: *T. MURATA;
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Abstract: Development of delayed cerebral ischemia (DCI) following subarachnoid hemorrhage (SAH), which results in an unfavorable clinical outcome, is thought to be caused by the combined effects of delayed cerebral vasospasm, arteriolar constriction and microthrombosis, cortical spreading ischemia, and processes triggered by early brain injury. Delayed cerebral vasospasm is one of the major causes of DCI, however, its pathophysiological mechanisms still remain unresolved despite progress in experimental and human investigations, thus limiting the number of available effective therapies. Beta-adrenoreceptor agonist, such as Ritodrine Hydrochloride, is a well-known vascular relaxant which treated in patients with threatened premature delivery. This study was therefore conducted to clarify the beta-adrenoreceptor agonist-induced vasorelaxation in cerebral artery tone, and also to investigate the messenger RNAs (mRNAs) expression of beta-adrenoreceptor on rabbit, dog and human basilar artery. In this study, rings of male rabbit basilar arteries were suspended in organ bath and measured with the beta-adrenoreceptor agonist as Ritodrine Hydrochloride and Clenbuterol Hydrochloride. Selective beta-adrenoreceptor agonists were also tested. Here is a brief summary of our results. (1) The beta-adrenoreceptor agonist, Ritodrine Hydrochloride and Clenbuterol Hydrochloride, dose-dependently relaxed on KCl-induced contraction of rabbit basilar artery. (2) The selective beta-1-adrenoreceptor agonist, Dobutamine Hydrochloride, dose-dependently relaxed on KCl-induced contraction of rabbit basilar artery. (3) Neither the selective beta-2-adrenoreceptor agonist as Procaterol Hydrochloride nor the selective beta-3-adrenoreceptor agonist as CL 316,234 relaxed on KCl-induced contraction of rabbit basilar artery. (4) The mRNAs expression of beta-1- and beta-2-adrenoreceptor were detected on rabbit, dog and human basilar artery, but beta-3-adrenoreceptor were not on these basilar arteries. In conclusion, the beta-adrenoreceptor agonist dose-dependently relaxed on rabbit basilar artery, and this vasorelaxation may be associated via the beta-1-adrenoreceptor. These results provide a background to develop in treatment against delayed cerebral ischemia or vasospasm following SAH.

Disclosures: T. Murata: None.

Poster

PSTR079: Neurovasculature and Blood Brain Barrier

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR079.04/H29

Topic: F.05. Brain Blood Flow, Metabolism, and Homeostasis

Title: Sex Differences in Cerebral Blood Flow and Glucose Metabolism Coupling in Alzheimer's Disease Cohort

Authors: *Y. ZHAO[1], J. N. ADAMS[2], M. A. YASSA[3];
[1]Dept. of Neurobio. and Behavior and Ctr. for the Neurobio. of Learning and Memory, Univ. of California, Irvine, Irvine, CA; [2]UC Irvine, Irvine, CA; [3]Neurobio. and Behavior, Univ. of California Irvine, Irvine, CA

Abstract: In Alzheimer's disease (AD), hypometabolism and hypoperfusion are the two of the most significant physiological changes observed in the brain. Reduced cerebral metabolic rate of glucose (CMR_{glu}) and reduced cerebral blood flow (CBF) have both been independently reported to be associated with increased amyloid deposition in AD patients and pre-clinical AD cohorts. Recently, a series of studies have suggested that neurovascular coupling -- the relationship between cerebral blood perfusion and metabolism -- is significantly affected by aging and the progression of Alzheimer's disease (AD). However, it is still unclear how neurovascular coupling in the human resting brain influences the progression of AD. In this work, we hypothesized that reduced coupling between CBF and CMR_{glu} would affect the brain's ability to clear metabolic waste through vasculature, leading to accumulation of amyloid in brain tissues, and affecting cognition. We also explored how sex differences modulate these associations. We analyzed a participant sample drawn from the Alzheimer's Disease Neuroimaging Initiative (ADNI) dataset who completed both an 18F-Fluoro-DeoxyGlucose PET (FDG-PET) scan and a 3D pseudo-continuous arterial spin labeling (pCASL) scan. The final sample includes 53 subjects (18 females, $mean_{Age}$= 69.4, SD_{age} = 7.16; 35 males, $mean_{Age}$= 73.5, SD_{age} = 6.52). Among the subjects, there were 3 healthy, 31 MCI and 19 Dementia. For each subject, the ratio between the absolute CBF and the SUVR of FDG-PET in FDG metaROIs (middle and inferior temporal gyrus, angular gyrus and posterior precuneus) was calculated as a proxy measure of resting brain neurovascular coupling. Two linear regressions were performed using CBF-FDG ratio and sex to predict whole-brain centiloids amyloid level and memory composite score. There was a significant interaction between CBF-FDG ratio and Sex (β = -39.80, SE = 14.90, t = -2.67, p < .05) in predicting amyloid accumulation. Post-hoc tests showed that the association between CBF-FDG ratio and amyloid accumulation was significant in males (β = -22.61, SE = 9.23, t = -2.45, p < .05) but not in females (β = 17.19, SE = 11.53, t = 1.50, p = 0.55). There was a trend of interaction between CBF-FDG ratio and Sex in predicting memory composite score (β = 0.68, SE = 0.46, t = 1.89, p = .06). Post-hoc tests showed that the association between CBF-FDG ratio and memory composite score was significant in males (β = 0.58, SE = 0.20, t = 2.86, p < .01) but not in females (β = -0.11, SE = 0.33, t = -0.32, p = 0.76). In summary, the result suggests that reduced neurovascular coupling is significantly associated with higher amyloid deposition and lower memory scores in males but not in females.

Disclosures: Y. Zhao: None. **J.N. Adams:** None. **M.A. Yassa:** None.

Poster

PSTR079: Neurovasculature and Blood Brain Barrier

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR079.05/H30

Topic: F.05. Brain Blood Flow, Metabolism, and Homeostasis

Support: NIH 1R01HL162575

Title: Interplay between hypoxia and acidification in the regulation of osmotic driven neurovascular responses in the supraoptic nucleus

Authors: *S. AGUS[1], L. SHOOK[2], J. E. STERN[2], J. A. FILOSA[1];
[1]Physiol., Augusta Univ., Augusta, GA; [2]Neurosci., Georgia State Univ., Atlanta, GA

Abstract: Neurovascular coupling (NVC) refers to the process by which increased neuronal activity leads to increases in cerebral blood flow and oxygen and nutrients delivery to working neurons. Studies from specific brain regions, have also reported an activity-dependent vasoconstriction or *inverse neurovascular coupling*, but the physiological implications are poorly understood. The hypothalamic supraoptic nucleus (SON) coordinates osmotic homeostasis and comprises vasopressin (VP) and oxytocin neurons. We previously showed that, *in vivo*, SON arterioles vasoconstrict to a hyperosmotic stimulus, resulting in local tissue hypoxia. Here, we hypothesize that functional evoked hypoxia in the SON, along with the associated decrease in pH, plays important roles in the dynamic neurovascular response evoked by the osmotic challenge. We specifically propose that inverse NVC in the SON is accompanied by a delayed opposing vasodilatory mechanism that terminates the stimulus-induced vasoconstriction and protects neurons from ischemia-induced damage. To further understand the mechanisms underlying inverse NVC in the SON, we used an ex-vivo approach, combining whole-cell patch clamp recordings from VP neurons and video microscopy to monitor parenchymal arteriole diameter during a hypoxic (20% O_2) or acidotic (pH 6.8) challenge. Experiments were conducted in 7-10-week-old male Wistar rats. To pre-constrict arterioles to a steady-state tone, SON brain slices were first perfused with a thromboxane A2 agonist (U46619, 200nM). For hypoxia, a bicarbonate buffered artificial cerebrospinal fluid (aCSF) (95% O_2-5% CO_2), was switched to one with reduced O_2 (20% O_2- 5% CO_2, balanced N_2). For acidification, we used a HEPES-buffered aCSF, pH 6.8. The hypoxic stimulus significantly ($P<0.05$) increased firing activity in 84% of VP neurons, n=18. In addition, n=15/21 SON parenchymal arterioles responded with a significant ($p<0.0005$) vasoconstriction, 35.3±4.9%. Contrary to the observed hypoxic-evoked vasoconstriction, 63% of SON arterioles (n=7/11) significantly ($P<0.05$) vasodilated (23.7% ±5.5) in response to low pH. Our findings indicate that while hypoxia stimulates VP neuronal activity leading to an initial vasoconstriction, low pH primarily stimulates arteriole vasodilation. We propose a positive feedback mechanism by which activity-dependent dendritic release of VP vasoconstrict arterioles and the resulting local hypoxia sustains neuronal activation. Future studies will investigate if this inverse NVC process is terminated by a hypoxia-driven acidification which dilates SON arterioles.

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Poster

PSTR079: Neurovasculature and Blood Brain Barrier

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR079.06/H31

Topic: F.05. Brain Blood Flow, Metabolism, and Homeostasis

Title: Sensory-evoked hemodynamics and the topology of blood vessels in the mouse visual cortex and white matter

Authors: *R. PAVAN[1], C. J. LIU[2], A. BHALERAO[2], P. KARA[2];
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Abstract: Macroscopic fMRI imaging studies of the neocortex have focused on the gray matter and undervalued hemodynamic signals from the white matter, whether that be ignoring them or using them for noise correction. Microscopic imaging studies with single-vessel resolution of the white matter have either focused on the topology of blood vessels in histological sections or baseline blood flow in vivo. Here we bridge the gap between prior macro- and micro-scopic imaging studies by examining the topological rules of the gray and white matter vessels that govern where and when sensory-evoked responses can be detected in blood vessels from the white matter. We first used in vivo multiphoton imaging of Alexa 680 dextran labeled blood vessels to classify all arteries, veins, and capillaries from the pia to the depths of the gray and white matter—in 1 mm^3 regions of the primary visual cortex (V1) in mice (Fig. 1a). We then examined whether there were visually-evoked blood flow responses (changes in red blood cell velocity) in vessels from the white matter below V1 (Fig. 1b). We found that white matter blood vessels can show significant increases in blood flow upon visual stimulation (Fig. 1c). However, only half of the white matter vessels we examined were visually responsive. We then used our segmentation and classification of the imaged volumes to determine which aspects of the vessel topology could explain these differences in visual responsiveness. First, nothing unremarkable was found regarding the density of vessels or the spacing of penetrating arterioles. However, we found that responsive white matter vessels had local anatomical connections with nearby penetrating cortical arterioles, separated by 1-2 capillaries. Moreover, unresponsive white matter vessels could be traced back to cortical veins rather than cortical arteries. Our results emphasize the preeminence of penetrating arterioles in shaping visually-evoked hemodynamic responses in the gray *and* white matter. Moreover, they also suggest that white matter fMRI signals should not be treated as a proxy for physiological or machine noise.

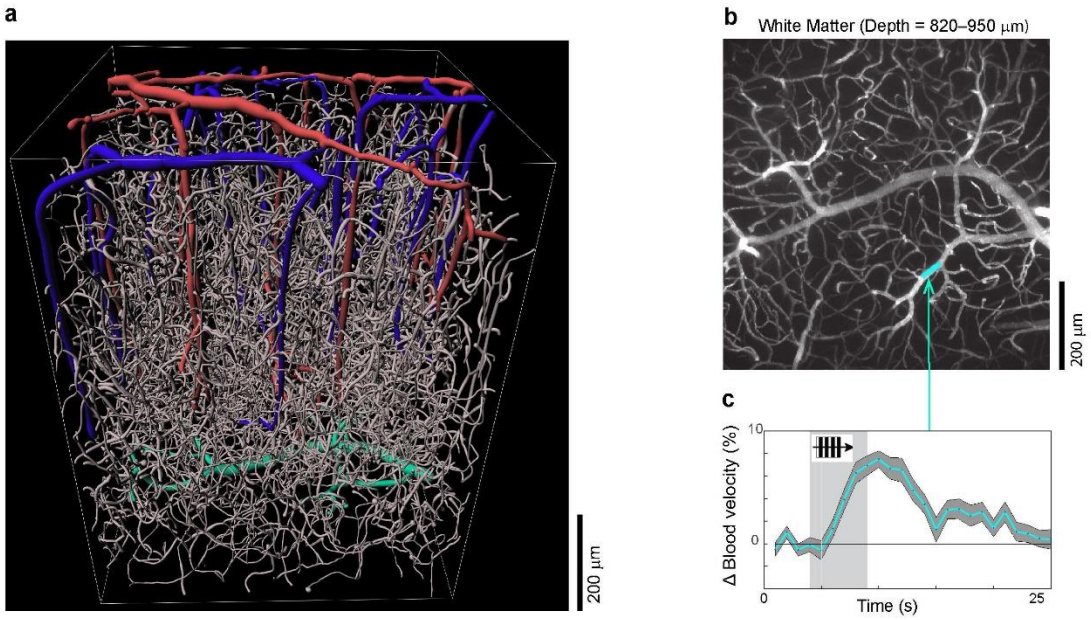

Figure 1. (**a**) 3D volume of blood vessels classified into arteries (red), veins (blue), capillaries (gray) and a white matter vein (green). (**b**) Max intensity 130-μm-z-projection from the white matter. (**c**) Time course of changes in blood velocity from a white matter vessel to visual stimulation.

Disclosures: R. Pavan: None. **C.J. Liu:** None. **A. Bhalerao:** None. **P. Kara:** None.

Poster

PSTR079: Neurovasculature and Blood Brain Barrier

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR079.07/H32

Topic: F.05. Brain Blood Flow, Metabolism, and Homeostasis

Title: Effects of Cisplatin on Vascular Dynamics and Pericyte Function in the Prefrontal Cortex of Wistar Rats

Authors: *O. TORRES-PINEDA[1], L. LOPEZ-MERAZ[2], C. A. PEREZ-ESTUDILLO[3], C. MORGADO-VALLE[4], L. BELTRAN-PARRAZAL[5];
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Abstract:

Cisplatin (CP), a widely used chemotherapeutic agent, may influence pericytes that regulate capillary dynamics in the prefrontal cortex, potentially impacting behavioral control. This study investigated the effects of CP on pericytes and vascular dynamics within the frontal association

cortex (FrA), and primary and secondary motor cortices (M1 and M2) of 3-month-old Wistar rats. We use in vivo optical imaging to assess spontaneous vascular dynamics and responses to an electrical stimulus (500 microamps, 50 Hz, 5s) in precapillary arterioles following CP at a dose of 60 mg/kg. Pericytes were identified via TO-PRO-3 iodide staining and immunofluorescence using the PDGFrβ antibody. Our findings demonstrate significant alterations in vascular dynamics and vasomotricity ($p<0.05$), correlating with increased PDGFrβ expression and pericyte density per capillary length unit.

Ethical Compliance and Experimental Design: All experiments adhered to the technical specifications for the production, care, and use of laboratory animals as mandated by Mexico's NOM-062-ZOO-1999, the NIH Guide for the Care and Use of Laboratory Animals, and the ARRIVE18 guidelines. The study included two groups: a control (sham) and an experimental group, each containing ten 3-month-old male rats.

Conclusion: Our results show significant alterations in vascular dynamics and pericyte behavior following CP treatment, marked by changes in vasomotricity and increased PDGFrβ expression and pericyte density. These findings suggest potential disruptions in the blood-brain barrier and cerebral microcirculation, highlighting the critical need for neurovascular monitoring in CP therapies. Understanding these effects could enable better prediction and mitigation the neurotoxic side effects associated with chemotherapeutic regimens, potentially leading to safer treatment protocols..

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Poster

PSTR079: Neurovasculature and Blood Brain Barrier

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR079.08/Web Only

Topic: F.05. Brain Blood Flow, Metabolism, and Homeostasis

Support: NIH Grant 1K08EY033013

Title: Capillary Density and Neuronal Homeostasis in Human Primary Visual Cortex

Authors: Y.-C. WANG[1], S. GUO[1], A. NEWTON[2], R. A. MCDOUGAL[3], W. W. LYTTON[4], *M. DISTASIO[5];
[1]Hlth. Informatics Program, Yale Sch. of Publ. Hlth., New Haven, CT; [2]Physiol. and Pharmacol., SUNY Downstate Hlth. Sci. Univ., Brooklyn, NY; [3]Ctr. for Med. Informatics, Yale Univ., New Haven, CT; [4]Physiology/Pharmacology, DHSU, Brooklyn, NY; [5]Yale Sch. of Med., New Haven, CT

Abstract: Hypoxia is a commonly known pathological condition that is related to spreading depolarization. Although neuronal density has been widely explored across brain regions, the distribution of distances between neurons and vasculature plays an important role in the availability of free oxygen to neurons to support their metabolism (which in turns supports maintenance of resting membrane potential).
This study analyzes the distribution of distance between neurons and vasculature in the primary visual cortex of humans. Using post-mortem samples of normal primary cortex from 3 subjects ages 65-75, we performed dual-label immunohistochemistry with antibody markers for NeuN (for neurons) and CD34 (for vascular endothelial cells). Region of interest (ROIs) of neocortical layers were delineated manually by a neuropathologist. Within these regions, object-based classification in Qupath software was employed to segment neurons, and pixel-based classification was utilized to identify capillaries. The centroids of the identified objects were employed in subsequent statistical analyses. A quadtree algorithm was employed to determine the nearest vessel to each id entified neuron, and the distance between neuron and vessel centroids was then calculated.
Our results show that as the cortical depth increases, the distance between neurons and their closest capillary tends to decrease, with layer 4 and layer 5 exhibiting the shortest (34.38μm and 34.03μm respectively). This effect likely represents specialized microanatomy driven by metabolic constraints at different levels of the cortical plate which contain elements of neuronal circuits with distinct roles in visual processing.

Disclosures: Y. Wang: None. **S. Guo:** None. **A. Newton:** None. **R.A. McDougal:** None. **W.W. Lytton:** None. **M. DiStasio:** None.

Poster

PSTR079: Neurovasculature and Blood Brain Barrier

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR079.09/H33

Topic: F.05. Brain Blood Flow, Metabolism, and Homeostasis

Support: Lundbeck Foundation
Novo Nordisk Foundation
Nordea Foundation Grant to the Center for Healthy Aging
Independent Research Fund Denmark

Title: The neurovascular coupling response of the aged brain is brain-state dependent.

Authors: *X. ZHANG[1], C. CAI[2];
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Abstract: Brain aging lead to reduced cerebral blood flow and cognitive decline, but how normal aging affects neurovascular coupling (NVC) in the awake brain is unclear. Here, we

investigated NVC in relation to calcium changes in vascular mural cells (VMCs) in awake adult and aged mice. We show that NVC responses are reduced and prolonged in the aged brain and that this is more pronounced at the capillary level than in arterioles. However, the overall NVC response, measured as the time integral of vasodilation, is the same in two age groups. In adult, but not in aged mice, the NVC response correlated with Ca2+ signaling in VMCs, while the overall Ca2+ kinetics were slower in aged than in adult mice. In particular, the rate of Ca2+ transport, and the Ca2+ sensitivity of VMCs were reduced in aged mice, explaining the reduced and prolonged vasodilation. Spontaneous locomotion was less frequent and reduced in aged mice as compared to young adult mice, and this was reflected in the 'slow but prolonged' NVC and vascular Ca2+ responses. Taken together, our data characterize the NVC in the aged awake brain as slow but prolonged, and underscoring the importance of brain state in understanding age-related mechanisms.

Disclosures: X. zhang: None. **C. Cai:** None.

Poster

PSTR079: Neurovasculature and Blood Brain Barrier

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR079.10/H34

Topic: F.05. Brain Blood Flow, Metabolism, and Homeostasis

Support: NINDS R35 NS097265
NINDS U19 NS123717
NIDA R01 DA050159

Title: Competitive neurovascular interactions shape the spatiotemporal vasodynamics of the pial arteriole network

Authors: *J. DUCKWORTH[1], T. BROGGINI[3,4,1], K. CHHABRIA[1], M. VERGASSOLA[5], D. KLEINFELD[2];
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Abstract: The pial arteriole network distributes blood across the surface of neocortex to nourish underlying brain cells. This network is dynamic; arteriole branches exhibit intrinsic ~ 0.1 Hz oscillations which are modulated through electrical communication from both underlying neurons and neighboring arterioles. Our previous findings show that vasomotor oscillations propagate as traveling waves with wavelengths of ~ 20 mm and modulate resting-state perfusion of cortex by ~ 20%, an amount that meets or exceeds modulation during sensory stimulation (Broggini, Duckworth et al. Neuron 2024). Here we test how rhythmic neuronal inputs and intrinsic vasomotion compete to form the spatiotemporal patterns of vaso-oscillations relevant to parcellation and stimulus responses measured both optically and by fMRI. We used wide-field

imaging to simultaneously measure arteriole diameter, via expression of GCaMP8.1 in arterial smooth muscle cells, and pan-neuronal activity, via expression of jRGECO1a in excitatory neurons, across the murine cortical mantle in awake head-fixed mice. We found strong evidence for resonance phenomena, i.e., the area of neurovascular entrainment is greatest when sensory-driven and intrinsic vasomotor frequencies match. Moreover, we found that localized medullary optogenetic activation near the intrinsic vasomotor frequency elicits neurovascular entrainment that can mask or even outcompete the sensory-driven responses. This dynamic competition for cortical territory implies that the pial network may be abstracted as a two-dimensional network of active, coupled oscillators. Within this framework, we use time and amplitude-varying analysis methods to explore vasomotor oscillations at the boundary of stimulated vibrissa and visual cortical regions. Our past and current data suggest that pial arteriole oscillators are weakly coupled and form frequency-locked regions at rest and in response to neuronal activation. We are exploring the impact of stimulus drive on oscillator amplitude, with a focus on the border of visual rostrolateral and vibrissa somatotopic cortices, as a potential mechanism for parcellation of vasomotor responses.

Disclosures: J. Duckworth: None. **T. Broggini:** None. **K. Chhabria:** None. **M. Vergassola:** None. **D. Kleinfeld:** None.

Poster

PSTR079: Neurovasculature and Blood Brain Barrier

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR079.11/H35

Topic: F.05. Brain Blood Flow, Metabolism, and Homeostasis

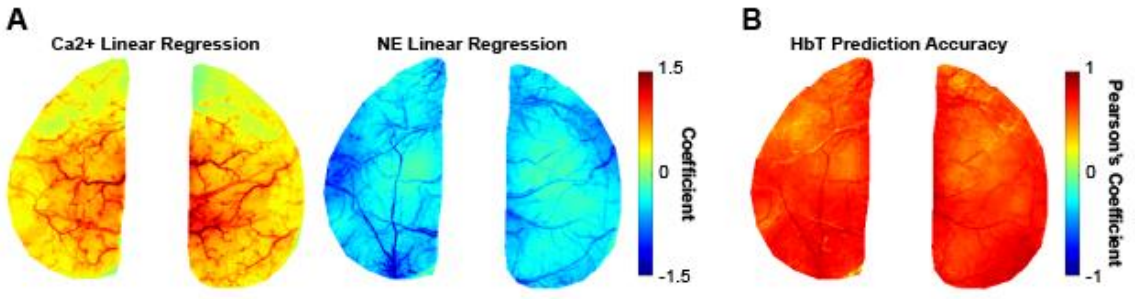
Support: U19NS123717
R01DA050159

Title: Loss of hemodynamic functional connectivity during high arousal does not reflect neuronal uncoupling

Authors: *B. C. RAUSCHER[1], N. FOMIN-THUNEMANN[1], S. KURA[1], P. DORAN[1], P. D. PEREZ[1], D. BALOG[1], P. BLONIASZ[2], K. KILIÇ[1], J. JIANG[1], E. MARTIN[1], N. CHAI[1], F. FROIO[1], E. P. STEPHEN[2], M. THUNEMANN[1], D. A. BOAS[1], A. DEVOR[1,3];
[1]Biomed. Engin., Boston Univ., Boston, MA; [2]Mathematics and Statistics, Boston Univ., Boston, MA; [3]Martinos Center for Biomedical Engineering, Boston, MA

Abstract: Ascending neuromodulatory projections from deep brain nuclei generate internal brain states that differentially engage specific neuronal cell types. Because neurovascular coupling is cell-type specific and neuromodulatory transmitters have vasoactive properties, we hypothesized that the impulse response function (IRF) linking spontaneous neuronal activity with hemodynamics would depend on brain state.
To test this hypothesis, we used mesoscopic optical imaging to measure (1) release of

neuromodulatory transmitters norepinephrine (NE) or acetylcholine (ACh), (2) Ca^{2+} activity of local cortical neurons, and (3) changes in hemoglobin concentration and oxygenation across the dorsal surface of cerebral cortex during spontaneous neuronal activity in awake mice. Fluctuations in total hemoglobin (HbT), reflective of dilation dynamics, were well predicted by a weighted sum of positive Ca^{2+} and negative NE contributions, while ACh signals were largely redundant with Ca^{2+}. The hemodynamic IRF varied in time and depended on the arousal (pupil dilation, whisking) which was captured by NE but not ACh release. In every case, we obtained a good fit for the IRF using a weighted sum of two alpha functions with the coefficients derived from the Ca^{2+}/NE contributions to HbT. During high arousal, the dynamic nature of the IRF resulted in the loss of hemodynamic coherence between cortical regions (known as "functional connectivity" in BOLD fMRI studies) despite coherent behavior of the underlying neuronal Ca^{2+} activity.
We conclude that dynamics of the hemodynamic IRF challenge the metric of functional connectivity because the loss of hemodynamic coherence can be falsely interpreted as "functional uncoupling" of the underlying neuronal activity.



Disclosures: B.C. Rauscher: None. **N. Fomin-Thunemann:** None. **S. Kura:** None. **P. Doran:** None. **P.D. Perez:** None. **D. Balog:** None. **P. Bloniasz:** None. **K. Kiliç:** None. **J. Jiang:** None. **E. Martin:** None. **N. Chai:** None. **F. Froio:** None. **E.P. Stephen:** None. **M. Thunemann:** None. **D.A. Boas:** None. **A. Devor:** None.

Poster

PSTR079: Neurovasculature and Blood Brain Barrier

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR079.12/H36

Topic: F.05. Brain Blood Flow, Metabolism, and Homeostasis

Support: NIH NINDS 5K00NS115336
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NIH NINDS U19 NS107466

Title: The ultrastructural geometry of vascular interfaces in the brain as revealed by large-scale volume electron microscopy data

Authors: J. J. HOW[1,2,3], B. P. DANSKIN[4], S. K. BONNEY[5], B. PEDIGO[4], M. SOSA[5], D. KLEINFELD[6], *A. Y. SHIH[5,7];
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Abstract: Cerebral blood flow regulation involves constant communication between active neurons and vascular endothelial and mural cells to control the size and stiffness of vessels that source blood. However, the physical interactions and ultrastructural anatomy that support this cell-to-cell communication remains largely uncharacterized. We make use of the Machine Intelligence from Cortical Networks (MICrONS) dataset, a cubic millimeter volume electron microscopy (EM) reconstruction of mouse visual cortex, to address this question. In particular, recent studies indicate that release of K+ from active neurons and astrocytes contributes to the activation of inward rectifying K+ channels on the endothelium (Longden et al. Nature Neuroscience, 2017). This triggers a propagating front of hyperpolarization along brain capillaries that can lead to upstream dilation and forms a basis of neurovascular coupling. The MICrONS dataset provides an opportunity to quantify the neuronal compartments, i.e., axons, dendrites, somata, and synaptic spines and boutons, and the non-neuronal compartments that are proximal to the vessel wall and could contribute to extracellular K+ flux. Beyond issues of neurovascular control of blood flow, initial examination of this data set revealed distinct compositions of perivascular cell types across vascular zones. Notably, we observe marked shifts in the distribution and morphologies of perivascular fibroblasts and macrophages that reside in the perivascular space and vascular basement membrane of arterioles and venules, with a complete absence of these perivascular cells along capillaries. The close association of perivascular fibroblasts and macrophages with both mural cells and astrocytes in the perivascular space is suggestive of an unrealized contribution to the regulation of vascular wall architecture, and potentially, interstitial fluid flow and brain lymphatics. Ongoing work supported by the Virtual Observatory of the Cortex (VORTEX) aims to define the cellular “parts list” and “assembly diagram” for the perivascular tissues across the brain microvasculature. This will provide a foundation to build hypotheses for complementary in vivo physiological studies and guided perturbation of specific cell types and cellular interactions that underlie the regulation of blood and interstitial fluid flow.

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Poster

PSTR079: Neurovasculature and Blood Brain Barrier

Location: MCP Hall A

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Program #/Poster #: PSTR079.13/H37

Topic: F.05. Brain Blood Flow, Metabolism, and Homeostasis

Support: NIH Grant R01NS091230
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Title: Two-photon microscopy imaging of resting-state fluctuations of absolute pO_2 and vascular diameters in aging mouse brain

Authors: *Q. PIAN[1], Y. ZHOU[1,2], B. FU[1], M. EL KHATIB[3,4], S. VINOGRADOV[3,4], J. TANG[2], D. KLEINFELD[5,6], A. DEVOR[1,7], S. SAKADZIC[1];
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Abstract: We utilized two-photon microscopy (2PM) to monitor the concurrent changes in the vascular diameter and intravascular partial pressure of oxygen (pO_2) in the pial arteriole vessels of awake mice at rest. The two groups of C57BL/6 mice were investigated: young mice (8-month-old; n = 6) and old mice (17-month-old; n =4). Two optical probes, 70KDa-dextran-conjugated fluorescein isothiocyanate (FITC) and Oxyphor 2P, were administered into the blood plasma via retroorbital injection and both excited at 950 nm for 2PM imaging. Vessel diameters were measured by line-scanning the laser beam across the vessels and collecting the FITC fluorescence signal at 525 nm, while the pO_2 was retrieved by parking the focus of the excitation beam inside the lumen of the vessels and recording the phosphorescence decay signal at 795 nm. The measurements in each pial vessel were performed at a 1 Hz sampling rate over a five-minute period. The power spectrum of resting-state arteriolar diameter fluctuations exhibited a peak near the natural vasomotor frequency of ~0.1 Hz for both age groups, with the spectral power of the peak for the old group reduced by ~60 % compared to the young group. In contrast, as a control venular diameters of both age groups exhibited no vasomotion peaks at ~0.1 Hz. We have also observed spectral power peaks of arteriolar and venular pO_2 oscillations at 0.15-0.20 Hz in both age groups. The arteriolar peak spectral power of pO_2 in the old mice was 23 % smaller compared to the young mice, while there was no significant difference in the venular peak spectral powers of pO_2 between the two age groups. Our findings suggest significantly diminished fluctuations of the arteriolar pO_2 in old mice compared to the young ones, which may potentially contribute to the reduced local brain tissue oxygen supply. Ongoing experiments are further addressing this question by assessing the relation between resting-state vascular diameter fluctuations and changes in the tissue pO_2.

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Poster

PSTR079: Neurovasculature and Blood Brain Barrier

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR079.14/Web Only

Topic: F.05. Brain Blood Flow, Metabolism, and Homeostasis

Support: SNSF P500PB_21149
NINDS R35 NS097265
NINDS U19 NS107466
NIDA R01 DA050159

Title: Real-time Cellular-level Mapping of Extracellular Metabolites in Awake Mice

Authors: Z. KU[1], *P. MAECHLER[1], R. LIU[2], J. DUCKWORTH[3], J. S. MARVIN[4], Y. NASU[5], D. KLEINFELD[1];
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Abstract: Glucose, oxygen, and, under specific conditions, lactate are known to be the main blood-borne energy substrates used by the healthy brain. However, there is only limited data available on the microscopic distribution of these energy compounds relative to neurological and behavioral states. We explore the cell-level distribution and utilization of these sources via optical imaging of genetically encoded glucose and lactate sensors targeted to sample the extracellular space in primary vibrissa cortex of awake mice. The functionality of the sensors was calibrated via measurements with subacutely implanted electrochemical probes and intravenous substrate injections. Direct wave-front sensing with adaptive optics / two-photon imaging was used to increase the x-y resolution as well as improve motion correction. Intrinsic optical imaging via one-photon absorption was used to map the neurovascular response to vibrissae stimulation. We previously described oxygen gradients around diving arterioles at different cortical layers that reflect local oxygen consumption at rest (Mächler et al, PLoS Biol 2022). Surprisingly, periarteriolar oxygen gradients did not correlate with local capillary density. In contrast, we now find that modulation of blood glucose levels following intravenous administration of insulin and L- or D-glucose are largest in brain areas with relatively high capillary density. Additionally, extracellularly targeted lactate sensors indicate a spatially homogeneous increase of extracellular lactate upon lactate injection. The dependency of extracellular glucose and lactate levels on their concentrations in blood indicates limited transport rates across the blood-brain barrier, with a relatively fast distribution within the extracellular space. Lastly, we observe a delayed increase of extracellular lactate and decrease of extracellular glucose that track changes in pupil diameter and trail either spontaneous or vibrissa stimulation-induced locomotion. The changes in lactate and glucose are consistent with an

increase of aerobic glycolysis during aroused brain states. In summary, global extracellular substrate levels in the primary vibrissa cortex preferentially track blood concentrations and behavioral states, as opposed to local changes in sensory activation.

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Poster

PSTR079: Neurovasculature and Blood Brain Barrier

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR079.15/H38

Topic: F.05. Brain Blood Flow, Metabolism, and Homeostasis

Support: 'Strategic Priority Research Program' of the Chinese Academy of Sciences (grant no. XDB32030200)

Title: Large-scale 3D Blood Flow Imaging with Light Field Microscopy

Authors: *Y. ZHAO[1,2], L. CONG[1], L. BAI[1], Z. SHI[1,2], Y. ZHANG[1], L. YE[1], Z. ZHANG[1], K. WANG[1,2];
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Abstract: To maintain optimal neural function, the brain requires adequate blood flow to satisfy its high metabolic demands. The capillary network, the most extensive and fine-scale system of blood vessels within the brain, is critical for delivering oxygen and nutrients to neuronal cells. While the static structure of these vascular networks is well-documented, dynamic three-dimensional blood flow within these capillaries is not fully understood. Here we introduce an advanced version of light field microscopy, equipped with a custom-designed objective and micro-lens that extend the field of view to 2.5 mm. By labeling part of the circulating blood cells with a deep red fluorescent dye, we can directly track these blood cells at high speeds of 200 Hz, with imaging depths reaching up to 440 μm in awake mice. We have developed blood cell tracking algorithms and achieved the acquisition of precise blood flow dynamics in the presence of densely labeled blood cells. This new version of light field microscopy allows us to get real perfusion pattern of penetrating arterioles and blood flow dynamics from arterioles to capillaries and veins. We found that penetrating arterioles tend to perfuse distinct regions with minimal overlap observed among them. Our results supported the lattice models of the brain vasculature, which supposed that ascending venules act as sinks, prevent neighboring blood from entering the occluded area. Precise measurements of vascular dynamics during neurovascular coupling and long-term blood cell imaging were also performed. To summarize, we have built a fast light field system for 3D blood cells imaging allowing us to reveal large-scale 3D blood flow dynamics at single-capillary level. Our novel light field microscopy enables the observation of the real

perfusion pattern of penetrating arterioles, providing a precise measurement of neurovascular dynamics and facilitating the assessment of long-term blood flow changes in health and disease.

Disclosures: Y. Zhao: None. **L. cong:** None. **L. Bai:** None. **Z. Shi:** None. **Y. Zhang:** None. **L. Ye:** None. **Z. Zhang:** None. **K. Wang:** None.

Poster

PSTR079: Neurovasculature and Blood Brain Barrier

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR079.16/H39

Topic: F.05. Brain Blood Flow, Metabolism, and Homeostasis

Support: ERC VIRGINS 101125555

Title: Whole-brain vascular network reconstruction reveals pregnancy-induced vascular plasticity in the adult brain.

Authors: *G. LIENHARD[1], D. D. FERNANDOIS[2], R. POMME[1], E. DOUMAZANE[1], C. ROUSSEAU[1], V. PREVOT[2], A. ASSALI[1], N. RENIER[1];
[1]Paris Brain Inst., Paris, France; [2]Lille Neurosci. & Cognition, Lille, France

Abstract: Pregnancy induces a wide range of plastic adaptations to the mother's brain. These include structural changes at all scales, ranging from synaptic plasticity to changes in the volumes of brain regions visible from MRI scans. The contribution of the neurovascular system to this brain plasticity has however seldomly been considered. We used 3D whole-brain clearing, light-sheet imaging, and data analysis with iDISCO+ and ClearMap 2.1, to reconstruct the evolution of the brain vasculature throughout pregnancy at the capillary level. We found an increase in the vascularization of several brain regions throughout pregnancy, that reverses after birth. This increase was found in particular in the preoptic region of the hypothalamus, involved in pregnancy regulation and maternal behavior, and in cortical areas, such as the somatosensory cortex. Using 3D whole brain fluorescent *in situ* hybridization, we measured in pregnant dams an increase in *vegfa* expression levels in the brain regions having increased blood vessel numbers. In the hypothalamic pre-optic area, the vascularization was associated with the presence of Ki67+ endothelial cells, as well as tip cells, confirming active vascular remodeling in the region. Steroid hormonal implants of estradiol, but not progesterone in virgin females, recapitulated the increase in hypothalamic vascularization and vascular remodeling seen in pregnant dams. This vascular plasticity was however absent from pseudo-pregnant mice. These data suggest that vascular remodeling in the hypothalamic pre-optic region is regulated by high levels of circulating estradiol during pregnancy and likely via the action of VEGFA. Future experiments will aim to uncover the cellular and molecular mechanisms underlying pregnancy-induced vascular adaptations, and its physiological relevance. Our data suggest an active role of vascular remodeling in shaping pregnancy- and maternal behaviors-related neuronal functions.

Disclosures: G. Lienhard: None. **D.D. Fernandois:** None. **R. Pomme:** None. **E. Doumazane:** None. **C. Rousseau:** None. **V. Prevot:** None. **A. Assali:** None. **N. Renier:** None.

Poster

PSTR079: Neurovasculature and Blood Brain Barrier

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR079.17/H40

Topic: F.05. Brain Blood Flow, Metabolism, and Homeostasis

Support: ERC NeuroRemod 758817

Title: A molecular and structural atlas of the post-natal development of the brain vasculature

Authors: E. DE LAUNOIT[1], S. SKRIABINE[2], E. DOUMAZANE[2], M. BIZOU[3], C. ROUSSEAU[2], *N. RENIER[2];
[1]Neurosciences, Paris Brain Inst., Paris, France; [2]Paris Brain Inst., Paris, France; [3]CHU Sainte Justine, Montréal, QC, Canada

Abstract: After birth, the mouse brain more than quadruples its volume, while neuronal circuits mature, myelination progresses, and glial cells divide and migrate. All these cellular anabolic processes require high levels of nutrients and energetic support, that are provided by the cerebrovascular network, which itself expands and matures after birth until adulthood. Here, we created and applied tools to describe the integrated structural and molecular development of the post-natal cerebrovascular network. We introduce a 3D light sheet atlas of the developing mouse brain tuned for organic solvent clearing, with 58 annotated brain regions across seven postnatal stages (P3, P5, P7, P9, P12, P14, and P21). This atlas enables the creation of a multimodal dataset of post-natal brain development combining multiplexed 3D RNA in situ hybridization, 3D myelination patterns, 3D vascular graphs and enriched with aligned spatial transcriptomic planes. These data revealed a multi-wave development of the cerebrovascular network, split between phases of isomorphic additions of vessels following brain growth, and phases of structural specializations and densification. Molecular interrogation of the dataset revealed gene modules correlating and anti-correlating with each of the maturation phases. In summary, our study provides insights into the dynamics and molecular control of neurovascular interactions during post-natal development. It also provides a framework to study complex cellular interactions shaping post-natal development.

Disclosures: E. de Launoit: None. **S. Skriabine:** None. **E. Doumazane:** None. **M. bizou:** None. **C. Rousseau:** None. **N. Renier:** None.

Poster

PSTR079: Neurovasculature and Blood Brain Barrier

Location: MCP Hall A

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Program #/Poster #: PSTR079.18/I1

Topic: F.05. Brain Blood Flow, Metabolism, and Homeostasis

Support: ERC-NeuroRemod-751788
RNID

Title: Deafness triggers brain-wide long-term vascular remodeling

Authors: *E. DE LAUNOIT[1,2], S. SKRIABINE[3], P. JEAN[4], T. DUPONT[4], A. VIEITES PRADO[3], S. SAFIEDDINE[4], N. MICHALSKI[4], N. RENIER[3];
[1]ICM, Paris, France; [2]Paris Brain Institute, Paris, France; [3]Paris Brain Inst., Paris, France; [4]Inst. Pasteur, Paris, France

Abstract: The brain is densely perfused by the vascular network, which provides nutrients and oxygen to support neuronal function. This vascular architecture is adapted to meet the unique demands of neural tissues, and sensory processing requires specifically high levels of support, as indicated by the increased vascularization of all sensory brain regions. It is known that early sensory deprivations alter the density of the vascular network in the primary sensory regions. However, it is not known whether the vascular deficits triggered by deafness early in life are mitigated later in life, or if the network is stabilized in an abnormal state for the rest of the animal's life. Indeed, the extent to which neuronal activity influences vascular topology in homeostatic conditions in an adult brain remains unclear. To address this question, we looked at how congenital deafness affects vascular maturation in several mouse lines. We measured in 2 and 3 months old *Otof*$^{-/-}$ mice a significant decrease in the vascular density of primary regions of auditory processing, correlated with a decrease of Fos+ cell densities in the same brain regions. However, starting in 6 to 12 months old animals, the vascular density decreased faster in deaf animals than in control animals in many non-auditory brain regions. Single cell transcriptomic analysis of cortical vascular cells suggested an increase in the expression of pro-apoptotic genes in the endothelial cells of deaf animals. Gain of function of wild type Otoferlin in the cochlea of Otof$^{-/-}$ mutants in young adults restored Acoustic Brainstem Responses and protected the vascular network brain-wide from its accelerated pruning. The findings emphasize the critical role of sensory activity in vascular development, but also on its maintenance throughout life. Moreover, the results reveal that auditory deprivation not only alters vascular development but also modifies its remodeling during normal aging. This research provides new insights into the long-term effects of sensory activity on vascular health and underscores the importance of addressing the consequences of sensory deprivation on vascular stability.

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Poster

PSTR079: Neurovasculature and Blood Brain Barrier

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR079.19/I2

Topic: F.05. Brain Blood Flow, Metabolism, and Homeostasis

Support: 5T32MH126388
F99NS125823

Title: Dopaminergic signaling drives rapid increases in BBB permeability

Authors: *K. L. TURNER[1,2], S. FEKIR[1,2], S. J. SCOTT[1,2], C. I. JOHNSON[1,2], A. LINDQUIST[3], J. NAMKUNG[1], D. M. BERSON[1], Y. ZHAO[3], C. I. MOORE[1,2];
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Abstract: Forebrain circuits driving behavior could benefit in a myriad of ways from dynamic access to the blood-brain barrier (BBB), in contrast to the common view that it is restrictive and sluggish. These structures evolved to allow mammals to choose correct actions and learn from them, processes that depend on knowing body state. Vessels contain a unique, high-dimensional aggregation of state signals, and tuned moments of elevated sampling could provide an ideal snapshot. Locally-active Forebrain circuits could also potentially benefit from facilitated metabolic delivery, timed to need. In parallel, local neural activity supporting computation makes ‘waste’ byproducts: Targeted clearance, at the time and place of generation, would be ideal for brain health. Dopaminergic (DA) inputs from the Ventral Tegmental Area (VTA) are ideally positioned to signal BBB dynamics: They index behavioral relevance and learning in real time, and are in close contact with vessels. Our ongoing work (Fekir et al., SfN 2023) supports these predictions. We have found ‘Plume Events,’ brief, local increases in BBB permeability timed to behaviorally relevant events—Valid Cues, instrumental actions and Rewards. Further, endogenous spiking and optogenetic activation of DA VTA Axons next to vessels also drive Plume Events, without accompanying vasodilation. These findings in Primary Somatosensory Neocortex (SI) are consistent with our anatomical data, showing DA VTA Axons make repeated, direct vessel appositions. To begin to directly test the possible role of DA specifically, the D1/D5 partial agonist SKF38,393 was infused across SI through an implanted cannula during simultaneous 2-Photon Imaging. Application of 100 microM SKF38,393 activated dLight and rapid, large-scale extravasation of 70kD RhoB into the parenchyma that was several times larger than control infusions (N = 7 mice). In summary, DA Axons and agonists drive transient increases in BBB permeability, indicating rapid brain-body signaling and that net transmission across the BBB over time in part reflects the accumulation of such stochastic events.

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Poster

PSTR079: Neurovasculature and Blood Brain Barrier

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR079.20/I3

Topic: C.01. Brain Wellness and Aging

Support: 2022R1F1A1061216

Title: The effect of quercetin on age-related cerebrovascular alterations by increasing SIRT1 and SIRT6 expressions

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Abstract: The cerebrovasculature is functionally and structurally altered with normal aging. During the normal aging process, functional changes in cerebrovasculature represented by a decrease in cerebral blood flow (CBF) lead to structural changes such as a decrease in the density of microvessels and an increase in tortuous and string vessels. Sirtuins (SIRTs) are NAD^+-dependent histone deacetylases that are known as regulators of anti-aging and lifespan. Among these, SIRT1 and SIRT6 are highlighted to play a crucial role in the maintenance of vascular aging and diseases as participates in the maintenance of endothelial cell functions. Quercetin is a natural bioflavonoid and is known to directly induce SIRT1 and SIRT6 expression to exert anti-oxidant and anti-inflammatory effects in adverse conditions like injury or diseases. In this study, we aimed to examine the effect of quercetin on age-related cerebrovascular alterations. Quercetin suppresses a decrease in cerebral blood flow and morphological alterations compared to same-age normal aging mice (15 months). In addition, the age-related decrease in total protein and density of brain microvessels and the increase in the shape of atrophic and string vessels, which are seen as a decrease in diameter, were suppressed by quercetin treatment. An assessment of blood-brain barrier (BBB) disruption using Evans Blue showed quercetin reduced age-related increases in leakage of BBB. At the molecular level, quercetin increased SIRT1, SIRT6, BBB tight junction protein (Claudin-5), and vascular stability-related proteins eNOS and Tie2 expression increased in microvessels. Our results suggest that quercetin might suppress age-related cerebrovascular alterations not only by directly increasing SIRT1 and SIRT6 expressions but also by increasing endothelial cell stability-related factors expression as a downstream target.

Disclosures: J. Mun: None. **C. Park:** None.

Poster

PSTR079: Neurovasculature and Blood Brain Barrier

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR079.21/I4

Topic: C.01. Brain Wellness and Aging

Support: NIH Grant F31-NS132422
NIH Grant R01-NS117515
NIH Grant R01-NS119410

Title: Investigating the Neural Basis of Glymphatic Clearance.

Authors: *F. JUAREZ ANAYA[1], S. ROSS[2], A. VAZQUEZ[3];
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Abstract: Glymphatic clearance is thought to be most active during slow wave sleep (SWS), which is neurally-mediated. However, the neural basis of glymphatic-associated clearance is unknown. We hypothesized that a sparse population of long-range projecting neurons—expressing both tachykinin receptor 1 (NK1R) and neuronal nitric oxide synthase (nNOS)—promote SWS and regulate vascular fluctuations that underlie glymphatic clearance. Here, we investigated the role of these NK1R/nNOS neurons in glymphatic clearance using a combination of *in vivo* two-photon calcium imaging, pharmacological manipulations, optogenetic and chemogenetic approaches, and laser Doppler flowmetry. We find that NK1R/nNOS neurons are most active during SWS. In addition, pharmacological induction of sleep was associated with increased activity in NK1R/nNOS neurons.Moreover, pharmacological inhibition of nNOS revealed that NK1R/nNOS neurons regulate vascular fluctuations by releasing nitric oxide. Finally, we provide evidence that chemogenetic activation of NK1R/nNOS neurons across the cortex induces SWS and alters cerebral blood flow. Thus, NK1R/nNOS may coordinate both SWS and slow vascular fluctuations that occur during SWS to promote glymphatic clearance.

Disclosures: F. Juarez Anaya: None. **S. Ross:** None. **A. Vazquez:** None.

Poster

PSTR080: Urinary, Gastrointestinal, and Renal Regulation

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR080.01/I5

Topic: F.06. Autonomic Regulation

Title: Quantifying intraoperative external anal sphincter responses to sacral nerve stimulation

Authors: *B. VANDEGRIFT[1], M. S. NISSEN[2], M. MOORE[2], P.-J. CHEN[2], P. GUPTA[3], T. M. BRUNS[2];
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Abstract: Patients with bladder and bowel dysfunction may receive a sacral neuromodulation (SNM) system in which a stimulation lead is placed by a sacral nerve. In these patients, SNM is applied continuously at comfortable amplitudes to help relieve symptoms. The activation of distal branches of the sacral nerve by different stimulation combinations of the four-electrode lead is not well understood. In this study we are collecting external anal sphincter (EAS) electromyography (EMG) with standard needle electrodes during the lead placement surgery. We

apply monopolar and bipolar stimulation at increasing amplitudes as referred to the threshold amplitudes per electrode. Across five female participants we have observed EAS EMG responses transition from single peak responses to multi-peak responses as the stimulation amplitude is increased above threshold. Bipolar stimulation tends to elicit more multipeak EMG responses than monopolar stimulation suggesting that bipolar stimulation drives greater activation of the sacral nerve. These preliminary results indicate that SNM can lead to varying EAS responses across patients, which may be a factor of the relative lead to nerve distances. This study may provide further insights into variations in SNM outcomes across patients and help guide further therapy development.

Disclosures: B. Vandegrift: None. **M.S. Nissen:** None. **M. Moore:** None. **P. Chen:** None. **P. Gupta:** None. **T.M. Bruns:** None.

Poster

PSTR080: Urinary, Gastrointestinal, and Renal Regulation

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR080.02/I6

Topic: F.06. Autonomic Regulation

Title: Mapping urethra responses to sacral nerve stimulation during electrode implant surgery

Authors: M. S. NISSEN[1], B. VANDEGRIFT[2], M. MOORE[1], P.-J. CHEN[1], P. GUPTA[3], *T. BRUNS[1];
[1]Biomed. Engin., [3]Urology, [2]Univ. of Michigan, Ann Arbor, MI

Abstract: Sacral neuromodulation (SNM) is a standard third-line treatment for overactive bladder, urinary incontinence, and fecal incontinence. In SNM a four-electrode lead is placed along a sacral nerve to apply continuous stimulation at a comfortable amplitude. The underlying mechanisms for SNM benefits are not well understood but are known to involve aspects of sensory and motor pathway activation. In this study we are collecting and analyzing changes in urethra activity in response to sacral nerve stimulation during lead implant surgery. We record lower urinary tract pressures with a multi-site pressure catheter inserted into the urethra and bladder. During pauses in the lead placement surgery, we perform monopolar and bipolar sacral nerve stimulation at varying amplitudes. We have collected data from five female participants so far. We have observed larger urethra pressures at higher stimulation amplitude and different evoked pressure responses in the proximal urethra as compared to the distal urethra. In addition, we have seen that bipolar stimulation has a larger urethra pressure response, indicating that bipolar may better recruit sacral nerve fibers. These preliminary results indicate that SNM can have a varying impact across the lower urinary tract at stimulation amplitudes at and above perceptible levels. This study may provide further insights into underlying mechanisms of SNM and help guide further therapy development.

Disclosures: M.S. Nissen: None. **B. Vandegrift:** None. **M. Moore:** None. **P. Chen:** None. **P. Gupta:** None. **T. Bruns:** None.

Poster

PSTR080: Urinary, Gastrointestinal, and Renal Regulation

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR080.03/I7

Topic: F.06. Autonomic Regulation

Support: NIH OT2OD028191

Title: The effects of pudendal nerve stimulation on the lower urinary tract during urodynamics

Authors: *A. LAGUNAS[1], P.-J. CHEN[1], P. GUPTA[2], T. M. BRUNS[1];
[1]Biomed. Engin., [2]Urology, Univ. of Michigan, Ann Arbor, MI

Abstract: Chronic pelvic pain (CPP) and lower urinary tract symptoms (LUTS) like overactive bladder and incontinence are major health issues that can have a severe impact on quality of life. Pudendal nerve stimulation (PNS) is an off-label treatment for LUTS and CPP that can help individuals who fail to respond to more conservative therapies. While several studies have shown the effectiveness of PNS at reducing symptoms, there is limited literature on the direct effects of PNS in humans on the lower urinary tract (LUT). In this study we evaluate the physiological changes in the LUT during PNS in humans using a manometry catheter that enables the recording of pressure along multiple parts of the urethra simultaneously. After the stage II implantation of the PNS lead and implantable pulse generator, participants underwent a flow cystometry exam to investigate bladder function. A pressure sensing manometry catheter was placed in the lower urinary tract alongside a three lumen cystometry/fluid infusion catheter. For each participant a series of PNS trials were performed in which the anode and cathode location, stimulation amplitude, and stimulation frequency were changed along with bladder volume. We identified 5-second average pressure changes of at least 5 cmH2O from the pre-stimulation baseline. We have performed 164 PNS trials in 13 participants (11 female) and observed varying responses. We identified bladder pressure changes in 13 trials, proximal urethra changes in 50 trials, and distal urethra changes in 24 trials. The pressure change caused by stimulation was the most varied in the proximal urethra. There were no statistically significantly differences between pressure changes at low (2-5 Hz) and high (31-33 Hz) frequencies. While data analysis is ongoing, it is evident that PNS can have varying effects on the LUT. In particular we can see clear differences in activation of the proximal and distal portions of the urethra. Future analysis will investigate the impact of bladder volume and electrode to nerve distance on LUT activation. This study may give insights into PNS mechanisms and inform improvements in stimulation program selection.

Disclosures: A. Lagunas: None. **P. Chen:** None. **P. Gupta:** None. **T.M. Bruns:** None.

Poster

PSTR080: Urinary, Gastrointestinal, and Renal Regulation

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR080.04/I8

Topic: F.06. Autonomic Regulation

Support: R21 NS116574
Noah's hope hope4briget
Department support from the pediatric department

Title: Gene therapy prevents bowel dysmotility and enteric neuron degeneration in lysosomal storage disorders

Authors: *E. ZIOLKOWSKA[1], M. JANSEN[1], L. WILLIAMS[1], S. WANG[1], B. EULTGEN[1], K. TAKAHASHI[1], H. R. NELVAGAL[2], J. SHARMA[1], M. SARDIELLO[1], J. R. GRIDER[3], M. SANDS[1], R. O. HEUCKEROTH[4], J. D. COOPER[1];
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Abstract: Children with neurodegenerative disease often have debilitating gastrointestinal (GI) symptoms. We hypothesized that this may be due at least in part to underappreciated involvement of neurons in the enteric nervous system (ENS), the master regulator of bowel function. We investigated bowel transit and contractility in mouse models of CLN1 and CLN2 disease, two early onset forms of Neuronal Ceroid Lipofuscinosis (NCLs). These are fatal lysosomal storage disorders caused by deficiencies in palmitoyl protein thioesterase-1 (PPT1) and tripeptidyl peptidase-1 (TPP1), respectively. We explored bowel transit and contractility, and the integrity the ENS in immunostained bowel wholemount preparations from these mice. Lastly, we administered adeno-associated viral gene therapy in different time point to neonatal mice and determined if this would treat these newly identified bowel phenotypes. Mouse models of CLN1 and CLN2 disease, both displayed slow bowel transit that differed in the timing of its onset. Organ bath preparations from CLN1 mice showed altered small intestine contractility, suggesting that bowel dysfunction is intrinsic to the bowel rather than secondary to CNS degeneration. Although the ENS appeared to develop normally in both mouse models, there was a progressive and profound loss of myenteric plexus neurons accompanied by changes in enteric glia. These effects differed in extent between bowel regions, with patches of neuron loss associated with downregulation of GFAP expression by enteric glia, and activation of bowel macrophages. Systemic reconstitution of PPT1 and TPP1 activities by neonatal intravenous administration of AAV-mediated gene therapy prevented bowel transit defects and prevented the loss of many ENS neurons, and significantly extended lifespan. Treatment after weaning was less effective, but still extended lifespan in CLN1, but not CLN2 mice, which die from fatal seizures as their brains are untreated. Our data reveal that in NCL mouse models progressive neurodegeneration of enteric neurons occurs, but this can be treated by gene therapy preventing bowel transit

defects and extending lifespan. This study may have general therapeutic implications for many inherited neurodegenerative disorders in which GI symptoms are present.

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Poster

PSTR080: Urinary, Gastrointestinal, and Renal Regulation

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR080.05/I9

Topic: F.06. Autonomic Regulation

Support: USC Neurorestoration Center
Hellman foundation

Title: Decoding micturition from the brain and spinal cord using functional ultrasound imaging (fUSI)

Authors: S. SAKELLARIDI[1], Y. LO[2], D. J. LEE[3], K. A. AGYEMAN[1], K. WU[3], E. KREYDIN[3], A. ABEDI[3], J. RUSSIN[3], H. ZHONG[4], V. EDGERTON[5], C. LIU[3], *V. CHRISTOPOULOS[1];
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Abstract: Micturition characterizes the process in which neural pathways coordinate the activity of smooth muscles in thebladder to expel urine. Diseases or injuries of the nervous system can cause the re-emergence of involuntaryurination, leading to urinary incontinence (UI). Elucidating the functional circuities in normal bladder control is keyto identifying abnormalities in UI patients. This study sought to utilize functional ultrasound imaging (fUSI) tocharacterize the brain and spinal cord hemodynamics in response to micturition in rats. We acquired power Dopplerimages of the brain and spinal cord while filling the bladder with saline. After inducing anesthesia, five and eight12-14 week-old female Sprague-Dawley rats underwent craniotomy and laminectomy, respectively, and were usedfor brain and spinal cord imaging. The craniotomy was sufficient to encompass the frontal cortex, midlinediencephalic structures, midbrain, and parts of the cerebellum, and the multi-level laminectomy at T12-L2 exposedthe lumbosacral spinal cord. These windows allowed the position of the ultrasound probe in a sagittal plane

Atransducer was inserted and secured to the bladder dome to record the pressure dynamics. A catheter connected toan infusion pump was inserted in the same location to fill the bladder with saline at a constant rate of 0.1 ml/min.We acquired fUSI images from the brain and the spinal cord for 50 minutes during which the animals werespontaneously voiding. We identified region-specific hemodynamical changes on the brain and spinal cordassociated with bladder pressure changes during voiding. Particularly, we found regions in the thalamus, basalforebrain, and neocortex (specifically the prefrontal and retrosplenial cortices, e.g., animals R2 and R5), as well asin the dorsal and ventral part of the spinal cord that are the most vascularly coupled with bladder states. We furtherextended these results to predict an impending voiding. We used principal component analysis (PCA) as a featureextraction to optimally discard shared information between the two classes (class 0: pre-voiding, class 1: voiding).We then used linear discriminant analysis (LDA) and found that the spinal cord PCA-transformed images predictan impending voiding with cross-validated accuracy ~90% about 4 seconds before the actual voiding, whereas thePCA-transformed images from the brain predict an impending voiding ~80% about 3 seconds before the actualvoiding. These results provide the first proof-of-concept that fUSI is a viable modality for developing ultrasonicspinal cord machine interface technologies to restore bladder function in patients with urinary incontinence (UI).

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Poster

PSTR080: Urinary, Gastrointestinal, and Renal Regulation

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR080.06/I10

Topic: F.06. Autonomic Regulation

Support: R01DK133605

Title: Cytometry markers for predicting chronic bladder function post-spinal cord injury: Insights from Awake Animal Models

Authors: *B. AFRASHTEH[1], S. KHAN[2], R. ADURY[3], Z. C. DANZIGER[4,5];
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Abstract: The lower urinary tract (LUT) is controlled by complex peripheral and central nerve systems. Spinal cord injury (SCI) can disrupt these systems, causing neurogenic bladder overactivity and complications such as renal impairment and urinary tract infections. Treatment is usually required to maintain low bladder pressure, prevent leakage, and ensure complete

voiding. Given the irreversible nature of many bladder function changes post-SCI, early prognosis of long-term bladder function is essential for patient counseling and treatment planning. This study aimed to understand and compare LUT function post-SCI at subacute and chronic phases. Approximately 5000 voiding events in 12 rats were recorded and analyzed. Rats were implanted with indwelling bladder catheters and underwent either spinal transection at the T8-T9 segmental level (n=10) or sham surgery (n=2).Bladder function was evaluated using metabolic cages, urodynamic assessments, and algorithmic estimations of voiding parameters, with continuous monitoring of voided volumes, bladder pressures, and other urodynamic signals 24h/day for 21-28 days post-implantation. Comparative analyses of urodynamic parameters were conducted between the early subacute phase (7-8 days) and the chronic phase (21-28 days) post-injury. The results indicated overactive bladder in SCI rats during the chronic phase, with or without detrusor-sphincter dyssynergia. Based on the bladder function of the SCI rats in the chronic phase, rats with voiding efficiency (VE) below 70% during the chronic phase and an increase in bladder pressure from the subacute to chronic phase were identified as high-risk. Conversely, rats with a VE exceeding 70% and a decrease in bladder pressure were identified as low-risk. Comparison of urodynamic parameters between these groups in the subacute phase highlighted significant differences in bladder capacity. The low-risk group had an initial low bladder capacity during the subacute phase, which was compensated by enhanced VE and lower bladder pressure in the chronic phase. The high-risk group with high bladder capacity during the subacute phase exhibited deterioration. The higher initial bladder capacity in the high-risk group may correlate with heightened thresholds for volume and tension perception post-SCI, potentially influenced by C-fiber afferents, prompting voiding at higher bladder capacities, or it may involve alternative structural and neurological mechanisms. These observations highlight the potential effectiveness of early interventions targeting neurological and structural bladder changes during the subacute phase of SCI to improve long-term bladder outcomes.

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Poster

PSTR080: Urinary, Gastrointestinal, and Renal Regulation

Location: MCP Hall A

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Topic: F.06. Autonomic Regulation

Support: NIH Grant DK134431
NIH Grant DK119183

Title: Sk2 overexpression attenuates pain-like behavior in mice subjected to chemical cystitis

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Abstract: Small-conductance Ca^{2+}-activated K^+ (SK) channels are widely expressed in neurons and play fundamental roles, including the control of neuronal excitability through the regulation of action potential firing. In this study, we investigated the contribution of SK channels to the development of pain-like behavior in a murine model of chemical-induced cystitis. Gene expression analysis showed that *Kcnn2* (SK2) is the most abundant isoform expressed in lumbosacral (L6-S2) dorsal root ganglia (DRG). Immunofluorescence *in situ* hybridization (immuno-FISH), combined with retrograde tracing using cholera toxin β subunit, revealed that 92% of bladder DRG neurons express *Kcnn2*. To assess whether SK channels regulate bladder sensory neuron excitability, we examined the firing evoked by an electrical pulse train under control conditions and in the presence of apamin (100 nM), a specific inhibitor of SK1, SK2, and SK3 channels. We found that inhibition of SK channels during sustained electrical stimulation cause a statistically significant increase in bladder sensory neuron spike firing. To assess whether SK2 channels modulate the behavioral response to chemical cystitis, we evaluated voiding and pelvic sensitivity to von Frey filaments in control and transgenic mice overexpressing SK2 ($SK2^T$), treated with either vehicle (saline) or the chemotherapeutic drug cyclophosphamide (CYP; 80 mg/kg every other day for a week). We noticed that $SK2^T$ and control littermate mice treated with CYP exhibit frequent urination with voiding events of smaller volume than mice that received saline. However, no obvious difference in urinary frequency or voided volume was observed between the control group and the $SK2^T$ group treated with CYP. Of note, while control littermate mice treated with CYP exhibited pelvic allodynia, CYP-treated $SK2^T$ mice showed no change in pelvic sensitivity when compared to the group treated with saline. These findings indicate that the overexpression of SK2 channels alleviates pain-like behavior in mice with chemical cystitis. Taken together, our study suggests that SK2 channels regulate the transmission of nociceptive information originating from the bladder to the supraspinal level.

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Poster

PSTR080: Urinary, Gastrointestinal, and Renal Regulation

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Program #/Poster #: PSTR080.08/I12

Topic: F.06. Autonomic Regulation

Support: NIH Grant R01HL166464
NIH Grant R03AG072016
NIH Grant R01DK125543

Title: Chronic neuroendocrine stress causes urinary bladder wall hypertrophy and overactive voiding behavior

Authors: *J. HUSAIN, A. K. PACE, A. BAKHAREVA, H. C. FALLON, M. F. NOTERMAN-SOULINTHAVONG, G. M. HERRERA, T. HEPPNER, B. ERDOS;
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Abstract: Chronic stress can lead to urinary bladder dysfunction through mechanisms induced locally and in the central nervous system. Prolonged upregulation of brain-derived neurotrophic factor (BDNF) in the paraventricular nucleus of the hypothalamus (PVN) has been shown to chronically elevate activities of all major stress pathways including the sympathetic nervous system, the hypothalamus-pituitary-adrenal axis and vasopressin (AVP) signaling. Taking advantage of these actions of BDNF, we created a novel model of chronic neuroendocrine stress by subjecting male Sprague Dawley rats to bilateral PVN injections of AAV2 viral vectors expressing either BDNF or GFP (for control). Non-invasive voiding behavior tests were conducted for 48h at weeks 3 and 8 post vector injections. In addition, bladder strip myography and Masson's trichrome histology were conducted on isolated bladder samples at week 14 post injections.

Hypothalamic overexpression of BDNF led to an emerging overactive bladder phenotype at week 3 that got progressively worse by week 8 after vector injections. Remarkably, BDNF rats showed a significantly higher number of urinary voids per hour (2.56±0.46) vs GFP (1.25±0.24, $p<0.001$) and lower average void volume (0.27±0.07 ml) vs GFP (1.19±0.15 ml, $p < 0.01$). Moreover, bladder strip myography indicated significantly higher contractility in the BDNF group in response to high K^+ concentration (GFP: 2.32±0.17 g, BDNF: 3.18±0.22 g, $p < 0.01$) and electric field stimulation (GFP: 2.43±0.23 g, BDNF: 3.40±0.24 g, $p < 0.01$), and histological analysis revealed marked smooth muscle hypertrophy and widened lamina propria in BDNF vs GFP rats. Additional findings indicated that activation of AVP signaling may play a role in the observed changes. Daily urine output was significantly lower in BDNF (14.82±2.18 ml) vs. GFP rats (33.85±4.94 ml, $p < 0.01$) with no difference in water intake. Plasma AVP levels were also elevated in BDNF rats at week 14 post injections, whereas AVP-induced bladder strip contractions were significantly reduced in BDNF vs GFP rats indicating potential AVP-induced AVP receptor desensitization.

In conclusion, we demonstrated that using our novel model of chronic neuroendocrine stress, we could emulate overactive bladder syndrome, a common complication in humans experiencing chronic stress. Our results suggest that bladder wall hypertrophy and increased contractility may play significant roles. Upregulation of AVP and literature evidence for smooth muscle hypertrophic actions of AVP imply that this hormone may be a key mediator in stress-induced bladder dysfunction.

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Poster

PSTR080: Urinary, Gastrointestinal, and Renal Regulation

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR080.09/I13

Topic: F.06. Autonomic Regulation

Title: Impact of proximal vs. distal tibial nerve stimulation on bladder function in female rats

Authors: *N. SLAVIK[1], J. A. HOKANSON[2];
[1]Med. Col. of Wisconsin, Milwaukee, WI; [2]Biomed. Engin., Med. Col. of Wisconsin, Milwaukee, WI

Abstract: Stimulation of the tibial nerve near the ankle has been shown to improve bladder function in
both animals and people. We are interested in pursuing studies of chronic tibial nerve stimulation in animals, to understand better mechanisms of action. Stimulation at a location proximal to the knee may provide a structural advantage for a chronic implant, but the impact of stimulating the tibial nerve at a more proximal location is unknown. To investigate this, 10 healthy female CD rats were anesthetized with urethane (1.2-1.6 g/kg). Bladders were instrumented with a catheter placed in the dome of the bladder which was connected to an infusion pump and an in-line pressure sensor. Rats were randomly divided into two groups and their tibial nerves instrumented with a MicroLeads nerve cuff at either the medial malleolus (ankle, distal location, 500 μm internal diameter) or just distal to sciatic nerve branching (proximal location, 600 μm internal diameter). Following implantation, rats underwent 5 control cystometry trials. Bladders were filled at a constant rate per animal (4-12 ml/hr) until voiding occurred. Voided and residual volumes were collected and used to calculate bladder capacity and voiding efficiency. Either proximal or distal tibial nerve stimulation (prox-TNS and dist-TNS)
was delivered at an amplitude of three times the threshold of observable motor twitch of the toe for 30 minutes at 10 Hz and 200 μs pulse width. After stimulation 5 cystometry trials were conducted. Post-stimulation increased bladder capacity by 35±12.9% (P=0.00095 n=5, t-test) and 20±10.1% (P=0.0044, n=5, t-test) for proximal and distal tibial nerve stimulation respectively
compared to pre-stimulation averages. Voiding efficiencies did not change (prox-TNS: P = 0.26; dist-TNS: P=0.25, t-tests). Despite larger increases in capacity from prox-TNS compared to dist-TNS, this difference was not statistically significant (P=0.0577, t-test). These results provide evidence that proximal tibial nerve stimulation, at least in our animal model, is as effective as the current clinical approach of stimulating the distal tibial nerve.

Disclosures: N. Slavik: None. **J.A. Hokanson:** None.

Poster

PSTR080: Urinary, Gastrointestinal, and Renal Regulation

Location: MCP Hall A

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Program #/Poster #: PSTR080.10/I14

Topic: F.06. Autonomic Regulation

Support: CONAHCYT AFH 1157306
CONAHCYT CQDL 1311312

Title: Electrical activity of the external urethral sphincter in response to mechanical stimulation of the rabbit urogenital tract: Effect of L6-S2 ventral root avulsion

Authors: *A. A. F. H. FLORES HERNANDEZ[1], Z. FLORES LOZADA[2], O. SANCHEZ GARCIA[2], Z. RENE[2], F. CASTELÁN[3], M. MARTINEZ-GOMEZ[3], D. L. CORONA QUINTANILLA[2];
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Abstract: The spinal cord plays a crucial role in processing stimuli. At the lumbosacral (L6-S2) that affect the functions of the lower urinary tract and the pelvic floor muscles are regulated. Nerve roots are susceptible to damage, such as stretching or avulsion, which can disrupt communication between the central nervous system and effects, such as the pelvic floor muscles. An important muscle for urinary continence is the external urethral sphincter (EUS). In rabbits, this muscle is activated during urine storage and inhibited during expulsion, similar to women without spinal cord injuries. In various species, sensory stimulation has been shown to influence the function of the pelvic viscera. This study aimed to determine the activity of the external urethral sphincter during stimulation of the rabbit urogenital tract and the effect of avulsion of the L6-S2 ventral root. To this end, electromyogram recordings were performed in anesthetized rabbits to record the activity of the external sphincter of the urethra in response to mechanical stimulation of the bladder, urethra (proximal, medial, and distal), as well as the perigenital skin, perineal vagina, pelvic and abdominal. The results showed that stimulation of the proximal urethra and pelvic vagina caused greater EEU activity compared to other areas. After L6-S2 ventral root injury, stimulation of the pelvic vagina generated only a few bursts of EUS reflex activation. Possibly, at the level of the proximal urethra, as well as the pelvic vagina, more sensory receptors are located that allow the reflex activation of the external sphincter of the urethra to exert greater force at this level to maintain urethral closure, and avoid episodes of expulsion of involuntary micturition.

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Poster

PSTR080: Urinary, Gastrointestinal, and Renal Regulation

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Title: Neuroanatomy of the lower urinary tract in female mice C57BL

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Abstract: A high incidence of lower urinary tract (LUT) disorders is associated with aging, reproductive processes, neurodegenerative diseases, and obesity. The rodents are the ideal model for understanding the pathophysiology of urinary incontinence, but despite mice being the most used animal model for urological studies, there is not a complete description of the LUT. The aims were to identify the neuroanatomy of the LUT in female mice and measure the zoometric parameters. In 5 adults female C57BL mice were used. Experiment 1 was executed to characterize the LUT, its anatomical relationships with genital structures, peripheral neural circuitry, and obtention of the metabolic parameters. Experiment 2 was in-blok acetylcholinesterase histochemistry (AchE) of the LUT. Results: The urinary bladder was 0.85±0.08 and 0.57±0.06 cm in length and width. The urethra was 1.1±0.2 and 0.069±0.0004 mm in length and width. In the supine position, part of the urethra can be visualized rostral to the pelvic bone (0.29±0.1). The rest of the urethra ran straight ventrocaudally to the pelvic cavity (0.2±0.05) and then to the perineal region, passing between the ducts of the preputial glands and opening in the urinary meatus (0.6±0.1cm). The nerves run adjacent to blood vessels, arriving at the rostral region of the urethra and originating from the major pelvic ganglia (MPG). Nearby nerves are the motor branch of the pudendal nerve (MBPN) and the sensory branch of the pudendal nerve (SBPN). The former spreads out to the distal region of the urethra and the clitoris, and the latter sends fibers to the pelvic region of the urethra. The AchE corroborates the neural circuitry observed. Dorsal dissection showed that the L6-S1 trunk arises from the pudendal and pelvic nerve and has at least two variants of the formation of the L6-S1 trunk. In 60% of the animals, the pelvic nerve arises from the spinal nerve S1. In the other 40% of animals, the pelvic nerve generates a main trunk L6-S1. In both neuroanatomical variants, the pelvic nerve bifurcates; one branch innervates the iliococcygeus and pubococcygeus muscle and the other branch enters the MPG. The SBPN originates in the pudendal nerve, enters the ischiorectal fossa, course dorsal to the ischium. The MBPN originates at the lumbosacral plexus and courses below the ischium, next to the SBPN. The MBPN innervates the external urethra sphincter and external anal sphincter. Zoometrics parameters. Weight at 34.2±3.3 g. The glucose, cholesterol, and triglycerides were 226.3±50.6, 158±9.8, and 296.7±30 mg/dL, respectively. Conclusion: These studies have pioneered descriptive neuroanatomy in the LUT in female mice.

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Poster

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Title: Role of GABAergic periaqueductal gray neurons for the maintenance of urinary continence

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Abstract: In continent adults, the switch between storage and voiding of urine is under direct control of the central nervous system. Afferent sensory information from the bladder is sent to the periaqueductal gray (PAG), and from here is relayed to higher cortical and subcortical areas that will ultimately decide on appropriateness of urination (e.g., bladder fullness, socially acceptable and safe location). The PAG has strong connections with the pontine micturition center (PMC), and activation of the PMC leads to voiding. When urination is not deemed appropriate, it is essential that continence is maintained. It is currently not clear whether storage of urine during these moments is facilitated by active neuronal suppression of the PMC or if the absence of excitation of PMC neurons is sufficient to prevent involuntary loss of urine. In the current project, we used chemogenetic manipulation of GABAergic PAG neurons in mice to assess whether these neurons directly influence continence and voiding behavior, and we recorded neuronal dynamics in neurons in specific locations in the PAG. We hypothesized that chemogenetic silencing of GABAergic PAG neurons, specifically those that respond to bladder filling and voiding, decreases the inhibition of PMC and leads to increased voiding frequency and an incontinent behavioral phenotype.We performed bilateral injections with Cre-dependent Designer Receptors Exclusively Activated by Designer Drugs (DREADDs) in the PAG of Vgat-ires-Cre/+ mice (n=3). Mice were subjected to micturition video thermography (MVT) measurements. In short, mice were volume loaded with 1ml dextrose 5% in water and micturition behavior was recorded using a thermal camera for a 2-hour period. Animals were run twice after injection with vehicle (NaCl 0.9%), and twice after injection with a DREADDs agonist (Compound 21 (C21), 1mg/kg) on sequential days. Number of continent voids and number of leaks were analyzed and quantified from the MVT recordings, and statistically compared between vehicle and C21 runs.The number of voids per 2 hours did not statistically differ between vehicle and C21 runs ($p \geq 0.05$), while the number of leakage episodes per 2 hours significantly increased after administration of C21 compared to vehicle ($p=0.031$).The results indicate that in the absence of activity of GABAergic PAG neurons, mice exhibit an incontinent behavioral phenotype. Indicating that activity of these neurons is necessary to prevent the involuntary loss of urine. Observed direct projections from GABAergic PAG neurons to PMC suggest that these PAG neurons may contribute to the maintenance of continence through direct inhibition of PMC neurons.

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Poster

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Topic: F.06. Autonomic Regulation

Support: Faculty of Health, Medicine and Life Sciences of Maastricht University

Title: Functional mapping of the human brainstem using ultra-high field 7T fMRI

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Abstract: The neocortex has traditionally been the main focus of brain mapping approaches using structural and functional neuroimaging. A common approach involves the utilization of graph theory-based parcellation algorithms, such as the Louvain method for community detection, on resting-state functional magnetic resonance imaging (fMRI). Similarities between ex vivo brain mapping approaches using cytoarchitectic or myeloarchitectonic approaches have been established. The emergence of ultra-high field fMRI and the improved spatial resolution and signal-to-noise ratio enable the utilization of these parcellation algorithms to the brainstem. In the current project, we parcellated the midbrain periaqueductal gray (PAG) based on intrinsic resting-state functional connectivity as well as based on functional connectivity patterns with Barrington's nucleus (a pontine region with strong structural and functional connectivity with the PAG). We expected that, the intrinsic parcellation approach would reliably subdivide the PAG into functional clusters and these clusters would have unique functional interaction patterns with Barrington's nucleus, therefore both approaches would yield functional clusters with significantly similar spatial distribution. Resting-state fMRI data was acquired for 8 adult female participants. The PAG was intrinsically parcellated into clusters using the Louvain module detection algorithm, resulting in 3 clusters per participant. To parcellate the PAG based on interaction with Barrington's nucleus, the mean fMRI signal of Barrington's nucleus was correlated with the fMRI signal of every voxel in PAG. PAG voxels were subsequently categorized into three groups: the most negative, the weakest, and the most positive one-third of correlation coefficients per participant. Spatial organization of clusters resulting from both parcellation approaches were then statistically compared within each participant, and significance was assessed. In all participants, clusters resulting from both parcellation approaches show a significantly similar spatial organization within the PAG ($p<0.05$ (corrected

for multiple comparisons)). These results indicate that brainstem structures can reliably be parcellated using the Louvain module detection algorithm, and that clusters resulting from this parcellation approach can have unique interaction patterns with other brain areas. These findings facilitate functional mapping of the brainstem and provide the necessary advancements to investigate functional activity and connectivity patterns for sub-regions of brainstem structures using ultra-high field neuroimaging methods.

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Poster

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Title: Molecular characterization of the spinal circuitries controlling lower urinary tract function

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Abstract: Lower urinary tract function (LUTF) is a complex physiological process involving the coordination of somatic and autonomic nervous systems. Efficient bladder storage and voiding rely on the precise interaction of various brain and spinal nuclei. Despite its clinical significance, the specific spinal cord neurons contributing to LUTF remain poorly characterized, presenting a barrier to targeted therapeutic interventions. This study aims to identify and characterize these spinal cord neurons. Adult TRAP2::H2B-Trap transgenic mice of both sexes were implanted with a catheter in the bladder dome. The open end of the catheter was tunneled to the back of the neck and connected to an infusion harness. After a one-week recovery period, saline was infused into the bladder of awake mice at 20 µl/min for 2 hours. 4-Hydroxytamoxifen (4-OHT, 50mg/kg) was injected *i.p.* and infusion continued for 2 more hours. One week after the experiment, the animals were sacrificed, and spinal cords collected to be either used for histological examination or single-nuclei RNA-sequencing (snRNA-seq). For snRNA-seq, single-nuclei suspensions were prepared by dounce homogenization, followed by a density gradient to remove myelin and debris. Fluorescence-activated nuclei sorting (FANS) was used to sort labelled nuclei before transcriptional profiling using the 10x Genomics single-cell gene expression assay. Continuous fill/void cycles elicited robust cFos expression in the lumbosacral spinal cord, with notable enrichment in the dorsal gray commissure (DGC) and intermediolateral cell column (IML). The TRAP2::H2B-Trap transgenic mouse model resulted in a more restricted labelling within the same regions, indicating that a strong stimulation is required after 4-OHT to induce

recombination and labelling of activated neurons. FANS of single nuclei facilitated the isolation of high-quality nuclei from both thoracic (T8-T13) and lumbosacral (L1-S3) segments. Unsupervised clustering analysis identified distinct populations of active neurons, comprising 28 clusters in the thoracic and 35 clusters in the lumbosacral segments, many of which are likely implicated LUTF regulation. Our study showcases the utility of the TRAP2::H2B-Trap transgenic mouse model in elucidating the molecular identity and, possibly, the functional role of spinal neurons involved in LUTF. These findings significantly contribute to our understanding of LUTF neurobiology in mice and lay the foundation for comparative investigations in humans, with implications for the development of targeted therapies aimed at addressing lower urinary tract dysfunction.

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Poster

PSTR080: Urinary, Gastrointestinal, and Renal Regulation

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Topic: F.06. Autonomic Regulation

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Title: Regulation of phasic smooth muscle contractions of mouse urinary bladder by Cl- channels and G-protein coupled receptors

Authors: *J. L. RENGO[1], H. C. FALLON[2], T. HEPPNER[3], G. W. HENNIG[1], M. T. NELSON[4], G. M. HERRERA[1];
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Abstract: Detrusor smooth muscle (DSM) of the bladder exhibits spontaneous action potentials that can be propagated in waves to produce phasic “non-voiding” contractions, called transient pressure events (TPE). These TPE drive sensory output from the bladder through bursts of afferent nerve activity during bladder filling. Calcium-activated chloride channels (Ca_{Cl}) modulate membrane potential and regulate smooth muscle excitability in other tissues, while G protein-coupled receptors (GqPCR) influence bladder contraction and relaxation. The purpose of this study was to determine the role of Ca_{Cl} and GqPCR on TPE in the isolated perfused mouse urinary bladder. We hypothesized the Ca_{Cl} blocker benzbromarone and GqPCR inhibitor YM-254890 (YM) would abolish bladder TPE and decrease Ca^{2+} activity. Urinary bladders were isolated from male C57Bl6/J mice (8-12 weeks, 23.2-24.5 g body weight) and B6-GC6f x SMMHC-CreER^{T2} (12-14 months, 29.0-31.4 g body weight). Ureters were tied off, the bladder was cannulated through the urethra, and submerged in an organ bath containing physiological saline solution (37 °C, pH 7.4). The bladder was attached to a syringe pump and inline pressure transducer to infuse at a constant rate of 1.8 mL/hr while recording intraluminal

pressure. Bladders were filled to 80% capacity and TPE allowed to stabilize for 30 minutes. TPE were recorded in the absence and presence of YM (500 nM) or benzbromarone (10 μM) and were analyzed with Spike2 software (Cambridge Electronic Design). Data are presented as mean ± SEM and statistical analysis was performed with paired t-tests. Under baseline conditions, TPE occurred at a frequency of 4.9 ± 0.4 events per minute. Inhibition of Ca_{Cl} with benzbromarone decreased TPE frequency to 2.6 ± 0.9 events per minute (n=5, p=0.09). Similarly, benzbromarone decreased TPE amplitude from 0.67 ± 0.15 mmHg to 0.22 ± 0.05 mmHg (n=5, p=0.02). Additionally, inhibition of GqPCR with YM decreased TPE frequency from a baseline value of 5.8 ± 1.6 events per minute to 2.0 ± 2.0 events per minute (n=2, p=0.27) and amplitude from 0.98 ± 0.75 mmHg to 0.07 ± 0.07 mmHg (n=2, p=0.41). Using wide field fluorescent microscopy, visual analysis revealed striking reductions in Ca^{2+} activity with both YM (n=2) and benzbromarone (n=1). In summary, we found that YM and benzbromarone disrupted TPE frequency, amplitude, and Ca^{2+} signaling. This suggests both GqPCR and Ca_{Cl} play a role in generating rhythmic DSM contractions. A connection between GqPCR and Ca_{Cl} remains to be explored. This work was supported by a grant from the National Institute of Diabetes and Digestive and Kidney Diseases (R01DK125543).

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Poster

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Topic: F.06. Autonomic Regulation

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Title: The effect of high frequency sacral root stimulation on lower urinary tract function in awake, healthy animals

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Abstract: Many individuals with spinal cord injury or other neurological disorders that affect lower urinary tract function require the use of a catheter to empty their bladder. Using a catheter is associated with risks of urethral trauma and urinary tract infection, and approaches that would eliminate the need for catheters are a high priority for these individuals. Reduction of urethral sphincter pressure may have the potential to promote bladder emptying without catheters. Peripheral nerve stimulation at frequencies of 500-10,000 Hz is associated with reduction of muscle contraction without causing muscle fatigue. We hypothesized that high frequency stimulation of the sacral roots, which include neurons that innervate the lower urinary tract, would be associated with reduced urethral pressures without also reducing bladder pressures. In this study, we implanted five healthy cats with nerve cuff electrodes bilaterally on sacral roots S1 and S2, which were connected to wireless implantable pulse generators that also measured pelvic floor electromyogram (EMG). Pelvic floor EMG acted as a proxy measure for urethral sphincter activity. We also implanted the Urological Monitor of Conscious Activity (UroMOCA), which is a wireless bladder pressure and volume sensor. During sessions wherein the animals were awake and behaving, we applied stimulation at frequencies of 20 Hz, 500 Hz, or 10 kHz, and amplitudes up to the tolerance limits of each animal. The stimulation was tolerated well by the subjects. Stimulation at a frequency of 10 kHz was associated with a 19% reduction in EMG amplitude compared to stimulation at 20 Hz ($p < 0.001$), suggesting blockade of the nerves that control the pelvic floor muscles. Stimulation at 500 Hz appeared to also result in reduced EMG responses compared to 20 Hz, but this difference was not significant. Bladder pressures were sometimes increased at stimulation amplitudes near the tolerance limit, regardless of stimulation frequency. These data indicate that high frequency sacral root stimulation has the potential to reduce pelvic floor activity and may also reduce urethral sphincter pressure in order to achieve catheter-free bladder emptying for individuals with neurologically-driven urethral sphincter overactivity.

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Poster

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Title: Evaluating the Effects of Slow Wave Abnormalities and Impaired Antral-Pyloric Sphincter Coordination on Gastric Emptying and Stomach Motility Using Compartmental Modeling Framework

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Med. and Rehabil., Harvard Med. Sch., Boston, MA; [3]Dept. of Biomed. Informatics, Emory Univ., Atlanta, GA

Abstract: Introduction Gastric emptying depends on stomach motility which is controlled by rhythmic electrical slow-wave activity from Interstitial Cells of Cajal (ICC) that causes stomach muscle wall contractions. In a healthy stomach, these contractions occur at about 3 cycles per minute (cpm), begin in the corpus of the stomach and propagate to the antrum. The coordination of an open sphincter with antral contractions facilitates emptying, while closure of the sphincter when the slow wave reaches the terminal antrum propels gastric contents for mixing. Motility impairments, such as ectopic pacemakers, can contribute to the etiology of stomach disorders such as functional dyspepsia (FD) and gastroparesis by influencing gastric motility and contributing in symptoms. Dysrhythmias, altering slow-wave frequency, include tachygastria (> 4 cpm) and bradygastria (< 2 cpm). Patients with FD and gastroparesis commonly exhibit abnormalities in peristaltic amplitude. Precise experimental study on stomach motility is challenging, motivating the use of computational approaches. Currently, in silico investigations focusing on dysrhythmias and sphincter coordination demand significant computational resources. To mitigate this computational effort, an efficient compartmental model is proposed, modifying sphincter coordination, slow-wave frequencies, and amplitudes to simulate GI diseases. **Methods** The stomach's spatial geometry is partitioned into four compartments: Proximal/ Middle/ Terminal Antrum, and Pyloric Sphincter, as these segments play pivotal roles in stomach motility during gastric emptying. Each compartment is spatially homogenous and modeled using algebraic or ordinary differential equations (ODEs) simulating electrical, mechanical, and fluid behaviors. The equations for electrical and mechanical behaviors model ICC slow-wave activity and translate it into mechanical contractions using a previously described framework (SFN 2021). For fluid behavior, equations derived from Shapiro et al. (1969), Schlichting (1961) for jet flow, and a squeeze flow equation simulate anterograde and retrograde movements in the stomach. An improved compartmental connectivity enhances the model's capability to simulate both healthy and unhealthy stomach conditions. **Results** The model evaluation encompasses gastric motility, emptying, and mixing efficiency, along with computational time, promising deeper insights into gastric disorders with a computationally efficient framework. The model is solved using an ODE solver in MATLAB and validated against studies such as Ishida et al. (2019), Ebara et al. (2022), and Du et al. (2018) from the literature.

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Poster

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Title: Medullary neuronal groups involved in the sympathetic control of renal function in mice differ from those in rats

Authors: *G. CANO[1], S. L. HERNAN[1], A. F. SVED[1], S. D. STOCKER[2];
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Abstract: Renal sympathetic nerve activity (SNA) is elevated in hypertension and chronic kidney disease. Animal models are extensively used to study the central control of renal SNA, including transgenic mice. We have previously described the central circuitry that controls the kidneys in rats using viral transynaptic tracing with Pseudorabies virus (PRV). In rats, the RVLM contains C1 cells (tyrosine hydroxylase (TH)+) and strongly regulates renal SNA via direct projections to spinal sympathetic preganglionic neurons (SPNs). In this study, we sought to characterize the medullary groups that regulate renal SNA in mice (project directly to SPNs), with emphasis in the RVLM. Male C57Bl6J mice (Jackson Laboratories; n=12) were injected with 2 ul of PRV-152 (expresses GFP) into the kidney and were perfused at different survival times (66-78 hrs). Additional mice (n=4) were injected with 150 nl of 1% CTb in the intermediolateral cell column of T2-T3 and were perfused 1 week later. Brains and spinal cords were removed and processed immunohistochemically to detect PRV-infected or CTb-labeled neurons and to identify their monoaminergic phenotypes. At early survival, medullary infection was restricted to the ventromedial medulla (VMM), mainly the lateral paragigantocellular nucleus (LPGi) (38.9 $\pm$ 2.4% of total brain infected neurons), and caudal raphe nuclei (cRN) (28 $\pm$ 5.1%). At intermediate survival, many infected neurons appeared in LPGi and cRN; a few infected TH+ neurons were observed in LPGi extended (LPGiE) and perifacial zone (P7), medial to the facial nucleus, at Bregma -5.8 to -6.10 mm. These PRV-TH+ cells were located more rostral than the RVLM, were smaller than C1 cells, and represented 2.8 $\pm$ 0.6% of total brain infected neurons. Around 54.3 $\pm$ 3.4% of infected neurons in cRN were serotonergic. At these survivals, there was no infection in the RVLM, which first appeared at 90 hrs post-injection. Most medullary CTb-labeled neurons from spinal injections were observed in VMM and cRN, but none in RVLM. Few CTb-TH+ neurons were found in LPGiE and P7, at the same Bregma levels as PRV-TH+ neurons, and these neurons constituted 22-40% of total TH+ cells in those sections. In marked contrast to rats, both PRV and CTb data show that RVLM neurons do not project directly to SPNs in mice. Instead, VMM (mainly LPGi) and cRN are the major medullary presympathetic groups that regulate renal SNA. Future studies are needed to assess how these medullary groups affect renal SNA and various aspects of renal function such as renin secretion, sodium excretion, glomerular filtration rate, and renal blood flow. Our data suggests that caution is crucial when extrapolating results between rats and mice.

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Poster

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Topic: F.06. Autonomic Regulation

Title: Effects on intestinal motility and acute stress with different euthanasia methods in rats

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Abstract: For research purposes, different methods of euthanasia are carried out on animals for further experimentation and study of varios phenomena *in-vivo* and *in-vitro.* One of the most employed methods of euthanasia in research is CO_2 inhalation. However, in recent years, the collateral effects in terms of physiological and emotional stress in animals have been studied. The combination of anesthesia followed by CO_2 inhalation is an alternative euthanasia method to the exclusive use of CO_2. In the study of the contractile activity of intestinal smooth muscle, different techniques can be used. *In vitro* techniques are spread used in research and teaching for pharmacology, toxicology, or for the study of physiological components related to the autonomic nervous system (sympathetic and parasimpathetic branches) and the enteric nervous system. The present study compares the effects of 3 different euthanasia methods and acute stress on intestinal smooth muscle motility. The experimental groups are 3-month-old female Wistar rats (n=32) divided into 4 groups: euthanasia with CO_2 (32.5 L/min, displacement rate of 30%); anesthesia with pentobarbital (90 mg/kg) followed by CO_2 inhalation (32.5 L/min, displacement rate of 30%); anesthesia with tiletamine-zolazepam (7mg/kg) followed by CO_2 inhalation (32.5 L/min, displacement rate of 30%); pentobarbital overdose 4 times the maximum dose (100 mg/kg). Measurements include recording the strength and frequency of intestinal smooth muscle contractions *in vitro,* through the BIOPAC data acquisition unit and BSL PRO software; and measurement of acute stress blood biomarkers (ACTH, C-reactive protein and lactate). In the case of intestinal tissue, the changes observed may due to a modification in intestinal motility, related to the euthanasia method itself or indirectly, in response to the acute stress presented by the animal after the euthanasia method used. We evaluated through stimulating smooth muscle with agonists drugs (acetylcholine and adrenaline), and in group 2 (pentobarbital + CO_2), the results indicate more strength and frequency of contractions, comparatively to others, while group 1 (CO_2) has the lowest strength and frequency in contractions. Interestingly, group 4 (pentobarbital overdose) showed a reduction in the strength and frequency of contractions, but no more than group 1. These preliminary results to explore and evaluate the effects of euthanasia methods, when isolating the organ *in vitro*. The purpose of this work is to contribute to improving euthansia conditions given to laboratory animals in research and teaching, and in this way, backing better results *in-vitro* intestinal motility in both fields.

Disclosures: M. Enríquez-Betancourt: None. **D.E. Castillo-Rolon:** None.

Poster

PSTR080: Urinary, Gastrointestinal, and Renal Regulation

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR080.20/I24

Topic: F.06. Autonomic Regulation

Support: Fundacao Araucaria PBA2021141000012

Title: High protein diet intake can intensify acute ulcerative colitis induced neuronal changes in the colon mice

Authors: *E. DE ALMEIDA ARAUJO[1], C. C. MACHADO[2], V. B. CORONADO[2], Y. G. SANTOS[2], L. BONASSA[2], A. OBA, Sr.[3], F. GUARNIER[4];
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Abstract: Ulcerative colitis (UC) is an inflammatory disease that causes enteric nervous system (ENS)-related signs and symptoms. Diet is one of the main factors that modulates the UC evolution. Our goal was to investigate the effects of excess protein intake on the colonic ENS during the acute phase of UC. Male C57BL/6 mice were distributed into a group feed with standard diet (SD) and other group feed with high-protein diet (HP). Half of the SD and HP groups were exposed to 3% of dextran sulfate of sodium (DSS) in the drinking water for 7 days to induce acute UC. Mice were monitored to obtain scores to calculate the Disease Activity Index (DAI). Besides, we have counted the number of fecal pellets from each mice during the experiment. Gastrointestinal transit time was determinate by gavage using a non-absorbable colored marker. Proximal and distal colon were collected separately to assay the superoxide dismutase (SOD) and glutathione (GSH) level, to perform histopathological analysis and to analyze general ($PGP9.5^{+}$), nitrergic ($PGP9.5^{+}/nNOS^{+}$) and cholinergic ($PGP9.5^{+}/nNOS^{-}$) in the myenteric plexus (MP) by immunofluorescence. In the submucosal plexus (SMP), neurons were labelled using anti-calretinin (CALR) antibody. Strong and weak CALR+ neurons were considered cholinergic and VIPergic neurons, respectively. Enteric neurons were counted in 32 20X-images and the area of 100 cell bodies were measured from each mice. We observed a DAI score higher in the HP/DSS vs SD/DSS groups from day 3 ($P<0.001$). Fecal pellets reduced mainly in the HP/DSS group ($P<0.01$). SOD was reduced in the distal colon of the HP, SD/DSS and HP/DSS vs SD ($P<0.001$). GSH was reduced in the proximal colon of HP and HP/DSS groups vs SD and SD/DSS ($P<0.01$). Histopathological score of SD/DSS and HP/DSS was higher vs SD and HP ($P<0.001$). Regarding the ENS, no neuronal loss was observed in both SMP and MP. However, in the MP of the proximal colon, general neurons was atrophied in the HP/DSS group vs SD/DSS ($P<0.001$), while nitrergic neurons were larger in the HP, SD/DSS and HP/DSS vs SD ($P<0.001$). In the distal colon, general neurons were larger in the SD/DSS and HP/DSS vs SD and HP ($P<0.001$), while nitrergic neurons were atrophied in the SD/DSS and HP/DSS vs SD and HP ($P<0.01$). Cholinergic neurons were larger in the SD/DSS and

HD/DSS vs SD and HD (P=0.01). Concerning the SMP, neuronal atrophy was found in the proximal colon mainly in the HP/DSS groups and also in the SD/DSS vs HP and SD, respectively (P<0.01). In the distal colon, neuronal atrophy was verified mainly in the SD/DSS group vs controls (P<0.001). We concluded that a high-protein diet intake is able to intensify acute UC-induced neuronal area changes in the colonic ENS.

Disclosures: E. de Almeida Araujo: None. **C.C. Machado:** None. **V.B. Coronado:** None. **Y.G. Santos:** None. **L. Bonassa:** None. **A. Oba:** None. **F. Guarnier:** None.

Poster

PSTR080: Urinary, Gastrointestinal, and Renal Regulation

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR080.21/I25

Topic: F.08. Food and Water Intake and Energy Balance

Support: Toyo Univ. Grant Enryo

Title: Hydrogen rich water, a neuroprotective agent, induces thinning of mucus layer with changes of bacterial flora in the small intestine

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Abstract: Molecular hydrogen (H_2) functions as an antioxidative and anti-inflammatory agent. The routes of H_2 administration can be roughly classified into two types: inhaling H_2 gas and drinking H_2-rich water (HW). We first reported that inhalation of H_2 gas has a marked neuroprotective effect against ischemia-reperfusion injury in the rat brain. On the other hand, drinking HW may alleviate neurodegenerative diseases including Parkinson's and Alzheimer's disease. It also mitigates retinal disorder and mental fatigue in daily life. To further translate these findings into clinical practice, the molecular mechanisms underlying H_2 functions should be elucidated. However, therapeutic effects of H_2 in HW is difficult to be explained by direct free radical scavenging capacity because H_2 exhibits very weak reactivity. Because the gastrointestinal tract is exposed to the highest concentration of H_2 just after drinking of HW, it is possible that H_2 has a direct effect on cells in the gastrointestinal tract and can modulate the gut-brain axis. Recently, we reported that HW suppresses both antigen absorption and dendritic cell (DC) activation in the Peyer's patches (PP) of mouse small intestine. Mucin, a major mucus component, has important functions in defense against foreign antigens, is secreted by goblet cells and degraded by intestinal bacteria such as *Akkermansia muciniphila.* We then investigated the effect of HW on the mucin layer. HW was administrated by gastric gavage once to mice. After 1–6 h, contents in the intestinal tract were collected, and mucin and intestinal bacteria were quantified with colorimetric method and RT-PCR, respectively. Muc2 in fresh frozen sections of the ileum PP was immunostained. Muc2 is a mucin expressed primarily in the small and large

intestine. To confirm *A. muciniphila* as a hydrogen bacterium, fresh feces were incubated in H_2-bubbled medium. Unfortunately, we found that the amount of mucin in the intestinal tract decreased 6 h after HW administration. We also confirmed that the Muc2 positive mucin layer was thinner and relative increase of *A. muciniphila* was observed 1 h after HW administration. Similarly, *A. muciniphila* in feces was grown in anerobic H_2-saturated media. This is the first report that HW administration decreases the intestinal mucin. Because of the suppressive effect of HW on antigen absorption, we initially expected thickening of the mucin layer. We speculate that H_2-activated *A. muciniphila* degrades mucin and secretes several molecules which are known to inhibit the activation of DC in the intestinal tract.

Disclosures: Y. Ueta: None. **M. Iketani:** None. **H. Kawaguchi:** None. **I. Ohsawa:** None.

Poster

PSTR080: Urinary, Gastrointestinal, and Renal Regulation

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR080.22/I26

Topic: F.06. Autonomic Regulation

Support: CONAHCyT Postdoctoral Scholarship CVU 598614

Title: Effect of chlorine dioxide on gastrointestinal regulation in male rats

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Abstract: Chlorine dioxide (ClO2) is a disinfectant that can effectively inactivate pathogens due tooxidation of cell surface proteins and increased membrane permeability; This technology hasbeen used as a food and surface disinfectant. However, derived from the COVID-19pandemic, many people began to consume ClO2 as a miracle treatment despite the greatcontroversy that exists about its use and its effects. Due to this controversy, various toxicitystudies have been carried out; However, the effect of ClO2 consumption on the large intestinehas not yet been investigated. Therefore, in this study, the effect of consuming 10 mg/kg ofClO2 on the large intestine of male rats was evaluated, since it is currently known that it isan extremely important organ for maintaining human health. For this, chlorine dioxide wasadministered intragastrically to male rats (2 months, 250 g) for three months. After this time,the rats were sacrificed and the large intestine was removed, subsequently staining withhematoxylin and eosin was performed. All experiments were carried out following theguidelines of Standard NOM-062-ZOO-1999. The results demonstrated that chlorine dioxidesignificantly decreases the thickness of the muscle and submucosa, affecting the absorptionof nutrients and consequently a decrease in weight was observed 90 days after

itsadministration. In conclusion, the consumption of chlorine dioxide is not recommended as itcould cause injuries to the large intestine.

Disclosures: N. Juárez Trujillo: None. **M. Alvarado:** None. **S. Sanchez:** None. **A. Peredo-Lovillo:** None. **M. Jiménez:** None.

Poster

PSTR080: Urinary, Gastrointestinal, and Renal Regulation

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR080.23/I27

Topic: H.08. Learning and Memory

Title: The protective effects of adiponectin in bile duct ligation mouse model

Authors: *S. CHOI[1], S. AHN[2], D. JO[3], J. SONG[4];
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Abstract: Hepatic encephalopathy (HE) is characterized by hyperammonemia, resulting in cognitive impairment and emotional changes. Adiponectin as an adipocyte-derived hormone has been known to regulate weight and glucose metabolism, and also enhanced cognitive function and the reduction of neuroinflammation in the central nervous system. In this study, we investigated the effects of adiponectin administration in brain of a HE mouse model. Using bile duct ligation (BDL) surgery, we divided them into two groups: the sham group receiving PBS and the case group receiving adiponectin (5μg/kg) intraperitoneally daily from the 7th day post-surgery for 7 days. BDL mice were sacrificed at 2 weeks after surgery. At the time of sacrifice, brain tissue was collected, and Western blot analysis was performed to assess protein expression of adiponectin receptor 1 and 2. Furthermore, alterations in the AMPK pathway were evaluated through Western blot and RT-PCR. RNA sequencing of brain cortex tissues was performed, followed by KEGG and GO pathway analyses to elucidate signaling changes induced by adiponectin injection. After analysis, statistically significant genes were identified, and their regulatory relationships were explored using siRNA in SH-SY5Y neuronal cells cultured under hyperammonemia conditions. Thus, we propose the potential of adiponectin as a therapeutic agent to address the various neuropathological issues observed in HE patients.

Disclosures: S. Choi: None. **S. Ahn:** None. **D. Jo:** None. **J. Song:** None.

Poster

PSTR080: Urinary, Gastrointestinal, and Renal Regulation

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR080.24/I28

Topic: H.08. Learning and Memory

Title: Transcriptional analysis of lung tissue in obese mice

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Abstract: Obesity is increasing all over the world and is associated with the incidence of diverse metabolic diseases including diabetes, cardiovascular disease and cancer etc. Recently, many studies have focused on the progression of lung fibrosis and lung cancer in obesity patients. In addition, high-fat fed diet animal studies demonstrated the small airways, reduced nasopharyngeal volume, and pulmonary inflammation, leading to pulmonary dysfunction. Therefore, we screened and compared genetic patterns in lung tissue of mouse fed a high fat diet (common obesity mimic mouse model) and those fed a normal diet to investigate the relationship between obesity and lung fibrosis. Through the RNA sequencing analysis, we found the differences in the expression of lung cancer related genes, and lymphocyte activation related genes. In GO and KEGG pathway data, we found upregulations in the nitrogen compound metabolic process, VEGF signaling, Notch signaling, non-small cell lung cancer and NK-cell mediated cytotoxicity. In summary, the increased inflammation and lung fibrosis were observed in lung tissue of high fat diet mouse model. Our results may provide the basic information to find critical genetic factors associated with pulmonary dysfunction in obesity.

Disclosures: D. Jo: None. **S. Choi:** None. **S. Ahn:** None. **J. Song:** None.

Poster

PSTR081: Food and Water Intake and Energy Balance: Neuropeptides, Monoamines, Amino Acids, and Other Regulators

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR081.01/I29

Topic: F.08. Food and Water Intake and Energy Balance

Support: NIH R01DK131441
NIH R01DK131474

Title: Differential Roles of Zona Incerta GABA and Dopamine Neurons for feeding regulation

Authors: *Q. YE, X. ZHANG;
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Abstract: The zona incerta (ZI) has emerged as a crucial brain region for the control of emotions and motivated behaviors such as feeding. Although the ZI predominantly consists of GABAergic neurons, it also hosts a small population of tyrosine hydroxylase (TH)-expressing dopamine (DA) neurons. However, the functions of these DA neurons remain largely unknown. In our recently studies, we found that ZI DA neurons and their projections to the paraventricular thalamus (PVT) display dynamic activity patterns correlated with feeding motivation. Our results indicate that stimulation of ZI DA neurons increases meal frequency to regulate food intake. This is different from activation of ZI GABA neurons that promotes binge-like eating to quickly cause overeating. Furthermore, operant behavioral tests reveal that activating ZI DA neurons markedly promotes food seeking. Using conditional place preference test, we also found that ZI DA neurons plays a crucial role in promoting contextual memories associated with food rewards. Using fiber-photometry calcium imaging, we observed differential responses of ZI DA and GABA neurons to food approach and consumption. Together, our studies reveal a differential role of ZI DA and GABA neurons in feeding control regarding food seeking and consumption. These findings will provide new insights into the neural mechanisms of feeding behavior, offering potential avenues for addressing eating disorders and obesity.

Disclosures: Q. Ye: None. **X. Zhang:** None.

Poster

PSTR081: Food and Water Intake and Energy Balance: Neuropeptides, Monoamines, Amino Acids, and Other Regulators

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR081.02/I30

Topic: F.08. Food and Water Intake and Energy Balance

Title: Perifornical area of the anterior hypothalamus regulates metabolic balance

Authors: *X. FANG, C. WANG, Y. XU;
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Abstract: Obesity is a common, serious, and costly chronic disease that continues to increase in the world. The fundamental cause of obesity and overweight is an imbalance of energy homeostasis between calorie consumption and expenditure. Energy homeostasis is strictly regulated by the central nervous system, and the hypothalamus is a brain region thought to play a critical role in the regulation of energy balance. The hypothalamus is classified into more than 10 compartments, and these regions and their functions in controlling food intake have been densely investigated. Surprisingly, a novel triangular-shaped area between the paraventricular hypothalamic nucleus (PVH) and the fornix area in the mouse anterior hypothalamus was identified in 2015, and it was named perifornical area of the anterior hypothalamus (**PeFAH**). The PeFAH has extensive extracellular structures, perineuronal nets (**PNNs**), to enmesh GABAergic neurons. I found that chronic disruption of PNNs in the PeFAH decreases the excitability of GABAergic neurons and prevents high-fat diet induced weight gain and higher fat

mass. My results also indicate that decreased PNNs leads to lower excitability of $GABA^{PeFAH}$ neurons and altered synaptic plasticity of these neurons. The ongoing project will determine whether directly manipulated the activity of $GABA^{PeFAH}$ neurons could influence the metabolic balance. The proposed studies are expected to advance the understanding about the newly discovered brain region in regulation of feeding behavior and metabolic process in general. They could be novel therapeutic targets for the treatment or prevention of obesity or overeating.

Disclosures: X. Fang: None. **C. Wang:** None. **Y. Xu:** None.

Poster

PSTR081: Food and Water Intake and Energy Balance: Neuropeptides, Monoamines, Amino Acids, and Other Regulators

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR081.03/I31

Topic: F.08. Food and Water Intake and Energy Balance

Support: CONAHCYT CF-2023-I-355

Title: Effect of stress and palatable food intake on accumbal dopaminergic and serotonergic circuits

Authors: *C. GARCIA-LUNA[1], E. ALVAREZ[1], E. ESPITIA[1], P. SOBERANES-CHAVEZ[1], G. MATAMOROS-TREJO[1], O. JAIMES[2,3], P. DE GORTARI[1];
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Abstract: Obesity is a pandemic related to rich-fat and sugar food intake along with a sedentary and stressful lifestyle. Alterations in central systems that regulate feeding behavior could be present in stressed-obese patients, leading to overeating of palatable food (PF). Hedonic circuits that regulate feeding depend on the rewarding properties of food, and one of those is formed by the mesolimbic circuit that involves the release of dopamine (DA) from the ventral tegmental area neurons into the nucleus accumbens (NAc). Additionally, serotonin (5HT) can modulate reward for food through its release from the dorsal raphe also into the NAc. The accumbal release of both DA and 5HT controls the rewarding effect of food and induces satiety; however, long-term PF intake may impair reward circuits, promoting its overconsumption and increasing body weight. Additionally, stressful situations shift food preferences favoring palatable choices, inhibiting satiety circuits while comforting stressed individuals, making lifestyle a relevant factor that alters the regulation of body weight. Although DA and 5HT effects on food intake are well established, it is unknown if a higher food intake due to chronic stress and long-term PF intake may result from alterations in accumbal DAergic and 5HTergic circuits' function. Therefore, we subjected 40 male rats that were fed with chow (n=20) or palatable food (n=20) to isolation stress for 2 weeks. After that time elapsed, rats were fasted for 48 h and 8 animals were euthanized, the rest of the rats were refed with chow (n=16) or with PF (n=16) for 2h and then

euthanized. We evaluated DA and 5HT content and their metabolites in the NAc by performing HPLC. Long-term PF fed-stressed rats showed the higher body weight; long-term PF fed-stressed animals had highest energy consumption at the end of the experiment; long-term chow fed-stressed group consumed the greater amount of PF after 48 h of fasting. Corticosterone serum levels were elevated only in chow-fed groups before fasting; in contrast, when fed with PF, there was no corticosterone increase. Rats with long-term PF intake independently of stress exposure and refeeding condition showed increased DAergic and decreased 5HT activity function in NAc. This points towards a differentially regulated accumbal aminergic response to palatable food intake that induced even non-stressed animals to overeat PF similarly to the stressed groups, which may favor obesity onset.

Disclosures: C. Garcia-Luna: None. **E. Alvarez:** None. **E. Espitia:** None. **P. Soberanes-Chavez:** None. **G. Matamoros-Trejo:** None. **O. Jaimes:** None. **P. De Gortari:** None.

Poster

PSTR081: Food and Water Intake and Energy Balance: Neuropeptides, Monoamines, Amino Acids, and Other Regulators

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR081.04/I32

Topic: F.08. Food and Water Intake and Energy Balance

Support: NRF-2021R1C1C2005067

Title: α2-adrenergic receptors in hypothalamic dopaminergic neurons:impact on food intake and energy expenditure

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Abstract: α2-Adrenergic Receptors in Hypothalamic Dopaminergic Neurons: Impact on Food Intake and Energy Expenditure

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SummaryThe adrenergic system plays an active role in modulating synaptic transmission in hypothalamic. While α2-adrenergic receptors are widely distributed in various organs and involved in diverse physiological functions, their specific relationship with the regulation of

energy metabolism in the brain remains incompletely understood. Here, we investigated the effects of α2-adrenergic receptors in the hypothalamus on food intake in mice. Our study confirmed the expression of α2-adrenergic receptors in hypothalamic dopamine neurons and assessed metabolic phenotypes, including food intake and energy expenditure, following treatment with guanabenz, an α2-adrenergic receptor agonist. Guanabenz treatment increased the activity of hypothalamic dopaminergic neurons. Furthermore, we demonstrated that the altered metabolic phenotypes induced by guanabenz were effectively reversed by inhibiting the activity of dopaminergic neurons in hypothalamic arcuate nucleus (ARCs) using a chemogenetic technique. Our findings suggest a functional connectivity between hypothalamic α2-adrenergic receptor signals and dopaminergic neurons in metabolic control.

Disclosures: Y. Kim: None. **Y. kim:** None. **S. Yang:** None. **B. Park:** None. **J. Kim:** None.

Poster

PSTR081: Food and Water Intake and Energy Balance: Neuropeptides, Monoamines, Amino Acids, and Other Regulators

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR081.05/I33

Topic: F.08. Food and Water Intake and Energy Balance

Support: NIG Grant 5R01DK115503
GSU Molecular Basis of Disease Program
GSU Brains & Behavior Program

Title: Chronic activation and inhibition of ventral segmental area melanocortin-3 receptor neurons

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Abstract: The hypothalamic melanocortin system, involving the central melanocortin receptors (MC3R and MC4R), is an essential component in the neural regulation of food intake and body weight. MC3Rs are highly expressed in the ventral tegmental area (VTA), which is the center of Mesolimbic Dopamine circuit (MLDa). The MLDa circuit is the primary neural circuit controlling reward behavior, but it also plays a role in multiple different aspects of feeding. We previously showed that acute excitation and inhibition of VTA neurons expressing MC3Rs (VTA MC3R neurons) caused a sex- and activity-dependent decrease in food intake. The effects of long-term changes in VTA MC3R neurons activity remain unknown, however. In these studies, we tested whether chronic activation or inhibition of VTA MC3R neurons affected food intake or body weight. Excitatory or inhibitory Designer Receptors Exclusively Activated by Designer Drugs (Gq and Gi DREADDs, respectively) were expressed in VTA MC3R neurons of male and female mice. Following baseline measurement of food intake and body weight, mice were treated with clozapine N-oxide (CNO) chronically in their drinking water for eight days. Similar

to our previous data with acute activation and inhibition of VTA MC3R neurons, chronic activation and inhibition appears to show sex and activity dependent effects on both food intake and body weight. These findings underscore the intricate interplay of MC3R signaling in the VTA, regulating feeding behaviors and body weight. Further exploration will delve into how VTA MC3R neurons activity control food intake and body weight, particularly on high-fat diets and in reward-based feeding paradigms.

Disclosures: M. Manieri: None. **A.G. Roseberry:** None.

Poster

PSTR081: Food and Water Intake and Energy Balance: Neuropeptides, Monoamines, Amino Acids, and Other Regulators

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR081.06/I34

Topic: F.08. Food and Water Intake and Energy Balance

Support: NIH Grant R00DK127065
Brain and Behavior Research Foundation Grant 100000874

Title: Hypothalamic AgRP neurons regulate lactational hyperphagia in mice.

Authors: *K. CATALBAS[1], P. SWEENEY[2];
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Abstract: Hypothalamic AgRP neurons regulate lactational hyperphagia in mice.
AuthorsKerem Catalbas[1], Tanya Pattnaik[2], Samuel Congdon, Christina Nelson, Lara Villano, Patrick Sweeney
Affiliations University of Illinois Urbana-Champaign, Department of Molecular and Integrative Physiology; Neuroscience Program
Abstract
The metabolic demands of lactation require significant behavioral adaptations in mammals, including hyperphagia. Although the hyperphagia of lactation is important for normal maternal behavior and development, both overeating and undereating of the dam during lactation increases the subsequent risk of the mother and her children developing metabolic disorders later in life. However, the specific neural circuitry and molecular mechanism(s) mediating the hyperphagia of lactation are not well understood. The hypothalamic agouti-related peptide (AgRP) neurons are activated in response to energy deprivation to promote food seeking behavior, although the role of these neurons in lactational hyperphagia is largely unknown. Here, we characterize the role of hypothalamic agouti-related peptide (AgRP) neurons in mediating the dietary adjustments necessary for lactation. Through an integrated approach combining home cage feeding assessments, pharmacological assays, chemogenetic techniques, and *in vivo* fiber photometry, we characterize the feeding behaviors of lactating and non-lactating mice. These

experiments reveal that lactating mice consume larger meals, exhibit unique circadian feeding rhythms, and have a decreased response to gut-brain satiety signals. Notably, AgRP neurons show elevated responsivity to signals of negative energy balance and are directly activated during nursing in lactating mice. Further, inhibition of AgRP neurons during lactation transiently reduced feeding levels in lactating mice to those seen
in non-lactating mice, highlighting the importance of AgRP neurons for lactational hyperphagia. Together, these findings demonstrate multiple behavioral adaptations associated with lactational hyperphagia and establish the hypothalamic AgRP neurons as an important cellular link between lactation and increased feeding behavior.

Disclosures: K. Catalbas: None. **P. Sweeney:** None.

Poster

PSTR081: Food and Water Intake and Energy Balance: Neuropeptides, Monoamines, Amino Acids, and Other Regulators

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR081.07/I35

Topic: F.08. Food and Water Intake and Energy Balance

Support: DOD W81XWH2210084
NIH R21-MH128574

Title: The attenuation of activity-based anorexia (ABA) by obese adipose tissue transplant is AgRP neuron-dependent

Authors: *D. J. YOON[1], J. ZHANG[2], M. ULIVIERI[4], S. C. DULAWA[4], E. UPPALAPATI[3], M. S. MCMURRAY[5];
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Abstract: Anorexia nervosa (AN) is an eating disorder observed primarily in girls and women, and is characterized by a low body mass index, hypophagia, and hyperactivity. The activity-based anorexia (ABA) paradigm models aspects of AN, and refers to the progressive weight loss, hypophagia, and hyperactivity developed by rodents exposed to time-restricted feeding and running wheel access. Recent studies identified white adipose tissue (WAT) as a primary location of the ‘metabolic memory’ of prior obesity, and implicated WAT-derived signals as drivers of recidivism to obesity following weight loss. Here, we tested whether an obese WAT transplant could attenuate ABA-induced weight loss in normal female mice. Recipient mice received a WAT transplant harvested from normal chow-fed, or HFD-fed obese mice; obese fat recipient (OFR) and control fat recipient (CFR) mice were then tested for ABA. During ABA, OFR mice survived longer than CFR mice, defined as maintaining 75% of their initial body weight. Next, we tested whether agouti-related peptide (AgRP) neurons, which regulate feeding

behavior and metabolic sensing, mediate this effect of obese WAT transplant. CFR and OFR mice received either control or neonatal AgRP ablation, and were assessed for ABA. OFR intact mice maintained higher body weights longer than CFR intact mice, and this effect was abolished by neonatal AgRP ablation; further, ablation reduced survival in OFR, but not CFR mice. In summary, obese WAT transplant communicates with AgRP neurons to increase body weight maintenance during ABA. These findings encourage the examination of obese WAT-derived factors as potential treatments for AN.

Disclosures: D.J. Yoon: None. **J. Zhang:** None. **M. Ulivieri:** None. **S.C. Dulawa:** None. **E. Uppalapati:** None. **M.S. McMurray:** None.

Poster

PSTR081: Food and Water Intake and Energy Balance: Neuropeptides, Monoamines, Amino Acids, and Other Regulators

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR081.08/I36

Topic: F.08. Food and Water Intake and Energy Balance

Support: National Institute of Health-National Institute of Diabetes and Digestive and Kidney Diseases Grant R00DK127065
Foundation for Prader-Willi Research
Brain and Behavior Research Foundation Grant 100000874

Title: Neuroanatomical dissection of the MC3R circuitry controlling energy rheostasis

Authors: *I. C. POSSA PARANHOS[1], J. BUTTS[2], D. CHO[3], P. SWEENEY[2];
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Abstract: Although mammals resist both acute weight loss and weight gain, the neural circuitry mediating bi-directional defense against weight change is incompletely understood. Global constitutive deletion of the melanocortin-3-receptor (MC3R) impairs the behavioral response to both anorexic and orexigenic stimuli, with MC3R knockout mice demonstrating increased weight gain following anabolic challenges and increased weight loss following anorexic challenges (i.e. impaired energy rheostasis). However, the brain regions mediating this phenotype remain incompletely understood. Here, we utilized MC3R floxed mice and viral injections of Cre-recombinase to selectively delete MC3R from medial hypothalamus (MH) or dorsal-medial hypothalamus (dMH) in adult mice. Behavioral assays were performed on these animals to test the role of MC3R in MH in the acute response to orexigenic and anorexic challenges. Additionally, RNAscope in situ hybridization was utilized to map changes in the mRNA expression of MC3R, POMC, and AgRP following energy rheostatic challenges in the different regions of MH, and to characterize the MC3R colocalization with other known genes important for energy homeostasis. Finally, chemogenetic approaches were used in MC3R-Cre

mice to localize and characterize the specific medial hypothalamic brain regions mediating the role of MC3R in energy homeostasis. As observed in global MC3R KO mice, deletion of MC3R throughout the medial hypothalamus or specifically in the dorsal portions of medial hypothalamus did not alter regular chow *ad libitum* feeding or body weight. In contrast, both deletion of MC3R throughout the MH or specifically in the dMH resulted in increased feeding and weight gain following acute high fat diet feeding in males. Conversely, deletion of MC3R in the dMH enhanced the anorexic and weight loss-inducing effects of the GLP1R agonist semaglutide, in a sexually dimorphic manner. Chemogenetic activation of DMH MC3R neurons increased energy expenditure and locomotor activity. Finally, we identify that DMH MC3R neurons are primarily GABAergic in females, while there is a significantly greater population of glutamatergic neurons in males. These cells are also largely distinct from other DMH cell types (i.e. melanocortin-4 receptor or leptin receptor expressing cells) implicated in energy homeostasis. Together, these results demonstrate that MC3R mediated effects on energy rheostasis result from the loss of MC3R signaling in the hypothalamus of adult animals and indicate an important role for DMH MC3R signaling in mediating some of these effects.

Disclosures: I.C. Possa Paranhos: None. **J. Butts:** None. **D. Cho:** None. **P. Sweeney:** None.

Poster

PSTR081: Food and Water Intake and Energy Balance: Neuropeptides, Monoamines, Amino Acids, and Other Regulators

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR081.09/I37

Topic: F.08. Food and Water Intake and Energy Balance

Support: NIH Grant R01HL153274

Title: Neuroanatomical and Functional Characterizations of Zona Incerta MC4R Neural Circuit in Metabolic Control

Authors: *O. MUSTAFA, U. SINGH, G. DENG, J. JIANG, H. CUI;
Neurosci. and Pharmacol., Univ. of Iowa, Iowa City, IA

Abstract: The name Zona Incerta (ZI) translates to the 'uncertain zone', indicating limited understanding of its functionality; however, accumulating research suggests that it may play an important role in certain behavioral regulations, including food intake, sleep-wake behavior, and learning/memory. During functional investigation of hypothalamic neurons expressing MC4R, a well-established obesity-associated gene, we discovered that a subset of neurons in the anterior ZI express MC4Rs. To gain insights into the functional role of these ZI MC4R+ neurons, we first performed anterograde tract-tracing by targeted unilateral microinjection of Cre-dependent AAV-DIO-synaptophysin-mCherry into the ZI of MC4R-Cre+ mice, which revealed that ZI MC4R+ neurons heavily innervate brain regions involved in feeding and autonomic function, including but not limited to the lateral habenula (LHb), periaqueductal gray (PAG), and

parabrachial nucleus (PBN). Based on these neuroanatomical observations, we hypothesized that the ZI MC4R circuit is critically involved in feeding and metabolic control. To test this hypothesis, we generated mice expressing hM3Dq-mCherry or mCherry (control) specifically in ZI MC4R+ neurons by performing stereotaxic microinjection of Cre-dependent AAV-DIO-hM3Dq-mCherry or AAV-DIO-mCherry into the ZI of MC4R-Cre+ male mice. These mice were then subjected to comprehensive metabolic phenotyping with an indirect calorimetry metabolic cage system (Promethion). We found that chemogenetic activation of ZI MC4R+ neurons by intraperitoneal injection of deschloroclozapine (DCZ, 0.5 mg/kg) significantly increases food and water intake, locomotor activity, brown fat temperature, and energy expenditure. These results identify the ZI as a novel candidate brain region through which the central melanocortin system might act to control metabolic homeostasis.

Disclosures: O. Mustafa: None. **U. Singh:** None. **G. Deng:** None. **J. Jiang:** None. **H. Cui:** None.

Poster

PSTR081: Food and Water Intake and Energy Balance: Neuropeptides, Monoamines, Amino Acids, and Other Regulators

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR081.10/I38

Topic: F.08. Food and Water Intake and Energy Balance

Support: FAPESP/ 2022/09101-3

Title: Metabolic phenotyping of transgenic mice that do not express neuropeptide y (NPY) in tyrosine hydroxylase neurons

Authors: *G. BATITUCCI[1,2], E. DOS SANTOS ALVES[1,2], E. A. ROMAN[2], A. DOMINGOS[3], L. A. VELLOSO[1,2];
[1]Sch. of Med. Sciences, Univ. of Campinas, Campinas, Brazil; [2]Obesity and Comorbidities Res. Center, Univ. of Campinas, Campinas, Brazil; [3]Univ. of Oxford, Londres, United Kingdom

Abstract: The brain, particularly the hypothalamus, integrates central and peripheral signals to control several autonomic functions, including the body's energy balance. A considerable fraction of this regulation is exerted through sympathetic connections with systemic organs and tissues regulating energy homeostasis and glucose metabolism. Preliminary data from our laboratories have identified a subpopulation of autonomic neurons, the tyrosine hydroxylase (Th) neurons, which express NPY and innervate the brown adipose tissue (BAT) controlling thermogenesis. However, the role played by these autonomic fibers in regulating systemic metabolism is currently unknown. Here, we evaluated a transgenic mouse model that does not express NPY specifically in neurons Th (Thcre/ Npyflox). Metabolic phenotyping of chow-fed males and females (n = 8/group/sex) was carried out over 16 weeks (16W) and included control (CT; Th^{cre+}/ Npy^{flox-}) and knockout (KO_NPY; Th^{cre+}/ Npy^{flox+}) mice groups, ethics committee

6273-1/2023 The results indicate that in males the KO_NPY group has smaller body mass than the CT group at the end of 16W (*P = 0.016*); food intake of the KO_NPY group is lower than that of the CT group at 9W (*P = 0.009*), 14W (*P = 0.021*) and 15W (*P = 0.009*). Furthermore, it was observed that the KO_NPY group had greater glucose intolerance only at 16W (*P = 0.003*), higher fasting glycemia only at 16W (*P < 0.0001*) compared to the control, as well as lower lean mass (g) (*P = 0.013*), without changes to the other parameters. Regarding females, there were no changes in the variables evaluated, except for the fact that the KO_NPY group also showed reduced lean mass (*P = 0.020*), compared to the control group. The 12-hour fasting tolerance test (FTT) and the pyruvate tolerance test (PTT) after 6 hours of fasting and a dose of 2g/kg of intraperitoneal pyruvate, were performed and there was no difference in the PTT between the groups for males and females, or in the FTT for females. However, KO_NPY males showed greater intolerance to prolonged fasting (*P = 0.007*) compared to the control group. Preliminary results demonstrate that NPY deletion in peripheral neurons can alter metabolic regulation under normal metabolic conditions on a chow diet.

Disclosures: G. Batitucci: None. **E. dos Santos Alves:** None. **E.A. Roman:** None. **A. Domingos:** None. **L.A. Velloso:** None.

Poster

PSTR081: Food and Water Intake and Energy Balance: Neuropeptides, Monoamines, Amino Acids, and Other Regulators

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR081.11/I39

Topic: F.08. Food and Water Intake and Energy Balance

Support: NIH NIDA R01 DA025634

Title: Dopamine and behavioral responses to the taste of sodium chloride are modulated by different need-to-satiety arc

Authors: *P. BAZZINO[1], M. K. LOH[2], M. F. ROITMAN[3];
[1]Univ. of Illinois at Chicago, Chicago, IL; [2]Dept. of Cell. and Mol. Pharmacol., UIC, Chicago, IL; [3]Psychology, Univ. of Illinois Chicago, Chicago, IL

Abstract: Sodium appetite is an innate, natural behavior where sodium deficit promotes vigorous seeking and consumption of sources of sodium at concentrations that would otherwise be avoided. We have previously shown that sodium depletion recruits phasic dopamine release in the nucleus accumbens to intraoral infusions of a hypertonic sodium solution. As sodium consumption continues, the appetite is sated. However, it remains unknown whether how dopamine responses to sodium are modulated as animals increasingly recover from sodium depletion. We made brief (10s, 400 microliters/trial, 50 trials) intra-oral infusions of different sodium chloride concentrations (0.1M, 0.15M, 0.3M, 0.45M) while measuring real time dopamine transients using *in vivo* fiber photometry. Rats were prepared by injecting a viral

vector to express the dopamine sensor GRABda in the nucleus accumbens lateral shell. Recordings were performed in sodium replete and deplete rats. Linear regression of the data showed significant differences in the y-intercept for each concentration of sodium in sodium deplete versus replete conditions - supporting past work that physiological state modulates the dopamine response to a sodium solution. In the deplete condition, slopes of the linear regression were statistically different from zero - suggesting that the dopamine response was sensitive to post-ingestive feedback based. Finally, the slopes also significantly differed from each other - supporting that higher concentrations of sodium more rapidly induced satiety which, in turn, contributed to the faster decay in the dopamine response. Rats exhibit stereotypical responses to appetitive and aversive stimuli. Quantification has traditionally relied on frame-by-frame video analysis but also more recently with pose estimation software. We implemented a model using pose estimation software (DeepLabCut) to automate and validate the tracing of head movement and overall locomotion in response to intraoral infusions and across physiological states. Preliminary results show, relative to pre-infusion baseline, NaCl infusion-evoked decreases in movement in deplete rats (a hallmark of appetitive stimuli). As intraoral infusions proceeded, movement increased (a hallmark of aversion). During deplete conditions, there was an inverse relationship between dopamine responses and movement evoked by intraoral infusions. Collectively, these data support a rapid negative feedback mechanism on dopamine responses to needed stimuli as that need is diminished.

Disclosures: P. Bazzino: None. **M.K. Loh:** None. **M.F. Roitman:** None.

Poster

PSTR082: Drugs of Abuse: Pharmacology and Behavior

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR082.01/I40

Topic: G.03. Motivation

Support: UL1GM118979
TL4GM118980
RL5GM118978

Title: Exendin-4, a glucagon-like peptide-1 receptor agonist, attenuates the acquisition of oxycodone preference in male and female Sprague-Dawley rats

Authors: *T. NGUYEN, A. R. ZAVALA;
California State Univ., Long Beach, Long Beach, CA

Abstract: Glucagon-like peptide-1 (GLP-1) is a hormone with receptors in the peripheral and central nervous systems. GLP-1 is found in the small intestines, and increases in this hormone are associated with regulating glucose levels and reducing food intake. Centrally, activation of GLP-1 receptors has been shown to decrease dopamine release in the mesolimbic pathway and the rewarding and reinforcing effects of cocaine. Systemic administration of GLP-1 with

exendin-4 (Ex-4) has also been shown to reduce the rewarding effects of alcohol and cocaine. More recently, activation of the GLP-1 receptor with Ex-4 also attenuates oxycodone and fentanyl self-administration and drug-seeking behavior in adult rats. However, studies that examine the role of GLP-1R in modulating opioid reward in adolescent rats have not been examined. Thus, the present study examines whether pretreatment with Ex-4 reduces the rewarding effects of oxycodone preference in adolescent male and female Sprague-Dawley rats. The rewarding effects of oxycodone were assessed using the conditioned place preference (CPP) paradigm, an animal model of reward using a 10-day procedure. On days 1 and 10, baseline and testing days, rats had free access to both sides of a two-chamber apparatus for 15 min to assess for place preference. During days 2-9, rats were conditioned 30 min daily with either oxycodone (0.0, 0.01, 0.1, 1.0, or 9.0 mg/kg) or saline on alternating days. During oxycodone conditioning sessions, rats were pretreated with Ex-4 (2.4 ug/kg) or saline 10 min prior to being administered oxycodone. Results indicated that Ex-4 attenuated oxycodone-induced CPP in male and female adolescent rats. Overall, the findings of this study are consistent with previous studies examining the role of GLP-1 in drug reward. Additionally, the findings indicate the viability of the GLP-1 receptor system in adolescent rats, and given the widespread use of GLP-1 drugs that are FDA approved, suggests a rapid pharmacological tool in treating opioid use disorder.

Disclosures: T. Nguyen: None. **A.R. Zavala:** None.

Poster

PSTR082: Drugs of Abuse: Pharmacology and Behavior

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR082.02/J1

Topic: G.03. Motivation

Support: R16GM145552
R25DA050687
R25MH055929

Title: Aggression modulates responses to mood-related stimuli in adult male CD-1 mice.

Authors: *A. THEMANN, J. A. GARCIA, J. REYES-ARCE, S. D. IÑIGUEZ;
Dept. of Psychology, The Univ. of Texas at El Paso, El Paso, TX

Abstract: Maladaptive aggression is a common feature of many personality, conduct, and substance use disorders - worsening the quality of life for patients and those around them. Although the relationship between maladaptive aggression and psychiatric dysfunction is not well understood, recent evidence indicates that aggressive displays towards conspecifics may be perceived as rewarding - and that this hedonic experience may, in fact, be similar to other rewarding experiences, such as food, sex, and drugs of abuse. Nevertheless, the relationship between aggression and mood-related illnesses has not been thoroughly assessed using preclinical affect-related models. To address this issue, we examined whether displays of

aggressive behavior result in changes in sensitivity to the rewarding properties of sucrose and novel environments, as well as responses to inescapable stress situations. Specifically, male (retired breeder) CD-1 mice were subdivided into high aggressive (HAGG) and low aggressive (LAGG) groups based on their latency to attack an intruder mouse in their home cage during a three-day screening paradigm. Mice were considered HAGG if they displayed attack latencies below 10 sec across the three screening days, while animals with attack latencies greater than 30 sec (or not attacking at all) were classified as LAGG. One hour after aggressive screening (day 3), responsivity to the sucrose (1%) preference, open field, elevated plus maze, and tail suspension tests were conducted in separate groups of experimental mice. We found that HAGG mice display an increased preference for a 1% sucrose solution, as well as increases in exploration in novel environments, per the elevated plus-maze and open field tests. Lastly, HAGG mice display decreased immobility in the tail suspension test, representative of a resilient-like behavioral response. Collectively, our findings indicate that aggressive behavior is associated with increases in sensitivity to reward-related stimuli, while also displaying decreases in sensitivity to behavioral despair measures. Therefore, our data suggest that aggression modulates responses in preclinical models for the study of mood-related illnesses.

Disclosures: A. Themann: None. **J.A. Garcia:** None. **J. Reyes-Arce:** None. **S.D. Iñiguez:** None.

Poster

PSTR082: Drugs of Abuse: Pharmacology and Behavior

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR082.03/J2

Topic: G.03. Motivation

Support: UL1GM118979
TL4GM118980
RL5GM118978

Title: Zolmitriptan, a 5-HT1B receptor agonist, attenuates the acquisition of ethanol preference in adolescent female Sprague-Dawley rats

Authors: *E. SIU, S. MOORE, A. GARCIA, A. R. ZAVALA;
Dept. of Psychology, California State Univ., Long Beach, CA

Abstract: Alcohol consumption typically begins in adolescence and is highly abused among youth. Serotonin (5-HT)1B receptors play a key role in mediating the effects of ethanol, as activating these receptors reduces the intake and reinforcing effects of ethanol in adult male rats. However, no studies have investigated the effects of a 5-HT1B agonist in adolescent female rats. Thus, the present study examined whether administering zolmitriptan, a 5-HT1B agonist, attenuates the acquisition of conditioned place preference for ethanol in adolescent Sprague-Dawley female rats. We predicted that rats given zolmitriptan would exhibit an attenuated

response to ethanol in a dose-dependent manner. Rats were given free access to both sides of a two-chambered CPP apparatus for 15 minutes on postnatal day (PD) 31 to determine initial preferences for a two-sided CPP apparatus. During the following 8 days of conditioning (15 min session per day), rats were administered alternating injections of zolmitriptan or vehicle (s.c.) 15 min prior to receiving 0, 0.625, or 2.0 g/kg (i.p.) of ethanol in their non-preferred side during drug-paired days and vehicle 15 min prior to saline in their preferred side on saline-paired days. Preference for the ethanol-paired side was assessed on PD 40, during which rats again had access to both sides of the CPP apparatus for 15 min. Rats preferred the 2.0 g/kg dose of ethanol, given that rats significantly increased the time spent on the ethanol-paired side compared to rats in the vehicle-saline group. The preference for the 2.0 g/kg dose of ethanol was attenuated in rats pretreated with zolmitriptan. Importantly, this decrease in ethanol preference was not associated with a decrease in locomotion. Interestingly, zolmitriptan pretreatment alone resulted in a marked preference for the zolmitriptan-paired side (i.e., without any ethanol). Our findings indicate that activating 5-HT1B receptors through administering zolmitriptan reduced the rewarding effects of ethanol in adolescent female rats, providing further evidence of the role of 5-HT1B receptors in modulating the rewarding effects of various drugs of abuse. Future research will examine the preference for zolmitriptan, as evident in the present study, using a wider range of doses in male and female adolescent rats.

Disclosures: E. Siu: None. **S. Moore:** None. **A. Garcia:** None. **A.R. Zavala:** None.

Poster

PSTR082: Drugs of Abuse: Pharmacology and Behavior

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR082.04/J3

Topic: G.03. Motivation

Support: UL1GM118979
TL4GM118980
RL5GM118978

Title: One-trial nicotine-induced locomotor sensitization induces sex- and age-dependent differences in male and female rats

Authors: *M. ROACH, B. P. SCHUESSLER, A. R. ZAVALA;
Dept. of Psychology, California State Univ., Long Beach, CA

Abstract: One-trial locomotor sensitization is the process in which a single drug exposure leads to an enhanced psychomotor behavioral response during subsequent drug exposure. The context or environment in which the initial drug exposure took place influences the development of this phenomenon in an age-dependent manner. Specifically, preweanling, adolescent, and adult rats differentially express both context-dependent and context-independent one-trial sensitization with psychostimulants like cocaine, amphetamine, and methamphetamine. However, one-trial

nicotine-induced sensitization has not yet been studied. Thus, the present study investigated the ontogeny of one-trial nicotine-induced sensitization in male and female rats at various developmental periods. In separate experiments, preweanling (PD 19), adolescent (PD 35), and adult (PD 75) male and female rats were pretreated with saline or nicotine (0.6 mg/kg, SC) prior to being placed in a novel test chamber where horizontal locomotor activity was measured for 45 min. Rats were given the opposite treatment in their home cage to test for context-dependent sensitization. Specifically, rats pretreated with saline were given nicotine (0.6 mg/kg, SC) (home-paired groups), and rats pretreated with nicotine were given saline in their home cage (activity-paired groups). The next day, rats from each group were given a challenge dose of nicotine (0.15, or 0.3 mg/kg, SC) before being placed in the novel test chamber, where locomotor activity was measured for 45 min. A separate control group (i.e., one pretreated with saline and challenged with saline) was also included. Results show that one-trial sensitization differs between males and females across the developmental periods, with female rats exhibiting nicotine-induced one-trial locomotor sensitization while males failed to exhibit sensitization. In addition to sex differences, one-trial nicotine-induced sensitization is also age dependent, as preweanling rats do not exhibit one-trial locomotor sensitization compared to adolescent and adult rats. These data are the first to examine one-trial nicotine sensitization and demonstrate significant sex and age differences.

Disclosures: M. Roach: None. **B.P. Schuessler:** None. **A.R. Zavala:** None.

Poster

PSTR082: Drugs of Abuse: Pharmacology and Behavior

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR082.05/J4

Topic: G.03. Motivation

Support: UL1GM118979
TL4GM118980
RL5GM118978

Title: Methylphenidate exposure during the juvenile period enhances the preference for nicotine without affecting nicotine-induced behavioral sensitization in male and female adolescent Sprague-Dawley rats

Authors: *C. H. NGUYEN, A. G. SEDILLO, A. D. GARCIA, S. SENG, A. R. ZAVALA; Dept. of Psychology, California State Univ., Long Beach, CA

Abstract: The long-term consequences of early use of methylphenidate (MPH) to treat attention-deficit / hyperactivity disorder (ADHD) in preschool-age children are not fully understood. Preclinical studies suggest that MPH exposure during postnatal days (PD) 11-20, a period of rat development analogous to preschool-age children, enhances the rewarding effects of morphine and the reinforcing effects of cocaine in adult rats. However, the long-term effects of early MPH

exposure on nicotine reward have not been examined. Thus, the present study examines whether MPH exposure during PD 11-20 in male and female preschool-age and adolescent rats affects nicotine reward and sensitization. Drug reward was assessed using the conditioned place preference (CPP) procedure. Preweanling rats were administered MPH (0.0, 2.0, or 4.0 mg/kg, i.p.) twice daily on postnatal days (PD) 11-20. Each dose was given five hours apart to account for the half-life of MPH, about 2.5 hours, and its clinical use. CPP conditioning occurred for eight days, starting on PD 27 (early adolescence) or PD 41 (late adolescence). During conditioning, rats were exposed to either nicotine (0.2 or 0.6 mg/kg, s.c.) on the nonpreferred side or saline on the preferred side during 30-min sessions. Rats were then assessed for nicotine preference on PD 34 (early adolescent group) or PD 48 (late adolescent group). In a separate experiment, male and female rats were pretreated twice daily with MPH (0 or 4 mg/kg, i.p.) during PD 11-20. Beginning on PD 32, rats underwent daily nicotine injections (0, 0.2, or 0.6 mg/kg, s.c.) for 7 consecutive days, during which locomotor activity was recorded. On PD 40, all rats were then challenged with nicotine (0.2 mg/kg, i.p.), and locomotor sensitization was assessed. Results indicated that early pretreatment with MPH resulted in an enhanced preference for nicotine using a sub-threshold dose of nicotine and an increased sensitivity to nicotine with the higher dose of nicotine in early adolescent male rats. A similar enhancement of the nicotine preference is evident in late adolescent rats. In females, a leftward shift in nicotine CPP for early and late adolescent rats was seen. Nicotine increased locomotor activity and induced sensitization in all rats, but MPH pretreatment during PD 11-20 did not modulate the development of sensitization. Overall, we demonstrate that MPH increases the rewarding effects of nicotine in a dose-depdent manner in male and female adolescent rats. The inability of MPH to enhance nicotine's sensitization effects may be due to the modulation of different neurocircuitry associated with drug reward from that of drug-induced locomotor behavior.

Disclosures: C.H. Nguyen: None. **A.G. Sedillo:** None. **A.D. Garcia:** None. **S. Seng:** None. **A.R. Zavala:** None.

Poster

PSTR082: Drugs of Abuse: Pharmacology and Behavior

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR082.06/J5

Topic: G.03. Motivation

Support: UL1GM118979
TL4GM118980
RL5GM118978

Title: Zolmitriptan, a 5-HT1B/1D receptor agonist, reduces the acquisition of methamphetamine preference in male and female adolescent Sprague-Dawley rats

Authors: *A. LIN[1], T. GONZALEZ-GUTIERREZ[1], R. A. CABRERA[1], B. COYNE[1], N. PENTKOWSKI[2], A. R. ZAVALA[1];

[1]Dept. of Psychology, California State Univ., Long Beach, CA; [2]Dept. of Psychology, Univ. of New Mexico, Albuquerque, NM

Abstract: Adolescent use of methamphetamine (METH) leads to poor treatment outcomes later in life, and currently, there are no FDA-approved medications for the treatment of METH use disorder. Previous studies have demonstrated that activation of serotonin 5-HT1B receptors reduces METH-induced conditioned place preference (CPP) expression in adult mice. However, the effects of activating 5-HT1B receptors on the acquisition of METH CPP or adolescent rats have not been investigated. Therefore, the present study examined the effect of zolmitriptan, a 5-HT1B/1D receptor agonist, on METH preference in adolescent male and female rats using a 10-day CPP procedure. On day 1, baseline, rats had free access to both sides of a two-sided apparatus for 20 min to assess their preferred and non-preferred sides. During days 2-9, conditioning, rats were injected on alternating days with METH (0, 0.125, 0.25, 0.5, 1.0 mg/kg, intraperitoneally) or saline and were immediately confined to their non-preferred or preferred side for 30 min, respectively. During METH conditioning days, rats received pretreatment of zolmitriptan (0 or 10 mg/kg, subcutaneously) 15 min before the administration of METH. On day 10, testing, rats were given free access to both sides of the two-sided apparatus for 20 min to assess their side preference. Results indicated that zolmitriptan reduced the rewarding effects of METH in male and female adolescent rats. Overall, the findings demonstrate that 5-HT1B receptors play a central role in the effects of methamphetamine across development (i.e., adolescent and adult) and that this receptor system is a viable pharmacological target for the treatment of METH use disorder.

Disclosures: A. Lin: None. **T. Gonzalez-Gutierrez:** None. **R.A. Cabrera:** None. **B. Coyne:** None. **N. Pentkowski:** None. **A.R. Zavala:** None.

Poster

PSTR082: Drugs of Abuse: Pharmacology and Behavior

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR082.07/J6

Topic: G.03. Motivation

Title: Functional consequences of juvenile exposure to methylphenidate on cocaine and methamphetamine reward in early and late adolescent male and female rats

Authors: *A. G. SEDILLO, C. H. NGUYEN, R. J. FLORES GARCIA, A. R. ZAVALA; Dept. of Psychology, California State Univ., Long Beach, CA

Abstract: The use of methylphenidate for the treatment of attention-deficit / hyperactivity disorder (ADHD) in pediatric populations continues to be prevalent despite few studies examining the long-term consequences of early use. Preclinical studies have demonstrated that early use of methylphenidate early in life results in changes in the rewarding and reinforcing effects of psychostimulants (e.g., cocaine) in adult rodents. However, examining the functional

consequences of juvenile methylphenidate administration in adolescence is not well understood. Thus, the present study exposed juvenile rats to methylphenidate during postnatal days (PD) 11-20 and examined changes in cocaine and methamphetamine reward during early and late adolescence. We employed the conditioned place preference paradigm (CPP) to examine reward, which has been well-validated in rodents. Male and female Sprague-Dawley rats were treated twice daily with methylphenidate (0, 2, or 4 mg/kg, i.p.) starting at PD 11-20. Rats were then assessed for cocaine (2.5 mg/kg, i.p.) or methamphetamine (0.05 or 0.1 mg/kg, i.p.) CPP beginning in early (PD 27) or late adolescence (PD 39 or 41) using a 10 or 12-day CPP procedure. Baseline and expression test days consisted of rats having unrestricted access for 15 min to the two sides of the CPP apparatus in a drug-free state to assess their preferences for the saline- or drug-paired environments. Conditioning sessions lasted 30 min and consisted of rats being confined to the drug-paired side on one day and to the saline-paired side on alternating days for either 4 or 6 days. The results indicate that methylphenidate modulated the expression of cocaine- and methamphetamine-induced preference in a dose-dependent manner and that these effects varied depending on sex and age (early or late adolescence). These data indicate that early use of methylphenidate has the potential to alter the rewarding effects of psychostimulants during adolescence, similar to what has been reported in adult animals. Further examination of the interaction of methylphenidate and pharmacologically related drugs is necessary to fully understand the consequences of early use of methylphenidate in pediatric populations.

Disclosures: A.G. Sedillo: None. **C.H. Nguyen:** None. **R.J. Flores Garcia:** None. **A.R. Zavala:** None.

Poster

PSTR082: Drugs of Abuse: Pharmacology and Behavior

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR082.08/J7

Topic: G.03. Motivation

Support: NSF Award HRD-1909824
NIDA Grant R00 DA04765
NHLBI Grant U01HL 150852
NJHF PC144-23
NJHF PC98-22

Title: High fat diet alters expression of sigma 1 receptors and potency of a sigma 1 receptor antagonist

Authors: *A. ARMANIOUS[1,2], R.-M. HUNTER[1,2], J. FINLEY[1,2], Y. PENG[3], B. WELSH[4], M. H. JAMES[1,2];
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Abstract: Introduction: Sigma-1 receptor (S1R) antagonists reduce food seeking in lean animals, however their efficacy in obese animals remains largely untested. Here, we tested how exposure to a high fat diet (HFD) alters expression of S1Rs throughout the brain and compared the efficacy of a novel S1R antagonist (PW507) at reducing food behaviors in HFD vs. lean rats. **Methods:** Female Long Evans rats were given ad libitum access to HFD or chow (n=8/group) for 12w, sacrificed, and brain sections processed for immunohistochemical detection of S1Rs. A second cohort (HFD: n=16, chow: n=8) underwent similar diet exposure before being tested for binge-like consumption of a sweetened fat mixture, as well as lever pressing for sucrose pellets on low effort (fixed ratio [FR] 1), high effort (FR5), and progressive ratio schedules of reinforcement. Rats were treated with PW507 (0, 5, 10, 15, 20mg/kg; i.p.) prior to behavioral tests and subsequent tests of general locomotor activity. **Results:** Density of S1R was decreased in anterior cingulate cortex, dorsal and ventral striatum regions of HFD rats. PW507 dose-dependently decreased binge-like eating, high-effort sucrose responding, and sucrose breakpoints in HFD rats but not in lean rats. PW507 did not affect general activity. **Conclusions:** Chronic HFD exposure is associated with altered S1R in reward-related brain regions, as well as increased potency of a S1R antagonist in reducing motivated food behaviors. Thus, body weight should be considered when developing and optimizing S1R antagonists for the clinical management of overeating.

Disclosures: A. Armanious: None. **R. Hunter:** None. **J. Finley:** None. **Y. Peng:** None. **B. Welsh:** None. **M.H. James:** None.

Poster

PSTR082: Drugs of Abuse: Pharmacology and Behavior

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR082.09/J8

Topic: G.03. Motivation

Support: R00045765

Title: Ventral tegmental area orexin (hypocretin) signaling mediates sleep and relapse following cocaine in rats

Authors: *U. GYAWALI[1], S. O'CONNOR[1], C. E. OLSON[2], M. BILOTTI[1], D. DE SA NOGUEIRA[3], M. H. JAMES[4];
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Abstract: Cocaine-exposed rats exhibit disrupted sleep patterns during abstinence, including decreased non-rapid eye movement (NREM) and rapid eye movement (REM) sleep. Restoring normal sleep during abstinence decreases drug behaviors, indicating overlap in brain arousal and reward circuits. Here, we tested the role of orexins (hypocretins) and their projections to ventral tegmental area as a potential circuit that commonly mediates these outcomes. To first implicate

orexin signaling in sleep disturbances following cocaine, we trained rats to develop a cocaine conditioned place preference (CPP; n=16) or to self-administer cocaine (n=17); rats then underwent extinction training during which sleep was monitored via continuous electroencephalogram (EEG) and electromyogram (EMG) recordings. Rats were treated with the dual orexin receptor antagonist suvorexant (0, 30mg/kg) prior to the inactive period throughout extinction training; this normalized sleep (increased NREM sleep, reduced wake) and facilitated extinction of drug seeking (p=0.046, p=0.034). To explore how these effects might be mediated by VTA, we first quantified changes in orexin receptor expression in VTA in cocaine CPP rats; this revealed increased orexin receptor 1, but not orexin 2 receptor, mRNA levels in cocaine rats (p=0.001). Last, we measured orexin population activity (using GCaMP) and orexin binding in VTA (using OxLight); this revealed a close association between waking events, orexin cell activity and orexin binding in VTA. Together, these data indicate that 1) orexin neurons mediate sleep disturbances and associated drug seeking during cocaine abstinence and 2) these effects might be mediated via projections to VTA.

Disclosures: U. Gyawali: None. **S. O'Connor:** None. **C.E. Olson:** None. **M. Bilotti:** None. **D. De Sa Nogueira:** None. **M.H. James:** None.

Poster

PSTR082: Drugs of Abuse: Pharmacology and Behavior

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR082.10/J9

Topic: G.03. Motivation

Support: NIH DA045765
NIH ES035848
Busch Biomedical Grant
New Jersey Health Foundation

Title: Blunted orexin binding in ventral tegmental area in response to food-predictive cues in rats maintained on a high fat diet - implications for binge-like eating

Authors: U. GYAWALI[1], A. J. ARMANIOUS[2], J. MEHR[3], ***M. JAMES**[4];
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Abstract: An allostatic state of the brain reward system, characterized by reduced reward thresholds, is believed to contribute to persistent drug use in addiction. A comparable mechanism may be at play in binge eating disorder (BED), as 1) prolonged exposure to high-fat diets can lead to hedonic deficits, and 2) individuals with BED often describe binge episodes as a temporary relief from negative emotional states like depression or dysphoria. However, the precise mechanisms by which changes in mood induced by diet can promote future binge

episodes, as well as the neural circuits involved, remain unclear. To address this, we exposed female Long Evans rats to high-fat diet (HFD) for 8 weeks, which resulted in elevated intracranial self-stimulation (ICSS) (n=6-7/group, $p<0.05$) thresholds and decreased social interaction (n=8/group, $p<0.05$), indicative of a dysphoric state. Subsequently, we investigated whether this altered hedonic state predisposed the rats to binge-like eating by providing them with limited (30 minutes) and intermittent (twice a week) access to a sweetened fat solution for 4 weeks, followed by assessment of their reward-related behaviors. Our findings revealed that compared to lean controls, HFD rats displayed heightened escalation of binge-like eating, with binge eating partially alleviating the hedonic deficits associated with HFD. Additionally, we examined the impact of HFD and binge eating on the functionality of the orexin neuropeptide system, a key regulator of reward behaviors, by measuring orexin binding (using Oxlight and fiber photometry) in the ventral tegmental area (VTA) during a food conditioning task in HFD rats before and after binge eating (n=5/group). We found that VTA orexin was blunted to food-associated stimuli in HFD rats compared to lean rats ($p<0.05$). In addition, we utilized an shRNA strategy to suppress VTA-projecting orexin neurons in HFD rats prior to the binge paradigm. Knockdown of orexin-VTA neurons abolished binge-like eating and prevented the reversal of hedonic deficits. Collectively, these results suggest that binge-like consumption of sweetened fat mitigates hedonic deficits and restores orexin signaling in the VTA. Similar to the allostatic model of addiction, binge eating may serve as a form of 'self-medication' driven primarily by the negative, rather than positive, reinforcing aspects of food.

Disclosures: U. Gyawali: None. **A.J. Armanious:** None. **J. Mehr:** None. **M. James:** None.

Poster

PSTR082: Drugs of Abuse: Pharmacology and Behavior

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Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR082.11/J10

Topic: G.03. Motivation

Support: New Jersey Health Foundation award
NIEHS P50 Pilot Grant Award
NIDA R00 (DA045765)
NIEHS R21 (ES035848)

Title: Bisphenol-a exposure alters puberty onset and orexin (hypocretin) function in adulthood: a role for microglia

Authors: *M. BILOTTI[1], C. BROWN[2], N. T. BELLO[3], T. A. ROEPKE[4], M. H. JAMES[5]; [1]Rutgers Univ., Piscataway, NJ; [2]Joint Grad. Program in Toxicology, Rutgers Univ., Piscataway, NJ; [3]Animal Sci., SEBS, Rutgers, The State Univ. of New Jersey, New Brunswick, NJ; [4]Rutgers Univ., New Brunswick, NJ; [5]Psychiatry, Rutgers Univ., Piscataway, NJ

Abstract: The timing of puberty is determined by a complex interplay between various endogenous factors, but it can also be significantly influenced by environmental cues. We previously showed that exposure to bisphenol A (BPA) beginning postnatal day (PND) 28 is associated with accelerated puberty onset in female rats. We also found a reduction in the number and activity of (hypocretin)-producing neurons in hypothalamus of BPA rats, which was associated with broad motivational deficits. Because BPA induces neuroinflammation throughout the brain, here we tested if changes in orexin levels might be associated with changes in local microglia number and morphology. Female rats (n=8/group) were exposed to BPA (0, 25, 250ug/kg/d) via their drinking water from PND28-56, sacrificed, and their brains sectioned for immunohistochemical detection of orexin-containing neurons and microglia. As in our previous studies, BPA treated rats had a decreased number of orexin-containing neurons compared to controls ($p < 0.05$). This was associated with an increase in the number of activated-state microglia ($p < 0.01$), and increased contacts between microglia and orexin neurons ($p < 0.05$, ANOVA and Tukey's post-hoc test). These data indicate that the alterations in behavior and orexin expression in our previous studies may be mediated by neuroinflammation. Thus, strategies that reduce neuroinflammation might protect against the consequences of BPA exposure on orexin system function and associated behaviors.

Disclosures: M. Bilotti: None. **C. Brown:** None. **N.T. Bello:** None. **T.A. Roepke:** None. **M.H. James:** None.

Poster

PSTR082: Drugs of Abuse: Pharmacology and Behavior

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR082.12/J11

Topic: G.03. Motivation

Support: NIH Grant DA 045765

Title: Selective Impairment of Sustained Attention by High-Dose Orexin Antagonism: Implications for Orx2 Involvement

Authors: *S. L. O'CONNOR[1], N. KRISHNAKUMAR[2], K. DEAK[2], M. PALADINO[3], B. GRUSZKA[4], Y. ZHANG[5], J. WISKERKE[6], U. GYAWALI[2], M. H. JAMES[2];
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Abstract: Introduction: The hypothalamic/orexin system modulates a spectrum of physiological and psychological functions, including the sleep/wake cycle, arousal, feeding, reward, motivation, and cognition. Preclinical studies support orexin signaling antagonism as a

novel and promising therapeutic for a variety of disorders. Suvorexant is a dual orexin receptor antagonist that is FDA-approved for the treatment for insomnia and thus could be readily repurposed. Given the crucial role of the orexin system in arousal, there are concerns that targeting this system could have off target effects on cognitive functions. Here, we tested how manipulating the orexin system affects performance on a rodent psychomotor vigilance task (rPVT), a translationally relevant measure of sustained attention. **Methods:** Male (n=12) and female (n=8) orexin cre+ rats were trained on the rPVT, which required them to make responses on a lever following presentation of a light cue that varied in onset time (3-10s after trial initiation); correct responses were rewarded with sucrose pellets and sessions ran for 30min. Following training, rats were injected with a cre-dependent viral construct containing the inhibitory hM4Di DREADD into the orexin cell field. Rats were subsequently injected with JHU37160 (J60; 0.1mg/kg) prior to subsequent testing on the rPVT. Performance was also assessed following injections of the orexin 1 receptor antagonist RTIOX-276 and the dual orexin receptor antagonist suvorexant (0, 3, 10, 30mg/kg; oral). All compounds were tested in a within-subjects design (counterbalanced). **Results:** Across all measures, there was no effect of sex and thus data from males and females were analyzed together. Two subpopulations of rats emerged: those with high (>65% accuracy) vs low (<65% accuracy) baseline performance on the rPVT (HP vs LP). JHU mg/kg and suvorexant decreased overall performance on rPVT, but only in high responders. RTIOX-276 had no effect in any rats. **Conclusion:** Inhibition of orexin neurons impairs measures of sustained attention on rPVT. These effects appear to be mediated by signaling at the orexin 2 receptor. These findings indicate that selective orexin 1 receptor antagonists might have limited off-target effects on cognitive outcomes.

Disclosures: S.L. O'Connor: None. **N. Krishnakumar:** None. **K. Deak:** None. **M. Paladino:** None. **B. Gruszka:** None. **Y. Zhang:** None. **J. Wiskerke:** None. **U. Gyawali:** None. **M.H. James:** None.

Poster

PSTR082: Drugs of Abuse: Pharmacology and Behavior

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR082.13/J12

Topic: G.03. Motivation

Support: Conacyt CVU No. 1267661.

Title: Differences between female and male CD1 mice in motivation by ethanol self-administration during development

Authors: *G. GALINDO SILLER[1], T. V. CAMPOS ORDONEZ[2], J. BURITICÁ[1];
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Abstract: A Progressive Ratio (PR) schedule is a reinforcement contingency that gradually increases the ratio requirement to obtain a reward, measuring motivation. In this study, adolescent female, and male CD1 mice without previous experience with ethanol were exposed to a PR schedule for ten sessions using: condensed milk or water (vehicles), condensed milk + ethanol, and water + ethanol. The control was exposed to the vehicle, and the experimental group was exposed to ethanol + vehicle. Mice were exposed to four phases (P) using the same schedule but changing reinforcement: P1, condensed milk vs. condensed milk + ethanol; P2, water vs. water + ethanol; P3, return to P1; P4, extinction. The breakpoint was recorded. Mice were sensitive to the change of substance in every phase. In P3 male mice exposed to ethanol had a higher breakpoint compared to females in both groups and the control male group. These data suggest that ethanol plus sugar consumption can be a risk for developing alcoholism in adolescence.

Disclosures: G. Galindo Siller: None. **T.V. Campos Ordonez:** None. **J. Buriticá:** None.

Poster

PSTR082: Drugs of Abuse: Pharmacology and Behavior

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR082.14/J13

Topic: G.03. Motivation

Support: NIH grant R01DK115503
GSU Brains and Behavior Seed Grant

Title: Nicotine and amphetamine decrease sucrose self-administration

Authors: *C. FULCO, A. G. ROSEBERRY;
Neurosci. Inst., Georgia State Univ., Atlanta, GA

Abstract: Amphetamine and nicotine are two widely used drugs that are taken for legitimate pharmaceutical purposes but are also highly abused through illicit recreational use. Both of these drugs have also been widely shown to decrease food intake in both humans and pre-clinical models. Although amphetamine and nicotine clearly affect food intake under normal baseline ('homeostatic') conditions, there has been limited examination of the ability of these drugs to affect reward-related ('hedonic') aspects of feeding. Furthermore, there are sex differences in the behavioral responses to both drugs that could also translate to their effects on feeding. This study examined whether nicotine and amphetamine regulate sucrose intake in a food self-administration paradigm in either a sex or dose-dependent manner across both fixed and progressive schedules of reinforcement. Amphetamine reduced operant responding for sucrose pellets in both FR3 and PR tasks in a dose-dependent manner, whereas nicotine reduced sucrose self-administration only at higher doses which also impaired locomotor activity in open field tests. The effects of both amphetamine and nicotine did not differ by sex for either drug. Overall, these results suggest that the mechanisms regulating the addictive qualities of these drugs and

their appetite-suppressing effects may be distinct, and therefore could be a potential target for future obesity therapeutics.

Disclosures: C. Fulco: None. **A.G. Roseberry:** None.

Poster

PSTR082: Drugs of Abuse: Pharmacology and Behavior

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Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR082.15/J14

Topic: G.03. Motivation

Support: 1153084-1-84320

Title: Sucrose exposure during adolescence leads to lower cocaine cue-seeking behavior in adult female rats

Authors: *K. F. HIGDON[1], A. L. GARCÍA-LÓPEZ[2], L. M. STRAND[3], D. FEDERICO[4], X. LI[4], A. M. GANCARZ[5], D. M. DIETZ[2];
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Abstract: Sucrose Exposure During Adolescence Leads to Lower Cocaine Cue-Seeking Behavior in Adult Female Rats

Authors*K. F. HIGDON[1], A. GARCIA-LOPEZ[1], L.M. STRAND[1], D. FEDERICO[1], X. LI[1], A. M. GANCARZ[1,2], **D.** M. DIETZ[1]State Univ. of New York at Buffalo, Buffalo, NYCalifornia State Univ., Bakersfield, Bakersfield, CA

Disclosures

K. F. Higdon: none, **A. Garcia-Lopez**: none, **L. M. Strand**: none, **D. Federico**: none, **X. Li**: none, **A. M. Gancarz**: none, **D. M. Dietz**: none

Abstract

Adolescence marks a key period of development, accompanied by neurobiological changes in response to environmental factors. Sucrose is one of these widely available factors that is ubiquitously available in the modern Western diet. Previously, our lab has demonstrated that adolescent sucrose exposure in male rats results in enhanced addiction-like behaviors during adulthood. However, given the large body of evidence of sex differences in response to both natural reinforcers and substances such as cocaine, it is imperative to directly examine how early life exposure may alter drug-taking behaviors in female rats. In male rats, early life exposure (PND 25-39) to sucrose enhances addiction-like behaviors during adulthood (>PND60). However, in females, this same exposure paradoxically results in decreased cocaine seeking and responses for cues previously associated with cocaine. Further, these findings were temporally driven as early abstinence periods (AD1) were less robust when compared to extended periods of

forced abstinence (AD 30). These findings indicate that exposure to sucrose during adolescence elicits sexually dimorphic effects, with sucrose serving as a potential environmental enrichment and acting as a protective factor against vulnerability to drug use in females. Alternatively, sucrose may diminish the salience of cues unrelated to drug use for female rats, as compared to those in the water condition.

Disclosures: K.F. Higdon: None. **A.L. García-López:** None. **L.M. Strand:** None. **D. Federico:** None. **X. Li:** None. **A.M. Gancarz:** None. **D.M. Dietz:** None.

Poster

PSTR082: Drugs of Abuse: Pharmacology and Behavior

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR082.16/J15

Topic: G.03. Motivation

Support: WVU Psychology Department Funding

Title: Cue reactivity in electronic cigarette users is unrelated to sign-tracking propensity but is influenced by length of use

Authors: *P. KROM[1], A. DOUGLAS[1,3], J. A. BREFCZYNSKI-LEWIS[2], M. BLANK[1], M. V. CHERKASOVA[1];
[1]Psychology, [2]Neurosci., West Virginia Univ., Morgantown, WV; [3]Psychology, West Virginia University,, Morgantown, WV

Abstract: Cue reactivity is an important predictor of addiction and relapse. However, it is unclear whether cue reactivity is primarily a product of powerful cue-reward associations established in the course of the addiction process or whether a trait-like propensity to attribute incentive salience to cues may facilitate this process. Animal studies have uncovered that individual variation in such a trait-like propensity expressed behaviorally as “sign-tracking” (ST) is associated with addiction-relevant behavioral and neurobiological features. The current study is first to examine the association between ST and cue reactivity in regular electronic cigarette (ECIG) users. Thirty-seven ECIG users (20 females) were characterized in terms of their ST propensity based on a Pavlovian conditioning paradigm accompanied by eye-tracking, and exposed to ECIG and neutral (water) cues after a period of overnight abstinence in two separate within-subjects sessions. The propensity to ST was prominent in the majority of the sample (n=28). Self-reported cravings increased significantly following ECIG cues relative to neutral cues. In contrast with our hypothesis, there was no significant association between cue reactivity (i.e., the increase in craving following ECIG cues relative to water cues) and ST propensity or self-reported ECIG dependence. However, ECIG use history (e.g., years of using) was significantly associated with cue reactivity, such as that participants with a shorter length of ECIG use reported higher craving to vape following exposure to ECIG compared to neutral cues. In contrast, participants who vaped for longer reported higher cravings following neutral cues

relative to those with a shorter vaping history and did not show an increase in craving following ECIG cues. This pattern of findings suggests that cravings in individuals with a longer vaping history may become increasingly driven by the physiological effects of nicotine withdrawal with diminishing appetitive effects of cues. In conclusion, our preliminary findings do not support the hypothesis that the propensity for incentive salience attribution to cues is a determinant of cue reactivity, which appears to be more dependent on the history of experience with the product and the physiology of nicotine addiction.

Disclosures: P. Krom: None. **A. Douglas:** None. **J.A. Brefczynski-Lewis:** None. **M. Blank:** None. **M.V. Cherkasova:** None.

Poster

PSTR082: Drugs of Abuse: Pharmacology and Behavior

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR082.17/J16

Topic: F.01. Neuroethology

Title: Neuropharmacology of cage-lid hanging behavior in mice: the role of endogenous opioid, cannabinoid, and corticosteroid systems.

Authors: *H. F. FILIPPINI[1,2], R. P. BONIN[2];
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Abstract: The translation of preclinical findings to humans in pain research is challenging. Our previous study (Zhang et al., 2021) showed that the depression of cage-lid hanging is a novel, translationally relevant pain outcome measure in mice. Stress contributes to psychiatric disorders like depression and anxiety. Under stress, the adrenal cortex secretes corticosterone in rodents. Chronic pain and depression frequently co-exist and exacerbate one another. This study aimed to assess the neuropharmacology of cage-lid hanging behavior and its association with anxiety-depression states. Eighty-one male C57BL/6 mice (6-8 weeks - old) were used in this study. Mice were treated with drugs or vehicles. To investigate if opioidergic modulation participates in hanging behavior, mice received morphine (1mg/Kg) or naloxone (3mg/Kg) IP 30 minutes before assessing hanging behavior. To determine whether endocannabinoid receptors modulate it, mice were treated with AM251 (1mg/kg) in the same conditions. To investigate the effect of anhedonia on it, mice received corticosterone (35 µg/ml) in drinking water over four weeks and then were evaluated. Naloxone 3mg/kg and AM251 1mg/Kg statistically decreased hanging behavior. Animals under corticosterone treatment displayed a significant increase in immobility in the forced swim test on week 4, compatible with depression states, and a significant decrease in hanging ($p<0.01$; 2way ANOVA + Bonferroni). These findings suggest that hanging behaviour is modulated by opioidergic and endocannabinoid signaling, and its depression seems to be related to anhedonia.

Disclosures: H.F. Filippini: None. **R.P. Bonin:** None.

Poster

PSTR082: Drugs of Abuse: Pharmacology and Behavior

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR082.18/J17

Topic: G.03. Motivation

Support: P50 MH096889
R01 MH132680
F30 MH126615

Title: Paraventricular thalamus neuronal ensembles encode early-life adversity and mediate the consequent sex-dependent disruptions of adult reward behaviors

Authors: *C. L. KOOIKER[1], M. T. BIRNIE[3], A. FLORIOU-SERVOU[2], M. HARDY[4], T. Z. BARAM[5];
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Abstract: Rationale: Early-life adversity (ELA) increases risk for mental illnesses including depression and addiction, characterized by dysregulated reward behaviors. However, the underlying mechanisms remain unclear. **Methods and Results**: In mice, we find ELA induces anhedonic behaviors in males and, in contrast, augmented motivation for palatable food and sex-cues in females. Genetic tagging demonstrated robust, preferential, sex-specific activation of thalamic paraventricular nucleus (PVT) neurons during ELA and their potentiated reactivation during adult reward tasks. Domain-specific manipulation of PVT neurons engaged during ELA uncovered that posterior PVT was required for aberrantly augmented reward behaviors in ELA females whereas by contrast, ELA-activated neurons in the anterior PVT executed reward behavior deficits in males. **Conclusions**: The PVT encodes ELA, prior to emergence of hippocampal memory systems, and contributes to its lasting impacts in sex- and domain-specific manners.

Disclosures: C.L. Kooiker: None. **M.T. Birnie:** None. **A. Floriou-Servou:** None. **M. Hardy:** None. **T.Z. Baram:** None.

Poster

PSTR083: Social Avoidance, Isolation, Aggression, and Other Social Behaviors

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR083.01/J18

Topic: F.02. Neuroendrocrine Processes and Behavior

Support: NIH Grant R15 MH122946

Title: Utilizing in vivo calcium imaging to identify changes in infralimbic cortex activity during social stress

Authors: *A. F. RADFORD, M. A. COOPER;
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Abstract: In Syrian hamsters, acute social defeat leads to a complete loss of territorial aggression and greater submissive behavior to unfamiliar animals. This defeat-induced change in social behavior is known as a conditioned defeat (CD) response. Social defeat has been shown to increase c-Fos expression in the infralimbic (IL) region of the ventromedial prefrontal cortex and greater c-Fos expression is associated with a reduced CD response. However, it is unknown which behaviors during social defeat elicit greater IL activity and attenuate subsequent stress-related anxiety. In this study, we used fiber photometry to measure *in vivo* calcium (Ca^{2+}) transients in the IL of male and female hamsters during social defeat, CD testing, and social avoidance (SA) testing to identify the social behaviors linked to changes in Ca^{2+} transients. Because animals that resist social defeat show a less pronounced CD response, we predicted that IL Ca^{2+} transients would be specifically associated with the aggressive behavior used to resist social defeat. We injected AAV-syn-jGCaMP8s-WPRE or pAAV-hSyn-eGFP into the IL followed by implantation of an optic fiber. A repeated measures design was used in which subjects received CD and SA testing 24 hours before and 24 hours after acute social defeat stress, which consisted of 3, 5-minute agonistic encounters with same-sex, trained aggressors. Ca^{2+} transients were recorded in the IL during pre-defeat CD/SA testing, social defeat stress, and post-defeat CD/SA testing. Preliminary data reveal elevated Ca^{2+} transients when animals receive an attack and when animals flee during social defeat. On the other hand, we found a decrease in Ca^{2+} transients when animals display vigilance or social sniffing. These findings suggest that agonistic behavior leads to elevated IL neural activity, while risk assessment leads to diminished IL neural activity. This line of research is a first step toward elucidating the specific behaviors that increase IL activity during stress and promote stress resilience.

Disclosures: A.F. Radford: None. **M.A. Cooper:** None.

Poster

PSTR083: Social Avoidance, Isolation, Aggression, and Other Social Behaviors

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR083.02/J19

Topic: F.02. Neuroendrocrine Processes and Behavior

Support: R15MH122946
NASEM Ford Fellowship

Title: Investigating the role of androgen receptors in a MeA-BNST pathway on dominance relationships and social defeat stress

Authors: *C. J. WHITTEN, A. GILLESPIE, M. A. COOPER;
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Abstract: Social stress is an aversive emotional experience that leads to increased fear and anxiety. Environmental factors such as dominance status can alter the way individuals react to and cope with social defeat stress. We have previously found that dominant male hamsters show a longer latency to submit during social defeat encounters, a blunted defeat-related anxiety as indexed by a conditioned defeat response, increased neural activity of androgen receptor (AR) expressing neurons in the posterior dorsal (MePD) and ventral (MePV) medial amygdala, and greater neural activity in MePD/MePV cells projecting to the bed nucleus of the stria terminalis (BNST) compared to subordinates. These findings suggest AR activity in a MePD/MePV-BNST pathway is necessary for proactive coping and stress resilience in dominant male hamsters. To test this hypothesis, animals received stereotaxic surgery with bilateral MePD/MePV infusion of a short hairpin adeno-associated virus to knockdown AR (AR-shRNA) expression or a non-functional scrambled virus (SCRM). Then, animals received conditioned defeat and social avoidance testing prior to and after acute social defeat stress. Knockdown of AR in the MePD/MePV did not alter agonistic behavior prior to social defeat, although it increased the condition defeat response following social defeat. In contrast, AR knockdown did not alter the latency to submit during social defeat or social withdrawal before or after social defeat. In a separate study, animals received rAAV-Cre into the BNST and pSICO-AR-shRNA or pSICO-SCRM into the MePD/MePV. Behavioral quantification for these animals is ongoing. Together, these findings indicate that loss of AR expression in the MePD/MePV leads to vulnerability to conditioned defeat, but does not alter proactive coping responses or stress-induced social withdrawal. Overall, these findings extend our understanding of the mechanisms by which gonadal hormone receptors promote stress resilience in specific social contexts.

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Poster

PSTR083: Social Avoidance, Isolation, Aggression, and Other Social Behaviors

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Program #/Poster #: PSTR083.03/J21

Topic: F.02. Neuroendrocrine Processes and Behavior

Support: NIH grant MH122622

Title: Vasopressin in the lateral septum differentially modulates aggression in male and female Syrian hamsters

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Abstract: Arginine-vasopressin (AVP) is a neuropeptide known for its role in many social behaviors, including offensive aggression. Aggression is a complex behavior that has been primarily studied in males. Recently, however, the investigation of aggression in females has been initiated and these studies suggest that there are fundamental sex differences in the mechanisms mediating aggression. In the present study, we examined the role of AVP within the lateral septum (LS) in mediating offensive aggression in male and female Syrian hamsters. The LS receives inputs from cortical and limbic areas and sends outputs to midbrain structures to regulate a variety of behaviors, such as social interaction, sexual behavior, maternal behavior, and aggression. AVP in the LS has been studied in the context of intermale aggression, but there are few studies investigating the role of AVP in the LS in both males and females. To investigate the role of AVP in the LS in aggression, we microinjected 10uM AVP (n=8 females, n=12 males) or saline (n=11 females, n=9 males) in the LS prior to a 10-minute aggression test with a same-sex non-aggressive intruder in the home cage of the subject. In a second study, we injected a highly selective antagonist of the V1a AVP receptor (i.e., Manning Compound) in a concentration of 90uM (n=5 females, n=4 males) or saline (n=10 females, n= 9 males). Microinjection of AVP into the LS significantly increased aggression in females but decreased aggression in males. On the other hand, Manning Compound significantly increased aggression in males, but had no effect in females. Our findings suggest that while AVP plays a role regulating aggression in both sexes, there may be different mechanisms - and potentially different circuitry - mediating these effects in males and females.

Disclosures: S.D. Lee: None. **H.E. Albers:** None.

Poster

PSTR083: Social Avoidance, Isolation, Aggression, and Other Social Behaviors

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Topic: F.02. Neuroendrocrine Processes and Behavior

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Title: Amygdala Crh cell activity required for territorial aggression

Authors: *K. THREADGILL, E. L. NEWMAN, K. J. RESSLER;
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Abstract: Introduction: Exposure to trauma can lead to posttraumatic stress disorder which can be accompanied by increases in emotional reactivity and aggression. The central amygdala

(CeA) is a point of intersection for threat and aggression neurocircuitry and corticotropin releasing hormone (Crh)-expressing CeA cells are necessary for adaptive active threat responding. The present study uses chemogenetics in mice to examine the role of Crh+ CeA neurons in territorial and self-defensive inter-male aggression.
Materials and Methods: Male CRH-ires-Cre mice were tested for aggression every other day for two weeks. During these 5-min resident-intruder confrontations, a submissive intruder male was placed into the territory of the aggressive resident CRH-ires-Cre male and aggressive behavior was quantified as latency to the first bite and total bite frequency. Aggressive resident males received intra-CeA adeno-associated virus (AAV) for Cre-dependent expression of designer receptors activated exclusively by designer drugs (DREADDs; hM3Dq, hM4Di) or control virus in Crh+ CeA neurons. After recovering from surgeries, mice were tested for aggression after receiving systemic vehicle or deschloroclozapine (DCZ) for chemogenetic manipulation of *Crh*+ CeA neurons. Territorial aggression tests were conducted using submissive intruders and self-defensive aggression tests were conducted using aggressive intruders.
Results: Chemogenetic inhibition of *Crh*+ CeA cells blocked territorial aggression but not self-defensive aggression. Chemogenetic activation of Crh+ CeA cells increased aggression, unleashing a hyper-aggressive arousal state in which the resident mice attacked familiar female companions and bit intruders on atypical body parts such as the face and tail tip. Activation did not alter self-defensive aggression.
Conclusion: *Crh*+ CeA cell activity is necessary for aggressive behavior onset in mice. *Crh*+ CeA neurons may serve as a therapeutic target to treat aberrant, offensive aggression with improved behavioral selectivity.

Disclosures: K. Threadgill: None. **E.L. Newman:** None. **K.J. Ressler:** None.

Poster

PSTR083: Social Avoidance, Isolation, Aggression, and Other Social Behaviors

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Title: Social isolation induces increased mPFC ensemble dynamics in response to social stimuli and distinct behavioral changes in male and female mice

Authors: *C. R. LEE[1,2], G. P. SCHNEIDER[1,3], F. TASCHBACH[1,2], T. B. TUAZON[1,2], A. GARCIA[1,2], T. TSIN[1,2], M. G. CHAN[1,3], K. BATRA[1,2], A. RUIZ D'ARGENCE[1,2], N. MOUSSA[1,2], A. BAKHTI-SUROOSH[1,2], J. A. WHITE[1], A. C. BASTUBA[1], B. NIELSEN[1], R. WICHMANN[1], Y. LI[4], T. D. PEREIRA[1], M. K. BENNA[2], K. M. TYE[1,2,3,5];
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Abstract: Reports of prosocial behaviors following acute social isolation and aggression following chronic social isolation led to a proposed conceptual framework for social isolation (Lee et al., 2021), but the behavioral and neural dynamics across social isolation remain unexplored. Previously, we found that dorsal raphe dopamine (DA) neurons mediate a loneliness-like state and innervate the medial prefrontal cortex (mPFC) (Matthews et al., 2016). To explore how the mPFC encodes social information and undergoes a state change following isolation, we used cellular resolution calcium imaging, genetically encoded DA sensors, ultrasonic vocalization recordings, and computer vision tools. Systematically spanning different durations (2hr, 6hr, 24hr, 7d, 14d, and 28d) of isolation, we performed a juvenile intruder task after isolating adult male and female mice. We performed pose estimation and behavioral feature extraction using a custom pipeline based on SLEAP (Pereira et al., 2022) and unsupervised clustering for behavioral motif discovery. In male mice, we found a negative correlation between isolation duration and interaction time (N=80 mice, r=-0.384, p=0.004) and that 2 and 6 hours of isolation promotes social interaction with juvenile mice (N=107 mice, $F_{6,100}$=5.875, p<0.0001; GH vs 2hr: p<0.0001; GH vs 6hr: p=0.0298). Contrastingly, in female mice, we found a positive correlation between isolation duration and interaction time (N=54 mice, r=0.425, p=0.001) and that 14 and 28 days of isolation promotes social interaction with juvenile mice (N=63 mice, $F_{6,56}$=6.152, p<0.0001; GH vs 14d: p=0.0219; GH vs 28d: p<0.0001). Furthermore, unsupervised clustering of behavior features reveals changes in male social behavior repertoire, promoting face sniffing and reducing chasing in 7 and 28 day isolated mice (N=107 mice, $F_{18,400}$=3.705, p<0.0001). Finally, we performed calcium imaging using microendoscopes in the mPFC of mice engaged in social behavior after group-housing and isolation. We found that isolation increases the responsiveness of mPFC neurons to social contact (N=18 mice, n=3938 cells, GH vs 24hr: χ^2 =9.090 , p=0.0106; GH vs 7d: χ^2=30.28, p<0.0001) by promoting excitatory responses (N=18 mice, $F_{2,15}$=5.189, p=0.0194; GH vs 24hr: p=0.0548, GH vs 7d: p=0.0146). Additionally, we found an increase in mPFC population trajectory length following isolation compared to a group housed session prior, an effect reversible followed by re-housing (N=6 mice, $F_{2,6}$=16.60, p=0.0036; GHD1 vs 24hr: p=0.0110; 24hr vs GHD2: p=0.0055). Overall, our findings support a role for mPFC in promoting features of the response to novel social stimuli following social isolation.

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Poster

PSTR083: Social Avoidance, Isolation, Aggression, and Other Social Behaviors

Location: MCP Hall A

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Title: Changing social rank alters medial Prefrontal Cortex representations to reward and punishment-predictive cues

Authors: *R. L. MIRANDA[1,2], K. N. KIM[3,4], C. R. LEE[1,2], A. GARCIA[1,5], R. CASTRO[1,5], K. BATRA[1,5], A. BASTUBA[1], R. SYED[6], B. NIELSEN[1,7], F. TASCHBACH[1,5], L. KEYES[1,7], R. WICHMANN[1], T. D. PEREIRA[1], K. M. TYE[1,7,5,8];
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Abstract: Many animal groups form social hierarchies, but the biological substrate underlying flexible representations of rank and how this influences emotional states is unknown. Previous work in our lab has shown that one's relative rank in a mouse social hierarchy is represented in the medial prefrontal cortex(mPFC)(Padilla-Coreano et. al, 2022). The mPFC has also been shown to modulate social dominance, and forced loss to a subordinate animal has been shown to induce a depressive-like state(Fan et. al, 2023).
To understand the mechanism of social rank formation and how social status affects valence encoding, we designed a novel rank reorganization paradigm to manipulate the social hierarchy of mice by rehousing like-ranks together, forcing a rank change in a subset of mice. Before and after rehousing, we used cellular resolution calcium imaging to track how the mPFC responds to positive and negative stimuli. Changes in social rank had a significantly positive correlation with the number of mPFC neurons responsive to sucrose in the sucrose preference task(N=7 mice, n=2385 cells, $F(4,2) = 42.11$, $p = 0.0233$), suggesting a link between social status and valence encoding. Additionally, change in distance between the top Principal Components(>90% variance explained) of sucrose and water consumption showed a strong trend of positive correlation with changes in social rank(N=7 mice, n=2385 cells, $F(4,2) = 15.38$, $p=0.062$). During a pavlovian discrimination task, principal component analysis between reward and shock cues revealed that dominant mice showed less variance in mPFC response to reward and shock,

while lower rank mice had longer shock trajectories(N=16 mice, n=4290 cells, p=0.0292). Additionally, changes in distance between the top Principal Components of reward and shock cues positively correlated with changes in social rank(N=8 mice, n=2067 cells, $F(4,3) = 10.39$, $p = 0.0419$). Lastly, cages of mice were placed in 24hr homecage monitoring systems before and after rehousing to quantify features leading to development of social hierarchies. Hierarchy analysis showed that intermediate mice rehoused together took significantly longer to stabilize compared to subordinates and dominants(N=27 mice, p=0.0403), and that chasing behaviors during the first 30 minutes of rehousing was sufficient to predict dominance status before the hierarchy had stabilized(N=12 mice, p=0.0352). Overall, our work provides a novel method for the manipulation of individual social rank and quantification for the formation of social hierarchies, and reveals that changes in social status positively correlate with responsiveness to positive and negative stimuli in the mPFC.

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Poster

PSTR083: Social Avoidance, Isolation, Aggression, and Other Social Behaviors

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Title: Discovering the individual differences in shared representations of neural dynamics and ethological behaviors

Authors: *F. H. TASCHBACH[1,2], C. R. LEE[1,2], G. SCHNEIDER[1,3], T. TUAZON[1,2], A. GARCIA[1,3], M. K. BENNA[2], K. M. TYE[1,2,3,4];
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Abstract: Understanding how social behavior evolves across social isolation is both an enormous priority and technical challenge. Exploring the neural underpinnings of self-initiated behaviors in a quantitative and rigorous manner is difficult without experimenter-defined trial structures. Although loneliness has been declared as an epidemic, there are no therapeutic targets and no mechanistic explanations for how social isolation negatively impacts our health. The dynamic time course of social isolation has been conceptualized in a model of social homeostasis (Lee et al., 2021). Multiple timescales for social behavioral dynamics have been observed in the PFC (Padilla-Coreano et al., 2022). Here, we investigate the neural representations of social interaction during a resident-intruder task with mice that have been acutely (24 hours) or chronically (7 days) isolated (Group Housed: N=6 mice, n=1283 cells; 24hr: N=6 mice, n=1201 cells; 7d: N=6 mice, n=1454 cells). We found that isolation (24hr and 7d) increased the responsiveness of mPFC neurons to social contact (n=18 mice, 3938 cells, GH vs 24hr: χ^2 =9.090, p=0.0106; GH vs 7d: χ^2=30.28, p<0.0001) by promoting excitatory responses (n=18 mice, F(2,15)=5.189, p=0.0194; GH vs 24hr: p=0.0548, GH vs 7d: p=0.0146). To uncover differences in their neural representations, we developed Shared Representation Discovery (ShaReD), a method for aligning high-dimensional paired multi-modal data across subjects. ShaReD identifies interpretable common feature combinations across all individuals in one modality (i.e. behavioral features) that are maximally correlated with specific feature combinations in another modality (i.e. neural activity) in each individual. After validating ShaReD with synthetic data, we applied it to the experimental neural and behavioral datasets. We discovered that neurons from each isolation group correlated strongly with multiple, distinct behavioral features. Notably, neurons in isolated mice demonstrated significantly stronger decoding of interactions with conspecifics, compared to controls (n=18 mice, F(2, 27)=15.52, p=0.0000326; GH vs 24hr: p=0.0017, GH vs 7d: p=0.00003). Further, we found differences in the encoding of behavioral repertoires of chronically isolated compared to acutely isolated mice (p=0.048). Our findings illuminate the distinct neural consequences of varying social isolation durations. This underscores ShaReD's utility in advancing neuroscience, particularly in examining neural correlates of behaviors in more ethological settings.

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Poster

PSTR083: Social Avoidance, Isolation, Aggression, and Other Social Behaviors

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Title: Homeostatic-need states shift amygdala valence-encoding in a projection-specific manner

Authors: *D. LEDUKE[1,3], A. BASTUBA[1], K. KIM[4], G. G. CALHOON[5], A. K. SUTTON HICKEY[7], K. FISCHER[1], A. A. COLEY[1], R. MIRANDA[1], L. KEYES[1], J. DELAHANTY[1], C.-J. CHANG[5], C. A. LEPPLA[5], C. SICILIANO[5], C. P. WILDES[5], B. NIELSEN[1], A. BEYELER[5], E. Y. KIMCHI[5], K. M. TYE[2,6,8];
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Abstract: Despite the fact that exercise and food deprivation are both physical stressors on the body, they induce oppositional emotional states. Historical evidence suggests that the basolateral amygdala (BLA) is a nexus for emotional processing. BLA projections to the nucleus accumbens (NAc) and the centromedial amygdala (CeM) encode good and bad associations, respectively. We have demonstrated how these two populations influence each other: BLA-CeM neurons supress BLA-NAc neurons in sated conditions, yet, under food deprived conditions, BLA-CeM neurons then excite BLA-NAc neurons (Mann-Whitney U=76.5, p-0.0036, N=16). We demonstrate that energy balance deficits impact BLA activity in a projection-specific manner: food deprivation impacts spontaneous firing rates of both BLA-CeM (Friedman Test, Chi-square=11.67, **p=0.0029) and BLA-NAc (Friedman Test, Chi-square=15.50, ***p=0.0004) projections. To assess the differential impact of food deprivation and exercise on projection-specific BLA neurons, we constructed a two-photon (2P) imaging pipeline to track single-cell activity, licking rate, and facial expression across days. We used a Pavlovian task to determine the functional role of these neurons, presenting an unconditional stimulus (US) paired with a conditioned stimulus (CS). Using a projection-specific viral approach, head-fixed animals were imaged in sated, idle, food deprived, and exercised conditions. Using measurement of fluorescent change of genetically encoded calcium indicators, we analyzed change in fluorescence from baseline over time. BLA-CeM valence-encoding neurons were not affected by food deprivation during CS presentation (ANOVA, F(3, 99)=2.21, p=0.081, N=100), while BLA-NAc neurons were significantly affected by food deprivation (ANOVA, F(3, 121)=3.66, p=0.012, N=122). When animals were given access to exercise, this projection-specific response was again altered. BLA-CeM valence-encoding neurons were significantly affected by exercise-wheel use (ANOVA, F(3, 141)=4.66, p=0.003, N=141) and BLA-NAc valence encoding neurons were not affected (ANOVA, (F, 3, 82)=0.85, p=0.463, N=83). Licking data demonstrate that animals discriminated between tones and homeostatic need alters motivation in tasks. Facial expression analysis demonstrate changes in facial features (Wilcoxon rank sum, z=-2.16, p=0.030, N=4) in food deprived conditions, suggesting that homeostatic needs are communicated through changes in facial expression. These findings suggest a model in which the BLA is an emotional nexus that alters valence-specific projections based on stress identity.

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Poster

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Title: Impacts of psilocybin administration on valence processing in the medial prefrontal cortex during a reward-punishment conflict task

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Abstract: In humans, the plant-derived indoleamine psilocybin heightens emotional sensitivity and arousal bidirectionally—increasing positive mood, decreasing negative mood, and reducing reactivity to negative emotional stimuli in some cases (Barrett et al., 2020; Kraehenmann et al., 2015; Kometer et al., 2012), while generating dysphoria, anxiety/panic, and impaired control/cognition in other cases (Carbonaro et al., 2016; Hirschfeld and Schmidt 2021). Despite this variability both across and within individuals and experiences, psilocybin and other psychedelics have been found to reduce symptoms of anxiety and depression when taken in the clinic (Griffiths et al., 2016; Ross et al., 2016; Gasser et al., 2014; Grob et al., 2011), and when taken in naturalistic settings (Argento et al., 2022; Sexton et al., 2020; Johnson et al., 2019; Pisano et al., 2017; Hendricks et al., 2015; Krebs & Johansen 2013). If a highly variable experience consistently yields similar outcomes, it raises the question: does the experience itself even matter, or is there an underlying common factor not yet captured by our current measures? Here, we investigate the acute and persistent effects of psilocybin on neural representations of valence in the medial prefrontal cortex (mPFC). To do so, a reward-punishment conflict task was designed in which conditioned stimuli predicting either an Ensure reward or a shock punishment were presented independently on some trials and simultaneously in others (Burgos-Robles et al.,

2017; Vander Weele et al., 2018). At baseline, we observed that mice spent more time exploring the reward port during reward trials compared to shock and conflict trials (N=4, $F_{1.072, 3.216}$ = 37.29, p=0.0070; Rew vs Fear: p=0.0449; Rew vs Conflict: p=0.0089), and more time freezing during shock trials compared to reward and conflict trials (N=4, $F_{1.104, 3.312}$ = 39.96, p=0.0057; Fear vs Rew: p=0.0235; Fear vs Conflict: p=0.0222). Neuropixels probes were used to perform high-yield, spatiotemporally precise in vivo electrophysiology in the mPFC as mice performed the conflict task before, the day of, two days following, and 14 days following an injection of psilocybin (1 mg/kg). Performing hierarchical clustering on neural responses to the reward, shock, and conflict trials yielded nine functional clusters of valence-tuned neurons, with a significant difference in the prevalence of clusters found between sessions conducted prior to, during, and post-psilocybin (X^2_{24} = 55.84, p=0.0002). Overall, our results suggest that the mPFC plays a role in modulating responses to valenced stimuli before, during, and after a psilocybin experience.

Disclosures: A. Bakhti-Suroosh: None. **F. Massa:** None. **M.G. Chan:** None. **M. Vasconcelos:** None. **K. Batra:** None. **L. Keyes:** None. **H. Li:** None. **B. Nielsen:** None. **C.R. Lee:** None. **J. Delahanty:** None. **J. White:** None. **R. Wichmann:** None. **T.D. Pereira:** None. **K.M. Tye:** None.

Poster

PSTR083: Social Avoidance, Isolation, Aggression, and Other Social Behaviors

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR083.10/J28

Topic: F.02. Neuroendrocrine Processes and Behavior

Support: European Union's Horizon 2020 research and innovation program (Grant Agreement 953327)

Title: The role of neuromodulation in the emergence of individuality in nest architecture

Authors: *A. CAPAZ[1], C. ROUSSEAU[1], P. GASPAR[2], N. RENIER[1];
[1]Paris Brain Inst., Paris, France; [2]Paris Brain Inst., INSERM-U839, Paris, France

Abstract: Understanding how interindividual variations in brain circuits shape personality and behaviors is essential to better designing treatments and therapies for psychiatric disorders. Nesting is a native and motivated behavior, crucial for the survival and adaptation of several species. In the mouse, disruptions in this behavior are observed when animals are subject to stress and anxiety, and many internal and external factors participate in shaping how the animal nests. Mice in the laboratory environment spontaneously build nests that can be either flat (not covering the animal) or hollow (providing a better shelter). We observed in adult congenic C57bl6/J male mice striking interindividual variations in their spontaneous nest building, with preferences for either flat or hollow nests that were stable over time for a given mouse. We hypothesized that variations in nest building styles could be a readout of personality traits, and

therefore set out to determine the neural correlates of these behavioral variations. We found that variability in nest building preferences can emerge a few days after post-weaning in isolation, regardless of social environmental factors or maternal lineage. Nesting styles are also not correlated with basal anxiety, corticosterone levels, social hierarchy, marble burying, olfaction discrimination, or preweaning experiences. The time spent interacting with nesting material does not predict the quality of the nest, indicating a dissociation between nesting effort and nesting style. Pharmacological and genetic manipulations targeting serotonin transmission, including fluoxetine treatment and Tph2 knockout, disrupted nesting style preferences. Whole-brain cFos mapping revealed decreased activity in the dorsolateral striatum and the olfactory tubercle (OT) in the hollow nest builders, compared to flat nest builders, in dopamine receptor 1-expressing (D1) neurons. This region expresses high levels of serotonin (5HT) receptors (5HTRs). Using RNA sequencing and in situ hybridization, we found that a decrease of 5HTR1b and 5HTR2a expression in D1+ neurons correlates with a flat nesting style. Our study further aims to dissect the role of neuromodulation within the striatum for the development of inter-individual variations in nesting behavior.

Disclosures: A. Capaz: None. **C. Rousseau:** None. **P. Gaspar:** None. **N. Renier:** None.

Poster

PSTR083: Social Avoidance, Isolation, Aggression, and Other Social Behaviors

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR083.11/J29

Topic: G.04. Emotion

Support: IBS-R001-D3
NRF2012R1A3A1050385

Title: The paraventricular nucleus of the thalamus mediates the regulation of anxiety and aggression

Authors: *H. JUNG[1,2], C. KWAK[1,2], J. LEE[2], A. M. ISLAM[2,3], C. LEE[1,2], H. PARK[1,2], I. HONG[1,2], S. J. KANG[2], J. OH[2], J.-I. KIM[2], J. LEE[2], H.-G. KO[4], C.-S. LIM[5], B.-K. KAANG[1,2]; [1]Inst. for Basic Sci., Daejeon, Korea, Republic of; [2]Seoul Natl. Univ., Seoul, Korea, Republic of; [3]North South Univ., Dhaka, Bangladesh; [4]Dept. of Anat. and Neurobiology, Sch. of Dent., Kyungpook Natl. Univ., Daegu, Korea, Republic of; [5]Dept of Pharmacol, Wonkwang Univ., Jeonbuk, Korea, Republic of

Abstract: Despite the well-established link between anger and aggression, it has been consistently suggested that anxiety is also associated with aggression. However, the specific brain region involved in the co-regulation of anxiety and aggression remains unclear. To identify such a brain region that controls both anxiety and aggression, we performed direct control of neuronal activities in the paraventricular nucleus of the thalamus (PVT) employing activity modulation techniques. This was coupled with behavioral tests including the open field test

(OFT), elevated zero maze (EZM), and light-dark transition (LDT) test to assess anxiety-like behavior, as well as the resident intruder test (RIT) to evaluate aggressive behavior in C57BL/6 mice. Our findings reveal that optogenetic activation of the PVT using channelrhodopsin-2 (ChR2) not only induced an increase in anxiety-like behaviors but also suppressed the aggressive behavior toward an intruder only in a laser-on session. These behavioral changes were not detected in the control group that was infected with AAVs lacking ChR2. Furthermore, circuit-level modulation indicated that the connection from the PVT to the basolateral amygdala (BLA) plays a more crucial role in regulating anxiety than the connection from the PVT to the bed nucleus of the stria terminalis (BNST). To investigate the molecular markers contributing to the co-regulation of anxiety and aggression, we targeted the Orexin receptor 1 (Ox1R) positive neurons within the PVT. 26.52 % of the total population among the PVT were confirmed to comprise Ox1R-positive neurons by immunohistochemistry, and 58.24 % of them were labeled to modulate neuronal activity using a customized Ox1R targeting promoter (n= 12 slices from 3 mice). We found that the activation of Ox1R-positive neurons increased anxiety-like behavior and discontinued aggressive behavior, whereas these behavioral alterations were not observed in the control group. Taken together, our results suggest that the Ox1R-positive neurons within the PVT induce a change in the emotional states of mice, primarily the anxiety-like state and aggression. These findings shed light on the neural mechanisms underlying the interplay between anxiety and aggression.

Disclosures: H. Jung: None. **C. Kwak:** None. **J. Lee:** None. **A.M. Islam:** None. **C. Lee:** None. **H. Park:** None. **I. Hong:** None. **S.J. Kang:** None. **J. Oh:** None. **J. Kim:** None. **J. Lee:** None. **H. Ko:** None. **C. Lim:** None. **B. Kaang:** None.

Poster

PSTR083: Social Avoidance, Isolation, Aggression, and Other Social Behaviors

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR083.12/J30

Topic: G.04. Emotion

Support: Sumitomo Foundation
Research Grant

Title: Plasticity in a limbic-hypothalmic circuit for the periodic expression of aggressive behaviors in lactating female mice.

Authors: *T. YAMAGUCHI[1], R. YAN[2], M. KHAN[3], D. LIN[4];
[1]New York Univ. Neurosci. Inst., New York, NY; [2]NYU langone Med. Ctr., New york, NY; [3]New York Unniversity Neurosci. Inst., New York, NY; [4]New York Univ. Neurosci. & Physiol., New York, NY

Abstract: While females are typically not as aggressive as males, the level of aggression in females increases dramatically during lactation in mammals for protecting their young. This

drastic behavioral change suggests the dynamic remodeling of the female brain during pregnancy and lactation. However, it remains ambiguous how the female brain switches to aggressive mode to protect their offspring. Using *in vivo* and *in vitro* recordings, and tools for neural perturbation, we found that a limbic-hypothalamic circuit dynamically changes neuronal responsivity and synaptic transmission to drive aggressive behaviors in lactating females. Moreover, we demonstrated that plastic changes in the oxytocin system during the lactating period boosts this circuit for the stable expression of maternal aggression. We focused on the posterior amygdala (PA) - ventrolateral hypothalamus ventrolateral part (VMHvl) circuit which I have previously identified as a regulatory hub for aggressive behaviors in male mice. First, we demonstrated the PA-VMHvl circuit bidirectionally regulates maternal aggression using chemogenetic and optogenetic tools. Importantly, VMHvl-projecting PA cells were strongly activated during maternal aggression and highly increased responses to social targets during lactation. These behavioral and *in vivo* response changes coincide with robust alternation in neuronal excitability and synaptic transmission in PA-VMHvl circuit. Moreover, we found that oxytocin release in response to suckling stimulus facilitated maternal aggression through the oxytocin receptor (OXTR) in the PA. Interestingly, OXTR gene expression in the PA cells was drastically increased during lactation. Importantly, both acute inhibition and chronic gene-knockout of OXTR in the PA significantly decreased aggressive behaviors in lactating females. Altogether, our study reveals the plastic changes of physiological properties in PA-VMHvl circuit to induce the transient expression of aggressive behaviors in lactating females and highlights the importance of oxytocin system in a limbic-hypothalamic circuit for protecting vulnerable offspring from social threat.

Disclosures: T. Yamaguchi: None. **R. Yan:** None. **M. Khan:** None. **D. Lin:** None.

Poster

PSTR083: Social Avoidance, Isolation, Aggression, and Other Social Behaviors

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR083.13/J31

Topic: G.04. Emotion

Support: RO1MH112593
RO1MH123612
RO1NS123916

Title: Neural Implementation of a Hypothalamic Line Attractor Encoding an Internal Behavioral State

Authors: *A. VINOGRAD[1], **A. NAIR**[2], J. KIM[1], S. LINDERMAN[3], D. ANDERSON[1]; [1]Caltech, Pasadena, CA; [2]Computation and Neural Systems, Caltech, Pasadena, CA; [3]Dept. of Statistics and Wu Tsai Neurosciences Inst., Stanford Univ., Menlo Park, CA

Abstract: Line attractors are emergent population dynamics hypothesized to encode continuous variables such as head direction and internal states. In mammals, direct evidence of neural implementation of a line attractor has been hindered by the challenge of targeting perturbations to specific neurons within contributing ensembles. Estrogen receptor type 1 (Esr1)-expressing neurons in the ventrolateral subdivision of the ventromedial hypothalamus (VMHvl) show line attractor dynamics in male mice during aggressive encounters. We have previously hypothesized that these dynamics may encode continuous variation in the intensity of an internal aggressive state. Here, we report that these neurons also showed line attractor dynamics in head-fixed mice observing aggression. We exploited this finding to identify and perturb line attractor-contributing neurons using 2-photon calcium imaging and holographic optogenetic perturbations. On manifold perturbations indicated that integration and persistent activity are intrinsic properties of these neurons, which drive the system along the line attractor, while transient off-manifold perturbations revealed rapid relaxation back into the attractor trough. Furthermore, single-cell stimulation and imaging revealed selective functional connectivity among attractor-contributing neurons. Intriguingly, individual differences among mice in line attractor stability were correlated with the degree of functional connectivity among attractor neurons. Mechanistic modelling indicates that dense subnetwork connectivity and slow neurotransmission best recapitulate our empirical findings. Our work bridges circuit and manifold levels, providing definitive evidence of continuous attractor dynamics in a behaviorally relevant mammalian system.

Disclosures: A. Vinograd: None. **A. Nair:** None. **J. Kim:** None. **S. Linderman:** None. **D. Anderson:** None.

Poster

PSTR083: Social Avoidance, Isolation, Aggression, and Other Social Behaviors

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR083.14/J32

Topic: G.01. Fear and Aversive Learning and Memory

Support: NINDS/BRAIN Initiative R01 NS113104

Title: Corticotropin releasing factor regulation of social avoidance and social attachment in the prairie vole (Microtus ochrogaster)

Authors: *L. NERIO MORALES[1], E. DUGAN[2], A. S. SMITH[3];
[1]Pharmacol. and Toxicology, The Univ. of Kansas, Lawerence, KS; [2]Dept. of Psychology, Univ. of Kansas, Lawrence, KS; [3]Dept. of Pharmacol. & Toxicology, Univ. of Kansas, Lawrence, KS

Abstract: The social defeat model in prairie voles (*Microtus ochrogaster*) is characterized by social avoidance of strangers and a heightened stress state, characteristic traits of social anxiety disorder in humans. Using this model, we have recently documented that social defeat induces sex-dependent effects on social attachment, inhibiting male partner preference while accelerating

it in females. Additionally, corticotropin-releasing factor (CRF) neurons in the bed nucleus of stria terminalis (BNST) play an important role in mediating these behaviors, as chemogenetic activation of CRF neurons in this region promotes pair bond formation in both sexes. Further, BNST CRF behavioral effects change from appetitive to aversive in response to social defeat stress and seem to vary in a sex-dependent manner. This may be due, in part, to a stress-induced shift in CRF regulation of dopamine transmission in the mesolimbic dopamine system, a circuit relevant to social attachment and pair bond formation. Here, we determined changes in CRF mRNA levels in the BNST of male and female defeated and paired prairie voles. Our results indicate that CRF production increases in the BNST of females after pairing regardless of defeat conditioning, while it increases in defeated and paired males. Additionally, we assessed the effects of pharmacological manipulation in the VTA of defeated male and female prairie voles to determine whether this manipulation prevents the behavioral effects observed in partner preference after social defeat. We found that CRF in the VTA promoted partner preference in stress-naïve male and female prairie voles. However, we found sex-specific effects after defeat conditioning as a CRF R1 antagonist administered in the VTA recovered social approach and partner preference in defeated males but did not block partner preference or recover social approach behavior in females. These results suggest that CRF plays sex-specific roles in social defeat and attachment, most likely through the regulation of the mesolimbic dopamine system.

Disclosures: L. Nerio Morales: None. **E. Dugan:** None. **A.S. Smith:** None.

Poster

PSTR084: Positive and Negative Emotional States

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR084.01/J33

Topic: G.04. Emotion

Support: NSERC Discovery 06248

Title: A computer vision pipeline to detect gradients of facial expressions of negative in freely moving mice.

Authors: A. TELFER[1], B. MACAULAY[2], ***A. ABIZAID**[3];
[1]AI in Med. Initiative, The Hosp. for Sick Children, North Vancouver, BC, Canada; [2]Dept. of Neuroscience, Carleton Univ., Ottawa, ON, Canada; [3]Carleton Univ., Ottawa, ON, Canada

Abstract: In preclinical research, animal models are often used in the study how stress impacts emotional states with the goal of translating findings that improve human health. Mice are a popular species as their physiological responses to stress are similar to those observed in humans, and their genome is routinely manipulated to study the role of specific genes in have a well-mapped genome. Behavioral responses, however, are often restricted to behavioral screens that require a substantial amount of time end effort to score, and that can be variable due to experimental bias and/or experimenter scoring accuracy. The rapid advancement of Deep

Learning has led to open-source machine learning software that can outperform commercial tools on fundamental tasks. AI has previously been applied to facial expressions in restrained mice in order to distinguish between a wide range of facial expressions induced using different stimuli such as pleasure, fear, and disgust. With freely moving mice, researchers have developed a deep learning pipeline that emulates human scoring of the Mouse Grimace Scale from video using a stochastic frame extraction technique. Our study builds on the Mouse Grimace Scale pipeline using a model that can score batches of sampled frames. In addition, we create a novel dataset with depressive-like symptoms using lipopolysaccharide (LPS) to induce a controlled sickness response known to promote anxiety-like and depressive-like behaviors such as appetite loss and social withdrawal in both humans and mouse models. Our dataset is designed to test for scale sensitivity by including multiple LPS dosages measured at multiple time points. We demonstrate that our trained model produces scores that align with what would be expected from scale-sensitive scoring of facial expressions, and provides evidence for ML-based techniques that can assay degrees of affective state from video frames.

Disclosures: A. Telfer: None. **B. MacAulay:** None. **A. Abizaid:** None.

Poster

PSTR084: Positive and Negative Emotional States

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR084.02/J34

Topic: G.04. Emotion

Support: KAKEN 22K07336
KAKEN 22K07608
KAKEN 22H02812
KAKEN 18K07401
ISHIBASHI FOUNDATION
KAKEN 22K07569

Title: The Ebb and Flow of Male Confidence in Attracting Females in Mice: Unraveling the Fragility and Reversibility

Authors: *Y. N. OHNISHI, Y. KAWAHARA, Y. HONDA-OHNISHI, A. NISHI;
Dept. of Pharmacol., Kurume Univ. Sch. of Med., Kurume, Japan

Abstract: The ability to attract mates is a critical determinant of reproductive success in males. Our previous studies (SfN 2017-2019, 2022, 2023) have highlighted that male mice's attractiveness is supported by physical appearance and self-confidence. This study focuses on the dynamics of male confidence and its impact on maintaining attractiveness. Over a three-month period, the most attractive males consistently ranked in the top two among four candidates, despite fluctuations in their popularity. Interestingly, no specificity was observed in the attractiveness of female mice. Furthermore, the resilience of attractiveness in males with induced

depressive states due to social defeat was investigated; results demonstrated that these males maintained their attractiveness, indicating no correlation between social confidence loss and male attractiveness. Additionally, using the tube test to assess the correlation between social hierarchy and attractiveness yielded no significant findings. Our study discovered that even genetically sight-impaired attractive C3H male mice could sense when less attractive males were in a harem-like situation, leading to a rapid decline in their own attractiveness within just one day, similar to what is observed in sighted males. This indicates that even without visual perception, male mice can detect other males interacting closely with females, and this perception negatively impacts their attractiveness. Additionally, we found that this decrease in attractiveness could be reversed within about a week if the experience of decreased attractiveness lasted only a day. Ongoing experiments aim to explore if testosterone administration or social interactions with females can mitigate the decline in attractiveness due to loss of confidence. Further experiments will investigate the effects of physical barriers and mirrors on male perception and subsequent attractiveness, to decipher the cognitive aspects influencing male mating success.

Disclosures: Y.N. Ohnishi: None. **Y. Kawahara:** None. **Y. Honda-Ohnishi:** None. **A. Nishi:** None.

Poster

PSTR084: Positive and Negative Emotional States

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR084.03/J35

Topic: G.04. Emotion

Support: KAKENHI JP19K17063
KAKENHI JP22K15764
SENSHIN Medical Research Foundation

Title: Refining mood assessment with the Chen-HAgiwara Mood Test (CHAMT): A novel scale for enhanced detection of mood variations

Authors: *K. HAGIWARA, C. CHEN, S. NAKAGAWA;
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Abstract: The assessment of mood plays a critical role in the domains of psychology, neuroscience, and psychiatry, but traditional scales for measuring mood, including the widely-used Positive and Negative Affect Schedule (PANAS) and Profile of Mood States (POMS), are often cumbersome due to their extensive item lists. Efforts to streamline these scales have led to the creation of shorter versions that typically use contrasting adjectives to quickly evaluate mood valence and arousal. Yet, these simplified scales have fallen short in accurately reflecting the complex interplay between valence and arousal. Additionally, the reliance on Likert scales for mood re-evaluation can induce a bias, as participants might compare their current mood

assessments to previous ones, potentially skewing results towards socially desirable responses.To tackle these limitations, we have recently developed the Chen-HAgiwara Mood Test (CHAMT, Chen, Hagiwara, et al., 2024, Asian Journal of Psychiatry). This three-item scale is rooted in the valence-arousal theory of affect and provides a detailed mood assessment through its focus on Pleasure, Relaxation, and Vigor. By employing a 10 cm continuous Visual Analog Scale, CHAMT aims to reduce the likelihood of response bias. Our research indicates that CHAMT offers robust internal consistency and reliable test-retest results within the same day. Furthermore, CHAMT has shown significant associations with well-established criteria for positive affect, depression, and anxiety, affirming its validity. The scale's application in various experimental settings has illuminated its capacity to detect mood changes across different interventions. Activities such as aerobic exercise and reminiscing about positive memories primarily alter Pleasure and Vigor but not Relaxation, whereas viewing natural scenes predominantly increases Pleasure and Relaxation without significantly affecting Vigor. Here we report new observation using 52-channel functional near-infrared spectroscopy (fNIRS) of a significant negative correlation between Relaxation scores from CHAMT and oxyhemoglobin levels in the orbitofrontal cortex after viewing natural scenes ($r=0.47$, $p<0.05$), aligning with evidence that contact with nature relaxes the brain. Together, these insights affirm the potential of CHAMT to advance mood assessment in psychological and neuroscientific research, offering a more refined tool to capture the intricate effects of interventions on mood dynamics.

Disclosures: K. Hagiwara: None. **C. Chen:** None. **S. Nakagawa:** None.

Poster

PSTR084: Positive and Negative Emotional States

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR084.04/J36

Topic: G.04. Emotion

Support: DGAPA-PAPIIT UNAM grant IN207923 (FB)
CONHACyT grant CB255462 (FB)
CONAHCyT CVU 2013153 Ayudante de investigador (SNI III)

Title: Socioemotional domains in family members of feminicide victims in Mexico

Authors: *A. PIÑA HERNÁNDEZ, D. ATILANO-BARBOSA, I. ESPINOSA MÉNDEZ, F. A. BARRIOS;
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Abstract: There is research showing a close relationship between homicide and the onset of psychological problems in bereaved individuals directly impacted by such events. In 2022, Mexico reported 976 cases of feminicide, reflecting a serious issue. Shockingly, for every 100,000 women in the nation, 1.5 fell victim to gender-based violence, yet only 23.32% of these cases led to convictions. Additionally, the legal and mental health support system has been

identified as inefficient and retraumatizing for the victims and their families. In this context, it is essential to understand how the socio-emotional and mental health domains are affected in the family members of feminicide victims. To approach this issue, a study was conducted using a sample that included 17 controls and 3 direct family members of attempted feminicide victims. The emotional battery of the NIH Toolbox, which assesses 17 emotional subdomains, was applied. Welch's t-test was used to detect possible significant differences between the groups, and Cohen's d was calculated to evaluate the effect size. The results showed significant differences in the domains of Friendship, Fear Somatic Arousal, and Anger Affect. Moreover, large effect sizes were observed in the domains of Instrumental Support, Loneliness, Perceived Rejection, Perceived Stress, Fear Affect, and Sadness. Although no significant differences were found in these latter domains, their effect sizes suggest they could be significant with a larger sample size.While this is an exploratory analysis, it provides an initial insight into the problem, and the sample size is planned to be increased in the following months. However, recruiting and evaluating this population requires attention and intervention protocols that will be sought to implement later. In the future, associations between these measures and post-traumatic stress disorder, anxiety, and depression, as well as their brain correlates using MRI, will be explored.

Disclosures: A. Piña Hernández: None. **D. Atilano-Barbosa:** None. **I. Espinosa Méndez:** None. **F.A. Barrios:** None.

Poster

PSTR084: Positive and Negative Emotional States

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR084.05/J37

Topic: G.04. Emotion

Support: Research Training Group GRK2350

Title: Influence of urban green space on human well-being and stress response: insights from neural functioning

Authors: *Y. LIN, N. ROYCHOUDHURY, O. BERHE, J. ANDOH, A. S. MEYER-LINDENBERG, H. TOST;
Central Inst. of Mental Hlth., Univ. of Heidelberg, Germany, Mannheim, Germany

Abstract: Psychiatric morbidity is high in cities, and exposure to urban green space (UGS) has been shown to have positive effects on emotion and stress regulatory systems. Thus, identifying how the emotional regulatory brain circuits respond to UGS and urban concrete spaces (UCS) is important. By modifying the Hariri FACES task, the Environmental and Emotion processing task (EnvoEmo task) which comprises of viewing negative and neutral emotional faces immediately after immersive viewing of two extreme types of landscapes (UGS and UCS) in a randomized block-event mixed design, making it possible to reliably activate emotion regulation brain circuits, e.g. amygdala, using functional magnetic resonance imaging (fMRI). In this study, 27

healthy adults performed the EnvoEmo task during fMRI. We compared the fMRI responses to viewing the UGS and UCS pictures and observed significant amygdala activation (t = 4.28, P<0.01) at the group-level when viewing UCS pictures. In addition to the amygdala, group results also showed rostral ACC activation when viewing UGS. We also observed that viewing UGS landscapes before viewing negative faces can significantly reduce amygdala activation (t = 5.24, P<0.01) in comparison to viewing UCS. Behavioural ratings administered inside the scanner showed that momentary affective well-being is significantly higher after viewing UGS compared to viewing UCS (P<0.00). These consistent findings suggest that viewing UGS landscapes may have a buffering and calming effect on stressful emotional processing and resulting stress regulation. Future research should investigate the potential impact of UGS exposure in real life on neural functioning and on momentary well-being in daily-life.

Disclosures: Y. Lin: None. **N. Roychoudhury:** None. **O. Berhe:** None. **J. Andoh:** None. **A.S. Meyer-Lindenberg:** None. **H. Tost:** None.

Poster

PSTR084: Positive and Negative Emotional States

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR084.06/K1

Topic: G.04. Emotion

Title: Heavy is the hand that throws the trash? Exploring the relationship between ecological guilt and engagement in pro-environmental behaviours

Authors: *E. CHEPEL, N. GAHOV, E. KANTINI, M. C. TUCCI;
Seneca Polytechnic, King City, ON, Canada

Abstract: Globally, over the last 10 years, discussion of climate change amongst researchers and the public alike has steadily increased (Church et al., 2023). Previous literature delves into the prevalence of such conversations and their psychological effects with new terms emerging such as ecological anxiety and ecological guilt identified across varying demographics (Pihkala, 2020). Abbreviated, eco-guilt is the specific manifestation of guilt characterized by a negative feeling about the environment, for example, violating social norms of eco-friendly or sustainable behaviors (Ágoston et al., 2022). Sustainable behaviors or pro-environmental behaviors are defined as initiatives beneficial to the environment or which reduce ecological harm (Verplanken & Roy, 2013). Most research on the relationship between emotions regarding climate change and sustainable behaviors have generated mixed results insofar. Moreover, results from a Canadian perspective have been absent. Adding to this budding sector of research, the current study aimed to assess whether a relationship exists between levels of eco-guilt and engagement in sustainable behaviors among a sample of Canadians over the age of 17. It is hypothesized that an increase in eco-guilt will be associated with an increase in pro-environmental behaviors. A 10-item Likert scale questionnaire was distributed to collect quantitative data measuring individual participant's ratings of perceived eco-guilt and engagement in sustainable behaviors. A total of 75 respondents

participated in the study. Results showed a positive, low-moderate correlational relationship between feelings of eco-guilt and engagement in sustainable behaviors; as eco-guilt increases, engagement in sustainable behaviors increases. Therefore it would appear as if eco-guilt plays a role in pro-environmental behaviors. The addition of future research could reveal a more comprehensive understanding of other roles or influencing components. The results of this study have implications for the future of climate change advertising and sustainable behavior modifications strategies.

Disclosures: E. Chepel: None. **N. Gahov:** None. **E. Kantini:** None. **M.C. Tucci:** None.

Poster

PSTR084: Positive and Negative Emotional States

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR084.07/K2

Topic: G.04. Emotion

Support: German Center for Mental Health (DZPG)
Research Training Group GRK2350

Title: The pet effect: psychosocial and physiological correlates of pet ownership

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Abstract: Strong social bonds and a healthy social environment are cornerstones of mental health and well-being. An understudied form of social connection is one between pets and their owners. Pets are considered family members globally, and, albeit contradictory, evidence suggests that pets can benefit physical and mental health. However, the psychobiological mechanisms underlying pet ownership-associated benefits on different facets of mental well-being remain unclear. We aimed to assess these mechanisms through a multimodal approach combining sociodemographic, psychological, neuroimaging, ecological momentary assessment, and epigenetic data in a cohort of healthy, community-representative individuals (N = 347, 89 pet owners, 199 females) aged 18-30. We performed a principal component analysis on a battery of psychosocial measures associated with psychological risk/resilience (e.g., neuroticism, self-efficacy, loneliness) to delineate risk scores in our sample. Comparing these values using an independent samples t-test showed that on average, pet owners had higher psychological risk (t = -2.239, p = 0.026). Next, we used an established fMRI emotional activation task that reliably activates the amygdala. Amygdala habituation is an adaptive evolutionary response to repeated emotional stimuli, deficits of which are transdiagnostically associated with psychopathology and psychiatric risk. Group-wise comparisons showed that despite initially displaying high amygdala activation, pet owners demonstrated significantly stronger (right) amygdala habituation than non-

owners (t = 3.14, $p_{FWE\text{-}corr}$ = 0.016). At the epigenetic level, we compared oxytocin receptor methylation- implicated in attachment, socioemotional contexts, and various psychiatric disorders. Methylation scores residualized for age, sex, smoking, population structure, and cell composition were averaged for 5 CpG sites in exon 3. Comparing these values between the groups using a t-test revealed that pet owners displayed lower methylation (t = 2.587, p = 0.012). Overall, despite the psychological risk profile exhibited, pet owners show strong, rapid amygdala habituation indicating adaptive responses at a neural level, and possibly also at the epigenetic level. Thus, we posit that pet ownership may confer compensatory benefits, possibly buffering against the risk predisposition. Future research that examines attachment to and interactions with pets is needed to better dissect the underlying mechanisms, potentially paving the way for evidence-based pet interventions.

Disclosures: A. Sreepada: None. **O. Berhe:** None. **T. Kremer:** None. **J. Andoh:** None. **A.S. Meyer-Lindenberg:** None. **H. Tost:** None.

Poster

PSTR084: Positive and Negative Emotional States

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR084.08/Web Only

Topic: G.04. Emotion

Title: Neural cadences: the impact of personal musical history on brain activity in traditional monophonic Iranian music performers

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Abstract: Rooted in the rich tapestry of Western Asian history, folklorian music (Also known as Maqami Music) from the Central Plateau of Iran offers a unique lens through which to explore the intersection of music and neuroscience. This study examines the neurophysiological responses of a seasoned musician to his own compositions, linking historical Maqami music traditions to contemporary neurological analysis.
Utilizing electroencephalography (EEG), we recorded the brain activity of a 52-year-old male musician as he listened to his compositions from different periods of his life. This approach allowed us to assess hemispheric dominance and the specific brain wave patterns elicited by various musical elements.
Analysis revealed a pronounced activation of the left hemisphere, particularly in regions associated with auditory processing and emotional engagement. Beta waves, indicative of focused attention, were significantly heightened in the frontal and temporal lobes. Notably, familiar musical pieces and rhythm tended to activate the left hemisphere, while melody and lyrics engaged both hemispheres differently depending on the musician’s familiarity with the piece.

The study underscores the profound impact of musical training on brain function, demonstrating that musicians exhibit distinct neural responses to music, characterized by enhanced hemispheric specialization and sensitivity to musical elements. This suggests a developed neural architecture in musicians that supports advanced auditory processing and cognitive engagement with music.

Disclosures: M. Moeini: None. **F. Moradi Yazdi:** None.

Poster

PSTR084: Positive and Negative Emotional States

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR084.09/K3

Topic: G.04. Emotion

Support: R01MH121009-02
R01MH121706

Title: Autonomic states influence decision making in rhesus macaques.

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Abstract: Every day we make a multitude of social and non-social decisions. Non-social decisions typically rely on cost-benefit analysis that weigh rewards and aversive outcomes against the effort needed to obtain or avoid them. Social decisions take into account the value and consequences of reciprocal interactions with social partners. We explored the role of autonomic signaling [or states] in both non-social and social decision-making in rhesus monkeys. The autonomic state was altered by subcutaneous administration of glycopyrrolate, a parasympathetic antagonist that does not cross the blood brain barrier. Rhesus monkeys were tested on an approach-avoidance conflict task and a social reciprocation task. Compared to saline control, glycopyrrolate elevated the monkeys' heart rate by 20 +/- 12 beats per minute suggesting a sympathetic-dominated visceral state. Under these conditions, monkeys were less tolerant of a mildly aversive heat stimulus (48°C), indexed by a significant reduction of the latency to turn off the heat stimulus, despite this decision also interrupting a juice reward (Wilcoxon rank-sum test, $p<.001$). Glycopyrrolate enhanced prosocial decisions in a social reciprocation task, (Wilcoxon rank-sum test, $p<.05$) where monkeys chose between rewarding their social partner and themselves, or only themselves. In this task, sympathetically-dominated visceral state also induced by glycopyrrolate also prolonged reaction times (statistical test and P values). In both tasks, the monkeys seemed to show an increased propensity to avoid potentially negative outcomes, either in the form of a non-social aversive stimulus or in the potential social consequences of behaving selfishly. Reward seeking, tested by two different tasks, was not

altered by glycopyrrolate. We also compared the effects of glycopyrrolate to isoproterenol, (a sympathetic agonist that does not cross the blood-brain barrier and increases heart rate) and found similar behavioral effects. Taken together, these results suggest that a sympathetic-dominated autonomic state is sufficient to bias behavior toward the avoidance of negative outcomes in both social and non-social decision making.

Disclosures: M. Cardenas: None. **T. Champ:** None. **A. Bowman:** None. **A. Yaw:** None. **R. Le:** None. **G. Ames:** None. **O. Baumann:** None. **A.J. Fuglevand:** None. **K.M. Gothard:** None.

Poster

PSTR084: Positive and Negative Emotional States

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR084.10/K4

Topic: F.03. Stress and the Brain

Support: Alexander and Lucy Levitan Endowment for Medical Student Research Fellowships
NIMH Grant R01MH115061

Title: Characterizing multiplexed neurons in A10, A9, and A8 subregions of young male macaque

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Abstract: Introduction. The midbrain dopamine (DA) system is central for emotional, cognitive, and motor processing. Its heterogeneity in terms of transmitter types is established in rodent models. The nonhuman primate is a closer anatomic model for humans, and its classic A10, A9, and A8 groups have not only different connectional features, but also different mixtures of DA cell types. Here we use RNAScope to begin to understand DA cell heterogeneity in a model closer to the human. **Methods**. We examined the distribution of probes for tyrosine hydroxylase (TH), glutamic acid dehydroxylase 1 (GAD1), and vesicular glutamate transporter 2 (VGluT2) in 2 male animals (Case 38, 3 years; Case 20, 6 years). The boundaries of the A10, A9, and A8 were assessed using adjacent sections labeled for the calcium binding protein, CABP28. After confocal imaging, we employed a combination of AI-driven methods (Neurolucida 360) and manual validation to determine TH, GAD1, and VGluT2 single labeled and multiplexed neurons in all subregions. **Results**. We quantified 9,053 ± 1,017 neurons. Most neurons contained TH-mRNA (82.1% ± 0.3%), as expected. Of the TH-expressing neurons, TH+/VGluT2+ neurons comprised the majority (39.7% ± 3.2%) and TH+ only neurons comprised 30.5%. TH+/GAD1+/VGluT2+ cells represented 26.35% ± 0.05% of TH-expressing neurons, and TH+/GAD1+ neurons comprised only 3.35% ± 1.85%. Of the total neurons, GAD1+ only neuron counts were 9.4 % (854/9053) and VGluT2+ only neuron counts were 6.6%

(606/9053). Among all multiplexed neuronal subtypes, the proportion of TH+/VGluT2+ was highest at (32.6% ± 2.8%, 2,922 ± 81) followed by TH+/GAD1+/VGluT2+ labeled neurons (21.64% ± 0.04%, 1,959 ± 216). Other multiplexed types (GAD1+/VGluT2+, GAD1+/TH+) comprised less than 10% each of total neurons quantified. Region-specific analyses revealed that the midline ventral tegmental area (A10, VTA) contained the highest proportion of TH+/VGluT2+ neurons (40.9% ± 3.1%), the more lateral parabrachial pigmented nucleus (A10, PBP) contained the highest proportion of TH+ only neurons (33.19% ± 0.69%), and the retrorubral field (A8, RRF) contained the highest percentage of GAD+ only neurons (16.23% ± 3.02). **Conclusion.** Surprisingly, TH+/VGluT2+ labeled neurons were the most prominent TH population (32.6% ± 2.8%) in the ventral midbrain as a whole. As well, TH+/VGluT2+ neurons were found across all regions in similar proportions. Both findings are different than existing findings in primates (marmoset and aged human). Since DA neurons arise from VGluT2 phenotypes during development, we hypothesize that the robust numbers of TH+/VGluT2+ neurons may in part reflect the young ages of the animals.

Disclosures: I. Mahoui: None. **J.L. Fudge:** None.

Poster

PSTR084: Positive and Negative Emotional States

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR084.11/K5

Topic: G.05. Mood Disorders

Support: R01MH118638

Title: Neural Mechanisms of Affective States in the Primate Brain

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Abstract: BACKGROUND: Determining how fluctuations in the rate of expectancy violations influence our affective states is key to understanding how environmental factors can impact our moods. Further, the neural mechanisms of mood are still poorly understood. One thing that is known is that in healthy individuals and those with depression, the subcallosal anterior cingulate cortex (sACC) appears to be central to controlling moods. Despite this, the patterns of neural activity within sACC that signal positive and negative affective states are unknown. Determining this is critical as it would provide insights in the neural basis of moods in the brain, an essential first step for understanding the basis of depression. Thus, our aim here was to establish how sACC and a set of interconnected areas encode mood-like affective states at the level of single neurons. METHODS: Macaque monkeys performed a three-armed bandit task with transitions across multiple contexts with different rates of expectancy violations for fluid reward while neural activity was recorded from sACC, amygdala, striatum, insula and ventrolateral prefrontal

cortex (vlPFC). Autonomic activity was also recorded. Specifically, the task was designed such that monkeys experienced different rates of positive and negative expectancy violations in blocks of trials in order to create different contexts to bias subjects' affective state. RESULTS: Context transition affected the animals' affective state. Animals showed a decrease in choice reaction times and a more negative encoding of reward predictions in contexts with higher negative expectancy violations, whereas they displayed more positive encoding of reward predictions in contexts with higher positive expectancy violations. Manipulation of expectancy violation was also associated with concomitant changes in autonomic states as indexed by heart-rate fluctuations. Neurons in sACC showed separate encoding signals associated with the timing of choice and with reward onset. Similar signals were encoded also in areas connected to sACC including amygdala, striatum, insula and vlPFC. CONCLUSIONS: Here, we show that we can manipulate affective states by altering the environment that the monkeys are experiencing. Different rates of expectancy violations across the tasks cause concomitant and heterogeneous deficits in behavior, cognitive and autonomic states. We also show that activity in sACC and within interconnected areas in limbic and prefrontal cortex encodes both choices and the outcome resulting from these decisions. Moreover, neuronal firing rates across sACC circuits were modulated by the type of expectancy violations and the specific context.

Disclosures: D. Folloni: None. **F.M. Stoll:** None. **P.H. Rudebeck:** None.

Poster

PSTR084: Positive and Negative Emotional States

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR084.12/K6

Topic: G.04. Emotion

Support: K01AA027832

Title: Emotion shapes memory in the lab and the real world: A novel measure of memory integration

Authors: *J. G. PRATT[1], S. WEMM[3], J. YE[2], S. KANG[1], G. LARRABEE[2], R. SINHA[4], E. V. GOLDFARB[2];
[1]Psychiatry, [2]Yale Univ., New Haven, CT; [3]SUNY - Univ. At Albany, Slingerlands, NY, ; [4]Yale Univ. Sch. Med., New Haven, CT.

Abstract: Emotional events are encoded uniquely in the brain, affecting their structure and later memory accuracy. In-lab studies have shown both positive and negative events are remembered better, with positive events having features that are more integrated. However, it is unknown whether these alterations, which have been found in highly controlled lab environments, extend to real-world memories. To test this, we developed a novel design harnessing ecological momentary assessment (EMA) methodology and in-lab memory measures, providing both experimental control and ecological validity. We complement these design innovations with

analyses derived from network neuroscience to model memory accuracy and integration in both settings. Participants (n=45) completed in-lab and real-world memory tests. In lab, participants encoded 80 trial-unique object-scene pairs, and rated whether each made them feel happy (n=1148), neutral (1621), or unhappy (619). The next day, we probed memory for item, associative, and affective features of each pair. Following the in-lab assay, participants responded to 2 weeks of smartphone prompts with 2 daily surveys in which they reported their current affect, energy level, temperature, activity, location, and company. The next day, we probed memory for each feature. Participants had high completion rates (M = 72% daily surveys completed), yielding 906 memories total (sorted by affect at encoding; n=440 positive, 263 neutral, 203 negative). We derived two main memory measures per modality: accuracy per feature, and co-accuracy (integration) between features. Our co-accuracy measure is modeled on the edge time series method of fMRI functional connectivity, z-scoring accuracy and computing an element-wise product across feature pairs. This yields a measure of how much remembering one feature tracked memory for another feature of that event - that is, how strongly they were integrated. Results thus far show that positive events were indeed remembered more accurately across all memory features in the lab. However, we found that positive affect only enhanced memory for select features in the real world. Critically, our novel measure of co-accuracy showed that positive memories are more integrated than both negative and neutral memories, both in the lab and in the real world. We have also replicated this pattern in a separate real-world cohort (n=748 memories). Together, these findings show that positive emotion consistently leads to more integrated memories, but has differential effects on memory accuracy in the lab and in the real world.

Disclosures: J.G. Pratt: None. **S. Wemm:** None. **J. Ye:** None. **S. Kang:** None. **G. Larrabee:** None. **R. Sinha:** None. **E.V. Goldfarb:** None.

Poster

PSTR084: Positive and Negative Emotional States

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR084.13/K7

Topic: F.03. Stress and the Brain

Title: Analyzing the correlation between acute peripheral inflammation and cognitive impairment in humans: a systematic review

Authors: *F. BAPTISTA BRUNHEROTO[1,2], E. COSTA DE OLIVEIRA[1,2], D. M. MIRANDA[1,2], M. A. ROMANO-SILVA[1,2];
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Abstract: Increasing evidence implicates a crucial role of systemic inflammation in cognitive regulation. Elevated peripheral inflammation has been associated with social avoidance and anhedonia, with experimental endotoxemia being proposed as an experimental paradigm of

depression. However, its underlying pathophysiology remains unclear. We hypothesized that acute peripheral inflammation in previously healthy adults, through an increase in serum cytokines, has a negative impact on performance in cognitive tasks, in at least one of the six DSM-5 domains of cognitive function. To investigate this possibility, we conducted a systematic review, registered in PROSPERO (ID: CRD42023486505). Our search yielded 1971 results across five databases. After deduplication and screening, we included 22 articles from 15 distinct studies, involving n=729 patients. Study designs varied, with double-blind crossover trials (5; 33.3%) and prospective studies (5; 33.3%) being most common, followed by randomized control trials (4; 26.7%), and a cohort study (1; 6.7%). All groups were matched for demographics when needed, and considered statistically comparable. Considering cytokine assessment, IL-6 emerged as a primary focus across all studies (15; 100%), followed by TNF-α (9; 60%). The most commonly assessed cognitive domains were executive function (10; 66.7%), complex attention (5; 33.3%), and social cognition (5; 33.3%). There were no specific or consolidated panels evaluating multiple cognitive domains for cognitive assessment following an acute inflammatory intervention or exposure. Analyzing study outcomes, IL-6 displayed a correlation with social cognition impairment, though its elevation was inconsistent across studies, suggesting a multifactorial mechanism for this impact. Reaction time seems to be compensatingly decreased for cognitive tasks involving working memory and social approach of supporting figures; and pro-inflammatory states tend to promote social avoidance, especially of strangers, and hinder long-term memory. We also observed that inflammation correlates with more negative self-reported mood and body image, as well as an overall reduced perception of physical ability, suggesting impacts in self-recognition and executive function. In this context, future research should explore other cytokines, e.g. CCL11, recently implicated in cognitive impairment, particularly in conditions like COVID-19. Furthermore, more studies employing standardized cognitive assessment panels are needed to elucidate the interplay between inflammation and cognition.

Disclosures: F. Baptista Brunheroto: None. **E. Costa de Oliveira:** None. **D.M. Miranda:** None. **M.A. Romano-Silva:** None.

Poster

PSTR084: Positive and Negative Emotional States

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR084.14/K8

Topic: G.04. Emotion

Support: University Grants Commission Nepal Research Grant

Title: Limbic Neural Response To Dyspnea

Authors: *S. DEO[1], B. PAUDEL[2];
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Abstract: Introduction Dyspnea is the subjective experience of breathing discomfort commonly reported in cardiorespiratory diseases, intense emotional states and heavy exercise. Despite extensive research, the neural mechanisms underlying emotional component of dyspnea remain largely unknown. This study was aimed to improve our understanding of some of the key psychophysiological factors that determine the perception of dyspnea in conscious human subjects. **Methodology** The study was conducted in consenting healthy male volunteers. Standard exercise stress test was performed using cycle ergometer to induce dyspnea and simultaneously showing emotional pictures displayed on a monitor in front to the subjects. The emotional pictures were categorized into positive, negative and neutral picture series. The study in each subject was conducted for 3 days, each day with a single category of picture series showing for 5 min with self-reporting of dyspnea and recording of respiratory rate and heart rate simultaneously. **Results** In comparison to neutral mood state, there was significant increase in shortness of breathing [4.6(4.2-5.4) vs. 3.4(3.0-3.8)], botherness to shortness of breathing [4.6(4.0-5.8) vs. 3.6(2.8-4.2)], respiratory rate [32.2(29.7-35.3) vs. 28.4(26.6-31.2) cycles/min] and heart rate [116.4 (105.4-128.4) vs. 123(109.9-144.3) beats/min] in negative mood state whereas there was no significant difference in those variables in positive mood state. Likewise, in comparison to negative mood state, there was significant decrease in shortness of breathing [3.2(2.0-3.9) vs. 4.6(4.2-5.4)], botherness to shortness of breathing [3.2(2.2-3.8) vs. 4.6(4.0-5.8)], respiratory rate [29.0(26.3-31.6) vs. 32.2(29.7-35.3) cycles/min] and heart rate [114(102.7-138.7) vs. 123(109.9-144.3) beats/min] in positive mood state. **Conclusion** The result suggests that negative mood state increase and positive mood state decrease perceived dyspnea. The results of this study establish emotion-dyspnea relationship and suggest the possibility of emotional intervention as a treatment method for attenuating the effects of troublesome dyspnea. The approach used in this study has the potential to bridge the gap between basic neuroscience and clinical research in treatment of dyspnea.

Disclosures: S. Deo: None. **B. Paudel:** None.

Poster

PSTR084: Positive and Negative Emotional States

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR084.15/K9

Topic: G.04. Emotion

Support: BPI I-Nov Innovation Competition grant DOS0192291/00 - DOS0192292/00

Title: Fusion of virtual reality with wearable real-time EEG neurofeedback for mindfulness meditation enhancement: an accessible neuromodulation tool

Authors: M. JOMAA[1], I. SEZER[1,2], M. LOUVIGNÉ[1], R. KHOUADRA[1], F. ZEIDAN[3], ***A. FILIPCHUK**[1,2];
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Abstract: Virtual reality (VR), with its immersive sensory experience, is becoming more accessible and impactful thanks to rapid technological progress and enhanced realism. Yet, the fusion of VR with real-time Brain-Computer Interface (BCI) technology remains largely unexplored. Neurofeedback (NF)-driven VR presents fresh opportunities, particularly for mental health and chronic conditions treatments that require sustained engagement. Its powerful immersive capacity combined with real-time brain activity monitoring, make it a promising framework for developing a neuromodulation tool targeting the Default Mode Network (DMN) by inducing and maintaining a state of mindfulness (MN) across multiple NF-driven sessions. Deregulation of the DMN is common in various mental health and neurodegenerative conditions, such as major depression, generalized anxiety disorder, post-traumatic stress disorder, and Alzheimer's disease, making it a promising target for treatment. Mindfulness-based psychotherapies have demonstrated significant effects on DMN circuit and the related symptoms, such as ruminative thinking in major depression. These therapies focus on emotional reactivity control and attentional regulation. While effective, they require complex expertise, resulting in a limited number of therapists capable of providing the guidance. Our project aims to democratize access to psychotherapies with a home-based plug-and-play tool and establish an autonomous VR NF training environment. To implement emotional reactivity control for MN induction, we conducted a study with 35 healthy participants (aged 18-60, 50% women), exposed to 80 referenced 10-second affective stimuli (OASIS database) in VR. We recorded neurophysiological metrics (EEG 64 channels, ECG, EDA, PPG, eye tracking) in a lab setting. Using this data, we developed subject-independent decoders predicting emotional valence and arousal with approximately 70% accuracy for a wearable 7-electrode headset, based on cortical information complexity and connectivity features. These decoders were integrated into four 20-minute emotional reactivity control VR immersive environments, incorporating basic mindfulness meditation scripts (e.g., lake meditation). Here, the ambiance and audio-visual modification rules are regulated in real time based on emotional reactions (10s sliding window). The objective is to induce and subsequently sustain a state of moderate arousal and neutral valence. We employ a combination of passive and active neurofeedback to assist individuals in achieving the target state initially and then in learning to maintain it, thus reaching the state of mindfulness.

Disclosures: M. Jomaa: A. Employment/Salary (full or part-time):; Healthy Mind. **I. Sezer:** A. Employment/Salary (full or part-time):; Healthy Mind. **M. Louvigné:** A. Employment/Salary (full or part-time):; Healthy Mind. **R. Khouadra:** A. Employment/Salary (full or part-time):; Healthy Mind. **F. Zeidan:** F. Consulting Fees (e.g., advisory boards); Healthy Mind. **A. Filipchuk:** A. Employment/Salary (full or part-time):; Healthy Mind.

Poster

PSTR085: Threat, Anxiety, and Avoidance in Animal Models

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR085.01/K10

Topic: G.06. Anxiety Disorders

Support: JSPS KAKENHI 22K06714
JSPS KAKENHI 23K14400

Title: Pulmonary inflammation induced by intratracheal lipopolysaccharide injection causes anxiety-like behavior in mice

Authors: *Y. IZUSHI[1], S. TANAKA[1], T. UEDA[1], T. AGO[1], S. USHIO[2], Y. TASAKA[1], I. MIYAZAKI[3], M. ASANUMA[3], Y. KITAMURA[1];
[1]Shujitsu Univ., Okayama, Japan; [2]Fukuoka Univ., Fukuoka, Japan; [3]Dept. of Med. Neurobiol., Okayama Univ. Grad. Sch., Okayama, Japan

Abstract: In our previous studies, we established that intraperitoneal injection of lipopolysaccharide (LPS) induces anxiety-like behavior in mice, as evidenced by light-dark and hole-board tests (Matsumoto et al., 2021; Ushio et al., 2022). This treatment also elevated the production of the pro-inflammatory cytokines IL-6 and TNF-alfa in the serum and hippocampus, respectively, and activated microglia within the hippocampus. These findings indicate that systemic inflammation triggered by an intraperitoneal LPS injection leads to anxiety-like behavior through neuroinflammation. Patients with COVID-19 display an exaggerated inflammatory response with inflammatory mediators, including pro-inflammatory cytokines, infiltrating lung tissues. Case reports have described prolonged fatigue and anxiety in these patients. This study aimed to examine the effects of both intraperitoneal and intratracheal LPS injections in modeling inflammatory states, and to investigate the underlying mechanisms of anxiety-like behavior induced by systemic and pulmonary inflammation in mice. Our results showed that both methods of LPS administration resulted in anxiety-like behavior, as demonstrated by the results of the light-dark and hole-board tests. Serum levels of IL-6 and TNF-alfa significantly increased following both types of injections. Additionally, a significant increase in the number of microglial cells was observed in the dentate gyrus region of the hippocampus after both LPS injections. Notably, the concentration of hippocampal brain-derived neurotrophic factor decreased significantly after both administrations. These findings suggest that intratracheal LPS injection leads to anxiety-like behavior, potentially via mechanisms similar to those associated with systemic inflammation.

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Poster

PSTR085: Threat, Anxiety, and Avoidance in Animal Models

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR085.02/K11

Topic: G.06. Anxiety Disorders

Support: IBRO early career
ISN CAEN 1B

Title: Anxiolytic-like effect of the aqueous lyophilisate of alchemilla kiwuensis on a rat model of epilepsy-induced anxiety

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Abstract: Background/aim: Anxiety is one of the most common psychiatric comorbidities of epilepsy and it greatly increases the burden, worsening the life quality of patients. Among the biggest challenges to treating anxiety in epileptics are drug interactions and treatment costs. This study aimed to assess the pharmacological potential of *Alchemilla kiwuensis's* aqueous lyophilisate in a rat model of severe anxiety caused by epilepsy. **Materials and Methods:** Thirty Wistar rat of both sexes, weighing between 150-80g, were submitted to a pentylenetetrazole-induced kindling model of epilepsy. The lyophilisate at the doses 40mg/kg and 80mg/kg, valproic acid 200mg/kg, and distilled water were administered orally each treatment day 1h before PTZ injections. To mark the severity of anxiety, animals received 7 extra PTZ injections following the full development of epilepsy in the control group. 24h later, animals were submitted to the EPM test to assess anxiety phenotype; 1h later they were dissected for their hippocampi. Oxidative stress(MDA and catalase), neuroinflammation(TGF-1B and TNF-α), glutamatergic(glutamate and EAAT-2), GABAergic(GABA and GABA-T) signalisation and CRH were evaluated. **Results and discussion:** Both doses of the lyophilisate and valproic acid reduced anxiety phenotype by reducing close arms activities and time spent into the close arms, while increasing open arms activities and time spent into the open arms. The EPM test is a paradigm which conflicts the innate exploratory habit of rats to their natural fear of open spaces. The treatments preserved animals' natural exploratory habits, marking anxiolytic phenotype. Biochemically, these treatments decrease GABA-T activity, glutamate, TNF-α, MDA and CRH levels. Likewise, increases in GABA, EAAT-2, TGF-1B and catalase activity were observed. Epilepsy is characterised by increased brain excitatory currents. The spread of these excitatory currents in the limbic structures is the physiological origin of anxiety. In accordance with behaviour the two doses of the lyophilisate and valproic acid reversed the changes observed in the control group. As such increases were observed in levels of GABA, EAAT-2, TGF-1B and catalase activity, favouring inhibitory currents. **Conclusion:** *Alchemilla kiwuensis* prevented epilepsy-induced anxiety by enhancing GABA signalling, favouring antioxidant mechanisms and modulating neuroinflammation both in the in the hippocampus. These results justify the traditional uses of the plant.

Disclosures: A. Foutsop: None. **G. Ngoupaye:** None. **M. Adassi:** None.

Poster

PSTR085: Threat, Anxiety, and Avoidance in Animal Models

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR085.03/K12

Topic: G.06. Anxiety Disorders

Support: CINVESTAV Funding

Title: Biie0246 reverses corticosterone-induced anxiogenic-related behavior and neuronal hypertrophy

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Abstract: Neuropeptide Y (NPY) is a prominent peptide of research in anxiety disorders. An increasing amount of evidence highlights the impact of NPY on corticosterone (CORT) secretion, which plays a crucial role in anxiety and stress regulation. Indeed, acute administration of CORT reduced entries into the open arm of the elevated plus maze (EPM), indicative of anxiety-related behavior, alongside neuronal hypertrophy in the basolateral amygdala (BLA). Our study aimed to investigate the effects of various compounds acting on NPY receptors Y1 and Y2 on CORT-induced anxiety behaviors. Specifically, we examined the interaction of the Y1-like receptor agonist [Leu31Pro34] PYY, the Y1 receptor antagonist BIBO3304, the Y2 receptor agonist PYY3-36, and the Y2 receptor antagonist BIIE0246 with CORT-induced anxiety-like behavior in rats. We found that giving the Y2 receptor antagonist BIIE0246 to CORT-treated rats increased their entries to the open arm. Interestingly, the Y2 receptor agonist PYY3-36 has the opposite effect on control rats, reducing their entries to the open arms. However, neither [Leu31Pro34] PYY nor BIBO3304 significantly affected anxiety-like behaviors in CORT-exposed rats or their controls. Furthermore, BIIE0246 caused a significant decrease in the enlargement of neurons in the BLA of CORT-treated rats but no changes in untreated control rats. Our findings suggest that blocking the Y2 receptor can reduce the behavioral and neuronal effects caused by CORT, revealing the potential usefulness of Y2 receptor modulation in managing anxiety-related disorders. These promising results give hope for future advancements in this field.

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Poster

PSTR085: Threat, Anxiety, and Avoidance in Animal Models

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR085.04/K13

Topic: G.06. Anxiety Disorders

Support: France Relance

Title: Identifying treatment-sensitive biomarkers for anxiety-related disorders using multi-site local field potential recordings

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Abstract: Post-traumatic stress disorder and anxiety disorders are highly prevalent psychopathologies with significant societal and economic burdens. Treatment development for these psychopathologies rely on behavioral assays with high face and construct validity, however there are a limited amount of biomarkers that exist for these disorders. Following the identification that 4-Hz oscillations in the prefrontal cortex and basolateral amygdala predict fear behavior (Karalis et. al, 2016), we decided to explore electrophysiological biomarkers of other anxiety-related behaviors. Male and female mice (n=11) were implanted with 4-site recording electrodes in the medial prefrontal cortex, anterior insular cortex, basolateral amygdala, and ventral hippocampus and underwent a battery of anxiety-related behavioral tasks such as the elevated plus maze, open field test, and light/dark transition test. We explored if this previously identified 4-Hz biomarker also emerges during anxiogenic behaviors in the tested assays and how the power of this frequency band responds to treatment with Diazepam (1 mg/kg), a medication currently used to treat anxiety disorders. We also explored other frequency bands and analyzed changes in coherence between structures that could serve as additional biomarkers to convey anxious-like states that are sensitive to current therapeutics. Uncovering the existence of simple biomarkers will be useful in future studies aiming to reduce the severity of anxious-like states as well as for exploring efficacy of future medications.

Disclosures: D. Conlisk: A. Employment/Salary (full or part-time):; Neuroservices Alliance. **C. Dejean:** None. **V. Deroche:** None. **B. Buisson:** A. Employment/Salary (full or part-time):; Neuroservices Alliance. **C. Herry:** None.

Poster

PSTR085: Threat, Anxiety, and Avoidance in Animal Models

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Program #/Poster #: PSTR085.05/K14

Topic: G.07. Post-Traumatic Stress Disorder

Support: JSPS KAKENHI Grant Number 19K17089

Title: Medium-chain triglyceride attenuates anxiety-related behavior in a PTSD rodent model

Authors: *D. YOSHIOKA, T. YAMANASHI, K. KOMATSU, C. USHIDA, N. KAJITANI, M. IWATA;
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Abstract: Post-traumatic stress disorder (PTSD) occurs after exposure to traumatic events such as war, disaster, or violence. PTSD symptoms typically include intrusive memories of traumatic events, avoidance of reminders of the event, anxiety, and hyperarousal. Accumulating evidence suggests that increased neuroinflammation and decreased brain-derived neurotrophic factor

(BDNF) contribute to the underlying pathophysiology of PTSD. Therefore, anti-inflammatory drugs or substances have been proposed as a new treatment strategy for PTSD. One such molecule is beta-hydroxybutyrate (BHB), a ketone body that supports mammalian survival during energy-deficient states. It has been shown that BHB reduces inflammatory cytokine release (Youm Y. H et al. 2015 Nat Med) and that BHB increases brain BDNF levels (Chen L, et al. 2017 Biochem. Biophys. Res. Commun). We previously reported that in a rat model of PTSD using single prolonged stress (SPS), repeated subcutaneous injections of BHB attenuated SPS-induced anxiety-related behaviors as assessed by the elevated plus maze. We also found that BHB administration suppressed SPS-induced serum tumor necrosis factor-alpha (TNF-α) and interleukin-1beta (IL-1β) elevations (Yamanashi et al. 2020 Sci Rep). From these results, we wondered about how we could impact the synthesis of BHB. It begins with medium-chain triglycerides (MCTs), which are fats composed primarily of fatty acids with carbon chain lengths of C6-C12. Exogenous MCTs are rapidly absorbed through the portal vein and oxidized to acetyl-CoA in the liver, where they are used for the synthesis of BHB. Therefore, we hypothesized that gastrointestinal administration of MCTs would also attenuate anxiety symptoms in the rodent PTSD model via elevated blood BHB levels. Male Sprague-Dawley rats weighing 200-220 g (6-week-old) were used for the experiments. First, we observed that MCT administration by gavage increased blood BHB levels. Next, we evaluated the anxiolytic effects of MCTs in a rat PTSD model using SPS. After SPS, rats were administered MCTs once daily. After 2 weeks of administration, we evaluated anxiety behavior using the elevated plus maze test (EPM). We found that repeated administration of MCTs attenuated SPS-induced anxiety-related behavior, including reduced time spent in the open arms in the EPM. This result suggests that oral administration of MCTs may be a potential new therapeutic candidate for PTSD. The current experiments were carried out in accordance with the Tottori University Animal Care and Use Committee (IRB approval number h34-Y004)

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Poster

PSTR085: Threat, Anxiety, and Avoidance in Animal Models

Location: MCP Hall A

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Program #/Poster #: PSTR085.06/K15

Topic: G.07. Post-Traumatic Stress Disorder

Support: VPR-75-12742

Title: Physiological and Behavioral Effects of a Murine Model of Fear Memory Incubation

Authors: *J. PAMPALONE[1,2], M. CAMPANILE[3], K. CASTELL[3], C. A. BROWNE[4], I. LUCKI[4];
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Advancement of Military Med., Bethesda, MD; [4]Pharmacol. & Mol. Therapeut., Uniformed Services Univ. of the Hlth. Sci., Bethesda, MD

Abstract: Posttraumatic stress disorder (PTSD) has a lifetime prevalence of 6% in the USA. PTSD symptom clusters emerge overtime after exposure to a traumatic event. However, current preclinical models of chronic stress and traumatic stress do not reflect the late onset of PTSD symptoms. This study validates a preclinical model of late onset PTSD symptoms in C57BL/6J mice. The overall hypothesis is that a history of prior exposure to stress will exacerbate the behavioral response to subsequent traumatic stress tested one month following exposure. Male and female C57BL/6J mice, age 2 months were allocated to the following group assignments: no stress-no shock, no stress-shock, stress-no shock, stress-shock. Stress groups were exposed to 20 minutes restraint stress for 10 days. On the following day, mice in the Shock groups were exposed to a 1.5-mA 2 s duration shock delivered in sound attenuation boxes (Ugo Basile), with control mice receiving no shock in the chambers. Electrocardiograms (ECG) for each mouse were recorded weekly using ECGenie (Mouse Specifics, Inc.). Recall of contextual fear memory, measured as percent of time freezing (Any-Maze software, Stoelting), was evaluated on day 28 post shock during a 5 min re-exposure to the context in which the mice were shocked. On day 29 post shock, mice were screened for social interaction, evaluating time spent interacting with a novel conspecific mouse in an open field apparatus. Acoustic startle responses (ASR) were screened on day 30 post shock in sound attenuated startle reflex chambers (Med associates, Inc.) for a 15 min session of tone trials ranging from 85-115 dB presented in a pseudorandomized order. Contextual fear memory recall was significantly impacted by the combination of stress and shock (StressXShockXSex interaction F (1, 140)=4.926, P=.0281). Significant StressXShock (F (1, 132)=4.930), P=.0281), StressXSex (F (1, 132)=6.053 , P=0.0152), and ShockXSex (F (1, 132)=4.085, P=.0453) interactions were observed for HRV. No changes were noted in social interaction. In the ASR, a significant stress effect (F (1, 138)=6.952, P=.0093) and ShockXSex (F (1, 138)=3.989, P=.0478) interaction were observed for the S2 latency to startle reflex at 85 dB. Overall, the data demonstrate that the combination of stress and shock does induce specific behavioral and physiological alterations that are distinct from those induced by stress or shock alone. These data suggest this model produces a behavioral and physiological profile in C57BL/6J mice with behavioral effects that are relevant to clinical late onset PTSD.

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Poster

PSTR085: Threat, Anxiety, and Avoidance in Animal Models

Location: MCP Hall A

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Program #/Poster #: PSTR085.07/K16

Topic: G.07. Post-Traumatic Stress Disorder

Support: NYSCF Robertson Investivator Award

Title: The development of a novel mouse model for gradual re-exposure to traumatic psychosocial defeat stress.

Authors: *H. J. KIM, M. AGOLLI, S. DAN, C. J. PENA;
Princeton Neurosci. Inst., Princeton Univ., Princeton, NJ

Abstract: Post-traumatic stress disorder (PTSD) arises following traumatic life events, and impacts nearly 4% of the world population. Conventional PTSD treatment strategies entail pharmacological agents aimed at dampening anxiety, in combination with exposure- or non-exposure-based cognitive behavioral therapy. In exposure therapy, patients are gradually and safely re-introduced to the original trauma in order to encourage mental processing and desensitization. Given this "gold standard" treatment in humans, there are currently no animal models of exposure therapy with which to examine its neurobiological mechanisms. Furthermore, it remains unclear how the environmental context of this stress re-exposure impacts trauma recovery, considering that PTSD therapy in humans is most successful when combined with supportive, enriched environments. In the current study, we systematically test how varying the timing, intensity, and context of stress re-exposure produces "susceptible" and "resilient" phenotypes, using a well-validated model of social defeat stress. Adult male C57BL/6 mice were separated into either standard control, or enriched cages filled with extra social, somatosensory, and cognitive stimulation. Mice were further assigned to non-stressed, repeated-regular stress, and escalating stress groups, the latter of which underwent 10 levels of gradually increasing psychosocial stress either before, after, or without repeated-regular stress. All mice were then evaluated on a behavioral battery including the social interaction test, novel object recognition test, and the elevated zero maze. While neither cage environment nor escalating stress alone improved behaviors as compared to controls, the combination of these variables significantly enhanced socialization and object discrimination, revealing a potentially synergistic relationship between environmental enrichment and gradual stress exposure. We are currently characterizing this novel behavioral paradigm in female mice, as well as identifying the neural plasticity-related genes mediating the enduring effects of escalating psychosocial stress within the brain. Developing a mouse model of "exposure therapy" will enhance our understanding of traumatic stress recovery, in addition to laying the foundation for future investigations into novel biomarkers and therapeutic targets for PTSD.

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Poster

PSTR085: Threat, Anxiety, and Avoidance in Animal Models

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Program #/Poster #: PSTR085.08/K17

Topic: G.06. Anxiety Disorders

Support: RO1 MH121829

Title: Elevated Neural Activity of Prelimbic Cortex During Threat Anticipation in California Mice

Authors: *R. PUREWAL[1], L. HARVEY[1], A. S. FOX[2], B. C. TRAINOR[3];
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Abstract: Elevated Neural Activity of Prelimbic Cortex During Threat Anticipation in California Mice The experience of anticipating uncertain threats is a core component of anxiety disorders. The prelimbic cortex (PL) is a key region in the medial prefrontal cortex of rodents that is implicated in risk assessment and fear induction processes. Previous work used Pavlovian fear conditioning in nonsocial contexts using artificial stressors such as foot shock. It is unclear if these mechanisms extend to more ethologically valid stressful contexts. Here we assess the impact of social threat anticipation using a novel waiting room task. We studied California mice (*Peromyscus californicus*) as a model for studying social defeat in males and females. This study builds on previous social defeat work by employing a novel experimental setup which includes a waiting room arena. Before social defeat or control exposures, each mouse was introduced into a clean polyurethane cage that acted as a waiting room. Experimental mice (n = 8) and control mice (n = 8) were placed in for 10 minutes in the waiting room before being transferred to social defeat or a second empty cage On days 1 and 2, after 10 minutes in the waiting room, experimental mice faced social defeat while controls were returned to their home cages. On day 3, all animals were placed in the waiting room to assess autogrooming and freezing changes. All animals were perfused ~60 minutes after the waiting room exposure on day 3 for c-FOS was analysis. Preliminary data show that freezing in the waiting room increases significantly on Day 3 in stressed mice ($t(7) = 2.8$, $p<0.05$) but not controls. Mean levels of autogrooming were higher in stressed mice but not significantly ($t(7) = 1.7$, $p=0.14$) with no change in controls. These results suggest that the waiting task is a useful paradigm for studying threat anticipation. We further hypothesize that c-Fos expression in the PL of stressed California mice will be increased on Day 3 compared to controls. Further study of neural circuits of threat anticipation could provide insights relevant to anxiety disorders in humans.

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Poster

PSTR085: Threat, Anxiety, and Avoidance in Animal Models

Location: MCP Hall A

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Topic: G.06. Anxiety Disorders

Support: LC R01 (R01MH112355-08)
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Mary Gates Endowment For Students
Washington Research Foundation

Title: Identifying the mechanisms of noradrenergic modulation of BLA-mediated avoidance behaviors

Authors: *S. THAI;
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Abstract: Acute stressors induce physiological anxiety, which is an adaptive survival response that influences how an organism reacts to threats in its environment. However, anxiety disorders are characterized by maladaptive anxiety responses that are disproportionate to the perceived threat. A key neuromodulatory system that responds to stress exposure is the locus coeruleus noradrenergic system (LC-NE), which projects broadly throughout the central nervous system. In particular, the activation of projections from the LC to the basolateral amygdala (BLA) is anxiogenic. However, it is unclear how the LC-BLA circuit modulates anxiety-like behaviors at the cell-type and receptor levels. We first used 1-photon and 2-photon imaging to record calcium activity of LC-NE neurons in response to aversive predator odor stimuli and found that predator odor synchronously increased LC-NE activity in a manner consistent with an increase in tonic activation. To explore the downstream effects of LC-NE activity, we then injected ChRimson into the LC and either GRABNE2m or GCaMP6s into the BLA to record NE release or calcium activity, respectively, in the BLA in response to predator odor and LC terminal activation. Robust and sustained NE was released and detected in the BLA both in response to predator odor exposure and following 5hz optogenetic activation of LC terminals, with similar magnitudes and durations of increase. This suggests we can mimic the stress-like NE release in the BLA with optogenetics. Using this same stimulation paradigm, we found that 5hz LC terminal activation increased synchronous activity of BLA neurons and enhanced population encoding of anxiogenic environments. To determine how adrenergic receptors (ARs) in the BLA influence anxiety-like behavior, we first found that systemic treatment with the β-AR receptor antagonist, propranolol, prevented both the anxiogenic effects of 5hz LC-BLA stimulation and the increased BLA synchrony. To identify the specific cell type expressing the β-AR subtype necessary for this change, we developed a cre-dependent CRISPR/SaCas9 virus for β2-ARs and injected it into the BLA of Vglut1 cre mice. These mice were then tested in a stress-induced anxiety assay. We found that CRISPR knockdown of β2-ARs in the BLA is effective and reduces stress induced anxiety-like behavior. By understanding the circuit-based mechanisms of how stress-induced anxiety is regulated, we can identify potential targets for therapeutic treatments of anxiety disorders.

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Poster

PSTR085: Threat, Anxiety, and Avoidance in Animal Models

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Topic: G.06. Anxiety Disorders

Support: Brain and Behavior Research Foundation Young Investigator Award 30616 (S.M.)
National Institute of Mental Health Award MH129040 (A.R.T.),

Title: Midbrain circuitry controls threat processing and innate defensive adaptive learning

Authors: *E. W. WILLIAMS[1,2], L. SNIVELY[3], B. O'MEARA[4], H. JACOBS[4], M. KOLB[4], R. ZHAO-SHEA[5], M. V. BARATTA[4], A. R. TAPPER[6], S. MOLAS[4,7];
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Abstract: Anxiety disorders are the foremost contributor to global mental illness, impacting an estimated 10-20% of adults in the United States. A core aspect among the clinical heterogeneity of anxiety disorders is the abnormal processing of threat-related information and the impairment in modifying the defensive response in the absence of real threat. Exposure to an overhead dark visual looming stimulus (VLS) elicits innate defensive responses across multiple species. However, there remains limited understanding regarding how animals adjust their threat response upon repeated exposure to these stimuli without encountering adverse outcomes. Understanding the neuronal circuits underlying these innate defensive behaviors and how they adapt is fundamental for improving therapeutic strategies for anxiety disorders. The interpeduncular nucleus (IPN) of the midbrain, an inhibitory region that is highly enriched with GABAergic neurons, has been implicated in anxiety and fear-related behaviors. The IPN receives information mainly from the medial habenula and sends projections to regions involved in affective behaviors including the laterodorsal tegmental nucleus (LDTg). However, the cellular and circuit mechanisms within the IPN-connected networks regulating innate defensive responses and adaptive learning are still largely unknown. Using the VLS paradigm, we identified specific behavioral signatures of threat responses and threat learning in mice. *In vivo* fiber photometry recordings of IPN GABAergic neurons revealed specific patterns of IPN activation during VLS presentations, which were conveyed via the LDTg area. Finally, we functionally assessed the role of IPN neurons and projections to the LDTg in defensive behaviors using optogenetics. Optogenetic silencing of IPN GABAergic neurons during VLS presentation led to a reduction in freezing and time spent in the shelter, whereas silencing the IPN-LDTg circuit occluded adaptive learning. These results introduce new behavioral signatures of innate defensive adaptive learning, and a circuit that regulates the essential features of threat processing, both of which are paramount to our conception of neuropsychiatric conditions.

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Poster

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Topic: G.07. Post-Traumatic Stress Disorder

Support: We acknowledge University of Tasmania, College of Health and Medicine for funding and support.

Title: New clinically translatable approaches for PTSD identify the MEK inhibitor mirdametinib combined with prediction error and D-cycloserine disrupts threat memory

Authors: S. RAUT[1], N. HAASS[2], F. JOLY[3], J. CANALES[4], R. URSANO[5], ***L. JOHNSON**[6]; [1]Psychological Sci., Univ. of Tasmania, Launceston, Australia; [2]Frazer Inst., Univ. of Queensland, Brisbane, Australia; [3]Univ. of Grenoble, La Tronche, France; [4]The Univ. of Canterbury, Christchurch, New Zealand; [5]Psychiatry, Uniformed Services Univ., Bethesda, MD; [6]Psychological Sci., Univ. of Tasmania, Tasmania, Australia

Abstract: This study establishes mirdametinib as the first MEK inhibitor that can undergo clinical development for psychiatric indications such as post-traumatic stress disorder (PTSD). PTSD is characterized by persistent traumatic memories with limited effective treatment options. A body of evidence suggests that memory storage is dynamic and constantly updated through post-retrieval modification a process termed reconsolidation. Although ERK/MAPK signaling plays a central role in threat memory consolidation, no clinically translatable MEK inhibitor has been tested in experimental models or in clinical trials to disrupt this process. Furthermore, there is a need to develop pharmacological and behavioral strategies to labilize the memory to make it susceptible for disruption. Here we disrupted fear memory reconsolidation with the clinically relevant MEK inhibitor mirdametinib in C57BL/6 mice and tested memory destabilization strategies using an auditory threat conditioning paradigm, with drugs administered following reactivation of memory. We found prediction error effective in labilizing weak threat memory and combined D-cycloserine (DCS) and prediction error effective in labilizing strong fear memory. Mirdametinib disrupted the weak threat memory and reduced ERK phosphorylation in lateral amygdala when coupled with prediction error at the time of memory reactivation but required a coordinated combination of DCS, prediction error and mirdametinib to disrupt strong threat memory. Barnes maze spatial memory test and open field test revealed that mirdametinib did not affect retrieval of other forms of long-term memory and locomotor activity. Thus effects were specific to threat memory. Furthermore, the effect of mirdametinib was specific to reconsolidation as it had no effect on threat memory when given without reactivation. These translational findings identify a new drug and combined behavioral approach that can be adapted for the treatment of PTSD.

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Poster

PSTR085: Threat, Anxiety, and Avoidance in Animal Models

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Program #/Poster #: PSTR085.12/K21

Topic: G.06. Anxiety Disorders

Support: BBRF grant 30616

Title: Effects of unpredicted stress on threat processing and adaptive defensive learning

Authors: *L. SNIVELY[1], E. WILLIAMS[2], S. MOLAS[3];
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Abstract: The selection of appropriate defensive behaviors in the face of potential threat is fundamental to survival. In prey animals, like mice, the presence of a predator elicits instinctive defense behaviors, such as freezing or fleeing. However, after repeated exposures to threatening stimuli that have not previously preceded real danger, an animal must learn to optimize and adjust defensive responses. Despite extensive research on innate threat processing, little is known about how individuals switch threat induced defensive behaviors through adaptive learning when presented with multiple threat exposures without evidence of a real risk, despite its critical application in better understanding psychiatric conditions such as anxiety disorders. Here, we use the visual looming stimuli (VLS) paradigm to investigate innate threat processing and adaptive defensive learning. As mice were repeatedly exposed to VLS over consecutive sessions, they switched their behavior from freezing to a flight response and reduced the time inside a sheltered area to engage in foraging behaviors. It has been suggested that the addition of chronic or repeated exposure to stress plays a role in fear learning and threat processing in mice. Several studies have found that exposure to stress can lead to mice expressing an anxiety-like state and having accelerated defensive responses when tested with VLS. Whether exposures to stressors impairs innate adaptive defensive responses remains unclear. Our preliminary data suggests that mice who underwent chronic unpredictable stress for four days displayed differences in VLS adaptation and anxiety-like behavior, when compared to control animals. These results provide a new understanding of the neuroethology behind stress-induced anxiety and help improving the design of therapeutic strategies in neuropsychiatric conditions.

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Poster

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Topic: G.07. Post-Traumatic Stress Disorder

Support: NIH Grant R15HD110925

Title: Acute social defeat during adolescence promotes long-lasting aggression through activation of the medial amygdala

Authors: *J. C. NORDMAN, N. MOJAHED, **M. ADJEI**;
Biomed. Sci., Southern Illinois Univ. Sch. of Med., Carbondale, IL

Abstract: Traumatic stress, particularly during critical developmental periods such as adolescence, has been strongly linked to an increased propensity and severity of aggression. Existing literature underscores that being a victim of abuse can exacerbate aggressive behaviors, with the amygdala playing a pivotal role in mediating these effects. Historically, animal models have demonstrated that traumatic stressors can increase attack behavior, with numerous studies implicating various amygdaloid complexes. Building on this foundation, our previous work has highlighted how traumatic stress invokes long-lasting aggression via an excitatory pathway within the posteriorventral medial amygdala (MeApv). In the current study, we sought to further delineate this mechanism by examining the effects of acute social defeat during adolescence on aggressive behaviors and neural activation in mice. Using a novel social defeat paradigm we developed, we first established that acute social defeat indeed promotes long-lasting aggression. Immunolabeling using c-Fos demonstrated that acute social defeat activates the MeApv. Chemogenetic inhibition of excitatory MeApv neurons significantly mitigated the aggression elicited by acute social defeat. These findings suggest that the MeApv plays a critical role in the onset of aggression following traumatic social experiences during adolescence. These results not only extend our understanding of the neural circuits underpinning traumatic stress-induced aggression but also offer the MeA as a potential target for therapeutic interventions.

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Poster

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Program #/Poster #: PSTR085.14/K23

Topic: G.06. Anxiety Disorders

Support: NIH-NCCIH (K99/R00) AT010903

Title: Molecular and cellular adaptations to chronic light cycle disruption in the medial amygdala during adolescence

Authors: *P. BONILLA VILLAMIL[1], A. SHANKS[1], A. PORCU[2];
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Abstract: Currently, more than 99% of the US and European populations live under light-polluted skies. Recent studies have linked altered light environments to increased anxiety and mood disorders among US adolescents. The intrinsically photosensitive retinal ganglion cells (ipRGCs) receive and transmit light inputs to the medial amygdala (MeA), a key region regulating emotion and anxiety behaviors. Our previous study showed increased anxiety-like behavior in adolescent mice exposed to chronic light cycle disruption and change in neuronal activity rhythms in the MeA. However, the molecular and cellular adaptation of MeA circuit in response to altered light environment remain unknown. To this aim, we exposed adolescent mice to our light cycle disruption paradigm (LCD) consisting of 19 hours of light and 5 hours of darkness (19L:5D) for 5 days and 12L:12D for 2 days or control condition 12L12D for 7 days, for 4 weeks. In this model, LED light (blue light) is turned on during the night phase of the animals' cycle, resulting in increased duration of light exposure for 5 days of a 7-day cycle. Mice were then tested for anxiety-like behaviors and brains were processed for single-cell RNA-sequencing (scRNA-seq), immunohistochemistry and RNA in situ hybridization. We found that adolescent mice exposed to LCD showed increased avoidance responses and risky behavior compared to the control group. ScRNA-seq data showed differences in cell type composition with significant change in neurons and astrocytes number. Interestingly, we found several downregulated genes involved in membrane potential regulation, synapsis organization and activity in MeA neurons of adolescent mice exposed to LCD compared to control. Differential gene expression profiles of neuronal cluster showed significant decrease of potassium channels expression (GIRK). Histological analysis revealed a significant increase in the number of somatostatin neurons and a reduction in GABA neurons and astrocytes in mice exposed to LCD compared to control, corroborating the scRNA-seq data. Our research reveals for the first time that exposure to altered light environment during pubertal development affects medial amygdala network likely contributing to anxiety-like behaviors observed in adolescent mice. Hence, we suggest that chronic light cycle disruption, similar to those experienced by humans during school-days and weekends, might represent a risk factor for developing emotional disorders.

Disclosures: P. Bonilla Villamil: None. **A. Shanks:** None. **A. Porcu:** None.

Poster

PSTR085: Threat, Anxiety, and Avoidance in Animal Models

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR085.15/K24

Topic: G.06. Anxiety Disorders

Support: NIH-NCCIH (K99/R00) AT010903

Title: Sex-specific effects of chronic light cycle disruption in the medial amygdala during adolescence.

Authors: J. KARTIK, P. BONILLA VILLAMIL, A. SHANKS, *A. PORCU;
Univ. of South Carolina, Columbia, SC

Abstract: Light serves as a sensory stimulus that exerts profound influences on both brain circuits and behaviors. Chronic exposure to altered light environment has been linked to various health problems, including emotional disorders. The medial amygdala (MeA) is a sexually dimorphic region regulating social behavior and directly receives light information from the retina. However, our understanding of sex differences in the light-induced response within the MeA remains elusive. In our study, we investigated sex-specific effects of chronic light cycle disruption in adolescent mice, focusing on social behavior and neuronal responses in the medial amygdala and target regions.To this aim, we implemented a recently developed light paradigm to mimic the light exposure patterns commonly observed in human adolescents. The model involved a prolonged light phase of 19 hours per day, with light exposure occurring during the biological night phase of the mice for 5 days per week. Adolescent mice, post-natal day 30, were exposed to either control conditions (12 hours of darkness and 12 hours of light) or light cycle disruption (LCD) (19 hours of LED light with a blue wavelength) for four weeks. Mice were tested for social behaviors while measuring MeA neuronal activity using fiber photometry. Brains were then processed to perform RNAscope and immunofluorescence analysis.We found that male adolescent mice exposed to LCD exhibited a reduction in social interactions compared to the control group and female mice. Fiber photometry analysis revealed an increased in somatostatin (SST) neuronal activity in the MeA during social interaction in male mice exposed to LCD compared to control. Sex-hormone receptor analysis showed a significant decrease in estrogen receptor expression in SST neurons in the MeA of male mice exposed to LCD. Using a viral tracing approach, we found that SST neurons in the MeA project to the Bed Nucleus of the Stria Terminalis (BNST), a brain region regulating social behavior. Moreover, we found a decrease in the activation of corticotropin releasing factor (CRF) neurons in the BNST following LCD exposure in male mice. Taken together, our data suggests the presence of sex-specific response to altered light environment regulating social behavior during adolescence.

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Poster

PSTR085: Threat, Anxiety, and Avoidance in Animal Models

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Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR085.16/K25

Topic: G.06. Anxiety Disorders

Support: NIH Grant AA027773

Title: The Role of Glutamatergic Astrocyte-Neuron Interaction in Adult Anxiety Susceptibility Induced by Adolescent Repeated Alcohol Exposure

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Abstract: Repeated ethanol exposure during adolescence increases the risk for displaying psychiatric disorders and medical conditions in adulthood, particularly generalized anxiety disorder accompanied by alcohol use disorder (AUD), but the underlying mechanisms are not fully understood. The paraventricular nucleus of the thalamus (PVT) is thought to be a hub brain region that controls the brain's anxiety network. Recent studies suggest the PVT presents a variety of neuronal signals in accordance with early life experiences and those signals are significantly correlated with anxiety-like behaviors. However, it remains unclear whether repeated ethanol exposure during adolescence impacts the PVT brain activities in adulthood, and subsequent behavioral outcomes. Using electrophysiological, optic, biochemical, and transgenic approaches, we compared the PVT cellular activities and behavioral consequences of the mice withdrawn from repeated adolescent intermittent ethanol exposure (AIE) and ethanol naïve counterparts (CON). The mice were exposed to air or vaporized ethanol in a vapor inhalation chamber for three weeks (P28 to P49). Each daily cycle consisted of ethanol vapor for 16 h followed by 8 h of abstinence in their home cage. This was repeated for 4 consecutive days, followed by 3 days of abstinence. Then, the cellular activities and anxiety-like behaviors were evaluated after 3 to 4 weeks withdrawal from the AIE paradigm. We observed an increase in anxiety-like behaviors in the AIE mice compared to those in the ethanol-naïve mice in adulthood. In parallel, the firing rates and the expression levels of ΔFosB immediate early gene in the PVT neurons were increased in the AIE group. Interestingly, chemogenetic inhibition of the PVT neurons alleviated the anxiety-like behaviors in the AIE mice. The neuronal activities and glutamate levels in the PVT of AIE mice were increased, at least partly, by the reduction of the GLT1, an astrocyte dominant glutamate transporter (known as EAAT2, slc1a2). The ethanol-naïve mice with astrocytic GLT1 knock-out in the PVT mimicked the anxiety-like behaviors shown in AIE mice, whereas the selective upregulation of GLT1 in the PVT astrocytes alleviated the AIE-induced anxiety-like behaviors. Our results indicate the significant role of PVT astrocytic GLT1 in adult anxiogenic phenotypes after long-term withdrawal from AIE exposure. This, coupled with the alteration of glutamatergic communication between astrocytes and neurons, suggests that GLT1 in the PVT could potentially serve as a therapeutic target for AUD and comorbid emotional disorders.

Disclosures: A. Bennett: None. **S. Kang:** None.

Poster

PSTR085: Threat, Anxiety, and Avoidance in Animal Models

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR085.17/K26

Topic: G.07. Post-Traumatic Stress Disorder

Support: NIH Grant NIAAA 7R01AA024526 to JTG
VA grant 1I01BX005367

Title: Sex-dependent fear behavior in a comorbid model of posttraumatic stress disorder and alcohol use disorder

Authors: *B. SCHWARTZ[1], L. J. WILLS[2], B. MCGUFFIN[3], J. T. GASS[2];
[1]Biomed. Sci., East Tennessee State Univ., Johnson City, TN; [2]Biomed. Sci., Quillen Col. of Med., Johnson City, TN; [3]East Tennessee State Univ., Johnson City, TN

Abstract: Post-traumatic stress disorder (PTSD) is a disorder commonly associated with alcohol use disorder (AUD). This comorbidity presents a significant treatment challenge due to limited effective treatments. The current study investigates the potential of the mGlu5 positive allosteric modulator, CDPPB, to improve recovery of behavioral deficits in a rat model of PTSD/AUD with a particular focus on sex-dependent effects. Previous research has shown that biological sex differentially impacts several behaviors in comorbid PTSD/AUD. Therefore, one goal of this set of experiments was to determine how stress and chronic alcohol exposure alter fear-related behaviors in a sex-dependent manner. Fear responses are often measured through active (platform-mediated) and passive (freezing) avoidance behaviors, which can exhibit sex differences. There is a strong association between PTSD/AUD and neuroinflammation within certain brain regions, however the precise effects of stress and chronic alcohol exposure on proinflammatory cytokine expression remains unclear. We employed a comorbid PTSD/AUD model in male and female Wistar rats using restraint stress (RS) and chronic intermittent ethanol exposure (CIE). This was followed by either contextual fear conditioning (CF) or platform-mediated avoidance (PMA) to assess sex-dependent changes in avoidance behaviors. The CF task involved conditioning the rats to associate a tone with a footshock, followed by extinction learning of the previously formed association. Animals received CDPPB or vehicle prior to each extinction training session. We found that both males and females exposed to RS+CIE displayed inhibited extinction learning, however, this effect was stronger in the males compared to the females. CDPPB treatment prevented this deficit in both sexes. To investigate the underlying neuroinflammatory response, we collected tissue samples from the prelimbic and infralimbic cortices, and hippocampus of rats exposed to CF. Enzyme linked immunosorbent assays (ELISAs) were used to measure levels of proinflammatory markers tumor necrosis factor (TNF) -α and interleukin (IL) -1β. Notably, exposure to RS+CIE resulted in a significant change in TNF-α and IL-1β in all three regions. Next, the PMA task measured avoidance behavior where the rodents learned to avoid a tone-signaled footshock by stepping onto a nearby platform. We found females to exhibit more active avoidance, while males displayed more passive avoidance. This research furthers our understanding of the fear behaviors and inflammation between sexes in PTSD/AUD that could aid in future discoveries of sex-dependent treatments for comorbid PTSD/AUD.

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Poster

PSTR085: Threat, Anxiety, and Avoidance in Animal Models

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR085.18/K27

Topic: G.07. Post-Traumatic Stress Disorder

Support: Student Touro Research Fellowship Grant Program Award 2022 (log # 017016).

Title: Sex-specific Microbial Responses to Single Prolonged Stress in Sprague-Dawley Rats

Authors: *A. TANELIAN[1], B. NANKOVA[2], F. HU[3], E. SABBAN[4];
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Abstract: Following traumatic stress, women are more likely than men to develop mood disorders; however, individual responses vary, with some developing stress-induced psychopathologies and others demonstrating resilience. The specific factors contributing to sex-related differences in mood disorders and variations in resilience remain unclear. Emerging evidence suggests that differences in the gut microbiota may contribute to this. Here, using an animal model for post-traumatic stress disorder, we aimed to characterize the pre- and post-existing differences in microbial composition, functionality, and metabolites that affect stress susceptibility or resilience in each sex. Sprague-Dawley male and female rats were randomly assigned to control or experimental groups exposed to single prolonged stress (SPS). Additionally, a separate cohort of male rats received oral supplementation of either 150 mM sodium acetate or 150 mM sodium chloride-matched water, either throughout the experiment or exclusively following the SPS procedure. Two weeks later, the animals underwent a battery of behavioral tests and were euthanized the following day, with various biological samples collected. Before SPS, only the male subgroups showed changes in the sympathoadrenal axis. Throughout the study, the alpha diversity remained consistently lower in males compared to females. Beta diversity revealed distinct separations between susceptible male and female groups pre-SPS, with these differences appearing in the resilient groups post-SPS. At the genus level, several genera exhibited sex-specific shifts. Sex-specific changes were also observed in microbial predictive functionality and targeted functional modules, both pre- and post-SPS, with histone acetylation modules being higher in males while crotonylation higher in females. Alterations in microbial short-chain fatty acids (SCFAs) included lower levels of major and minor SCFAs in SPS-susceptible males and higher levels of branched-chain SCFAs in SPS-susceptible females. Continuous oral acetate supplementation reduced SPS-triggered behavioral impairments, induced epigenetic modifications, inhibited neuroinflammation, and increased serum β-hydroxybutyrate levels, without affecting the controls. However, delivering it only after SPS did not produce these effects. This study highlights distinct pre- and post-trauma differences in the microbial composition, functionality, and metabolites associated with stress resilience in male and female rats. These findings underscore the importance of developing sex-specific therapeutic strategies to address stress-related disorders effectively.

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Poster

PSTR085: Threat, Anxiety, and Avoidance in Animal Models

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Topic: G.07. Post-Traumatic Stress Disorder

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T32 MH119049-02
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NSF GRFP DGE #1845298
UCI UROP
UCI SURP

Title: The Role of Hippocampal Estrogen in Posttraumatic Stress Disorder (PTSD)-like Memory Disruptions Provoked by Acute Traumatic Stress

Authors: *R. E. HOKENSON[1], K. RODRIGUEZ[2], Y. CHEN[3], G. D. ANGELES[3], S. A. SAMRARI[1], B. DEVIREDDY[1], S. KOTTHRU[1], M. T. BIRNIE[3], N. KAMEI[3], E. A. HELLER[2], T. Z. BARAM[1,4];
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Abstract: Background: Posttraumatic stress disorder (PTSD) is a serious, debilitating neuropsychiatric disorder characterized by intrusive memories of the traumatic event, avoidance of trauma-associated cues, and memory problems that can persist years after the trauma. While chronic trauma has been known to provoke PTSD, it is increasingly recognized that acute *traumatic* stress (ATS), such as mass shootings or terrorist attacks, can also lead to PTSD. However, the mechanisms underlying these distinct memory deficits provoked by ATS are unclear. Additionally, prevalence of PTSD is significantly higher in women than men, even when controlling for trauma type, providing impetus for the study of the profound impacts of sex and sex hormones on PTSD. **Methods:** To probe the mechanisms of PTSD, we modeled acute traumatic stress (ATS) in mice by imposing simultaneous physical, social, and emotional stressors for a single, two-hour period. We tested the role of hippocampal estrogens in both spatial memory deficits and the emergence of PTSD-like behaviors in the weeks following ATS. We probed estrogen receptor (ER) contribution by treating mice with selective ER blockers or employing transgenic mice with selective, conditional deletion of ERα or ERβ (ERKO mice). Impacts on cognition were assessed through hippocampus-dependent memory tests. To investigate PTSD-like memory or augmented susceptibility to a second stressor, we examined memory and fear generalization towards ATS-associated cues or behaviors in response to a second, acute stress. To identify the mechanisms by which ATS enduringly disrupts spatial and emotional memory, we tested differential gene expression among male, proestrous, and estrous female hippocampus at baseline and following ATS. Additionally, we tested differential enrichment of permissive and repressive histone modifications across all groups. **Results:** ATS enduringly disrupted spatial and emotional memory in males and in females stressed during proestrous. Blocking estrogen receptors through ER antagonists or using ERKO mice prevented spatial and emotional memory deficits in males and proestrous females. We identified ERα in males and ERβ in females as those receptors mediating the deleterious effects of estrogen. Ongoing experiments are probing differential gene expression and enrichment of permissive and

repressive histone modifications among male, proestrous, and estrous female hippocampus at baseline and following ATS.

Disclosures: R.E. Hokenson: None. **K. Rodriguez:** None. **Y. Chen:** None. **G.D. Angeles:** None. **S.A. Samrari:** None. **B. Devireddy:** None. **S. Kotthru:** None. **M.T. Birnie:** None. **N. Kamei:** None. **E.A. Heller:** None. **T.Z. Baram:** None.

Poster

PSTR085: Threat, Anxiety, and Avoidance in Animal Models

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Program #/Poster #: PSTR085.20/K29

Topic: G.07. Post-Traumatic Stress Disorder

Support: Office of Naval Research
USU VPR Graduate Student Research Award

Title: The Impact of Sex and Sleep Restriction on Delayed Fear Incubation in Mice

Authors: *M. LITTLEPAGE-SAUNDERS[1], M. RUSNAK[2], M. C. TSUDA[3], T.-Y. J. WU[4]; [1]Uniformed Services Univ. of the Hlth. Sci., Bethesda, MD; [2]Pharmacol., Henry Jackson Fndn., Bethesda, MD; [3]NIMH, Bethesda, MD; [4]Lab. of Neuroendocrinology and Women's Hlth. Res., Uniformed Services Univ. of Hlth. Sci., Bethesda, MD

Abstract: Post-traumatic stress disorder (PTSD) is a neuropsychiatric disorder that can be defined as one of the fear-related psychopathologies where cues associated with a traumatic event triggers excessive responses associated with fear. In about a quarter of PTSD cases, these responses are not displayed until 6 months post-traumatic event, categorizing it as delayed-onset PTSD. It is not fully understood why some are more prone to develop PTSD, nor why some have delayed-onset symptoms. Statistics show that women and people belonging to populations pre-exposed to stress have a higher risk of developing PTSD. To test this we evaluated the impact that sex and sleep restriction has on fear response using a delayed fear incubation behavioral assay. This assay exposed the mice to a two second 1.5 mA foot shock, then had them return back to the same chamber but in absence of the shock 1, 14, or 28 days post-shock day. First, we examined sex differences using a 2 (sex) x 3 (time) factorial design (n=16/group). Both male and female mice assigned to later recall days displayed increased freezing, decreased distance traveled, and decreased latency to the first freezing episode compared to their sham and recall day one counterparts. Next, using separate cohorts of mice and a 2 (sex) x 2 (sleep restriction) x 3 (time) factorial design (n=16/group), we evaluated the impact of sleep restriction on fear response. We restricted the mice from 20 hours of sleep using a modified multiple platform model, a paradoxical sleep restriction model that targets disrupting REM sleep. Sleep-restricted mice showed increased freezing and decreased distance traveled compared to their non-sleep restricted counterparts. Ongoing experiments will look at difference in expression of HPA axis markers and more into circuitry-level changes by comparing neuronal activation through cFos

expression in different brain regions that are a part of the limbic system and/or have been associated with fear: the amygdala, hippocampus, prefrontal cortex, and paraventricular nucleus.

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Poster

PSTR085: Threat, Anxiety, and Avoidance in Animal Models

Location: MCP Hall A

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Program #/Poster #: PSTR085.21/K30

Topic: G.06. Anxiety Disorders

Title: Ovarian hormones tune amygdala inhibition to drive avoidance behavior across the reproductive cycle

Authors: A. J. TELLEZ[1], P. J. TERAVSKIS[2], A. L. BUNCE[3], A. FARTHING[4], J. SIMON[5], *E. LUCAS[2];
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Abstract: In both humans and rodents, high levels of ovarian hormones reduce anxiety, but the cellular mechanisms driving this effect remain enigmatic. The basolateral amygdala (BLA) regulates anxiety, but little is known about the regulation of BLA function across the female reproductive cycle. Using mice as the model species, we first conducted single nucleus sequencing of the BLA in males and females in the high (proestrus) versus low (diestrus) hormone stages of the reproductive cycle. We observed profound changes of the transcriptional landscape of most BLA cell types in proestrus females compared to diestrus females and males. All neuronal subtypes expressed the progesterone receptor and estrogen receptor alpha, but estrogen receptor beta expression was limited to one type of principal neuron and parvalbumin-expressing interneurons (PVIs). Considering that BLA activity is tightly regulated by PVIs, we targeted this neuronal population for subsequent electrophysiological and behavioral experiments. We performed whole-cell patch clamp electrophysiology in BLA PVIs in proestrus females, diestrus females, and males and observed effects of both sex and estrous cycle. BLA PVIs were hyperpolarized and received fewer excitatory postsynaptic currents in proestrus versus diestrus. However, we also observed increased intrinsic excitability and reduced frequency of inhibitory postsynaptic currents in females versus males independent of estrous cycle. We next harnessed chemogenetics to depolarize BLA PVIs in males, proestrus females, and diestrus females to establish a causal relationship between the observed electrophysiological changes and regulation of anxiety-like behavior across the reproductive cycle. We found that activation of BLA PVIs reversed the anxiolytic effects of proestrus in the elevated plus maze and open field tests but decreased social interaction in females compared to males independent of

estrous stage. Ongoing work is monitoring *in vivo* activity of additional interneuron and principal neuron populations across the estrous cycle in these behavioral assays. Contrary to current models, our data suggest that increased BLA PVI activity promotes, rather than inhibits, anxiety-like behavior. Our work further implicates a role for biological sex and cycling ovarian hormones in regulating the critical balance of excitation and inhibition in the BLA to guide behavior.

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Poster

PSTR085: Threat, Anxiety, and Avoidance in Animal Models

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Topic: G.06. Anxiety Disorders

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HiREC Endowment Fund at UPR MSC
NIGMS COBRE at MSC

Title: The effects of herbicide consumption on avoidance behaviors in female rats

Authors: *L. L. MENDEZ-SANTACRUZ[1], N. JIMENEZ-RIVERA[2], T. M. JIMÉNEZ RIVERA[3], T. SALCEDO[3], O. MARTÍNEZ GUZMAN[2], D. SIERRA-MERCADO[2]; [1]Biol., Univ. of Puerto Rico, San Juan, PR; [2]Anat. & Neurobio., Univ. of Puerto Rico Sch. of Med., San Juan, PR; [3]Biol., Univ. of Puerto Rico Bayamon, San Juan, PR

Abstract: The use of glyphosate-based herbicides (Glyph) increases each year in the United States. Interestingly, there is a correlation between Glyph exposure and anxiety disorders. Unfortunately, increases in anxiety may exacerbate other behaviors, such as avoidance. Avoidance is a defensive response where an individual takes actions to avert potential harm. Notably, avoidance can be modeled in rodents using platform-mediated avoidance. Here, rodents learn to avoid a foot shock by stepping onto a safe platform during presentation of a conditioned auditory stimulus (e.g. tone). Stepping on the platform protects the rodent from the shock, but does not eliminate the auditory stimulus. Of note, when the animal steps onto the avoidance platform, it cannot access a sugar-pellet reward. Thus, platform-mediated avoidance creates a conflict that requires rodents to make a choice between avoidance (no shock) and reward (receiving sugar pellets). In the current study, we hypothesized that glyphosate exposure would result in excess avoidance as observed by more time on the platform. To test this idea, female rats were trained on platform-mediated avoidance. Next, rats were exposed to Glyph (2.0 mg/kg/day) through drinking water for 12 weeks (n=8). Control rats receive filtered water during

this period (n=8). At the end of exposure period, rats were tested for avoidance behaviors over four days. Anxiety levels were also measured through open field and elevated plus maze. Contrary to our hypothesis, we observed that Glyph reduce the time spent on the platform during the avoidance test compared to controls (p = 0.0294, T-Test), but not across subsequent days. Furthermore, uur results demonstrated that glyphosate increased anxiety-like behaviors in the elevated plus maze (p = 0.0264, T-Test), but not in the open field tests. Thus, we are currently performing additional experiments and analysis to clarify the interpretation of our results. Moreover, we are using immunohistochemical techniques to assess for changes in brain regions implicated in avoidance.

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Poster

PSTR085: Threat, Anxiety, and Avoidance in Animal Models

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Topic: G.06. Anxiety Disorders

Support: NSERC
CFI

Title: Predator odor stress augments kindling-induced emotionality in rats

Authors: G. E. EKINS, G. A. SILVER, *N. M. FOURNIER;
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Abstract: It is widely accepted that stress can worsen seizure disorders in both human patients and animal models of epilepsy. Most studies investigating this relationship have generally focused on the proconvulsant actions of stress hormones on seizure susceptibility. However, seizures, particularly those that arise from mesial limbic structures, are also commonly associated with a higher occurrence of several neuropsychiatric conditions, such as generalized anxiety disorder, that are known to be worsened by stress. In the present study, we explored the impact of exposure to a predator-derived kairomone (TMT) found in fox feces on emotional behaviour in amygdala-kindled rats. Rats underwent 60 kindled or sham stimulations before undergoing a safety learning task. In this procedure, the presentation of a “safe” cue (i.e. a tone) during conditioning serves to predict the absence of an aversive event (i.e. a foot shock) leading to an attenuation in fear responses when the cue is presented. We found that both kindled and sham controls exhibited reduced freezing during the presentation of the safe cue. One week later, all animals were exposed to fox odor (10% TMT) or control odorant (tap water) for 10 minutes. Examination of the safety cue recall testing found that TMT-exposed kindled rats showed higher generalized freezing to the safety cue compared to TMT-exposed sham controls as well as the control odorant condition for either group. Moreover, TMT-exposed kindled rats exhibited

greater anxiety-like behaviour in the elevated plus and open field arena compared to all other groups. These findings suggest that kindling might sensitize neural circuits important for processing threat-related cues, which in turn may enhance stress-evoked affective responses.

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Poster

PSTR085: Threat, Anxiety, and Avoidance in Animal Models

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Program #/Poster #: PSTR085.24/K33

Topic: G.06. Anxiety Disorders

Title: Running Solo: Investigating behavioral and neuroendocrine responses to voluntary exercise in socially isolated prairie voles.

Authors: *C. WRIGHT[1], M. L. COX[1], N. HOLZAPFEL-CULVER[2], S. SUJET[2], O. AKINBO[2], S. CIOSEK[2], W. WATANASRIYAKUL[3], A. J. GRIPPO[1];
[1]Psychology, Northern Illinois Univ., Dekalb, IL; [2]Northern Illinois Univ., Dekalb, IL; [3]Psychological & Brain Sci., Univ. of Delaware, Newark, DE

Abstract: Social isolation affects the health of millions worldwide. Among its many known negative consequences, increased anxiety is especially prevalent and often significantly debilitating. Without intervention, such increases in anxiety mediate risk factors for neuroendocrine dysfunction and cardiovascular disease. In adjacent spheres of research, exercise has recently emerged with particular promise as a therapeutic adjunct for emotion-related disorders. For instance, exercise protects against depression in lonely humans. Rodent models have yielded similar findings; in socially isolated prairie voles, exercise protected against depressive behavior and its associated neuroendocrine responses. However, exercise's therapeutic potential for anxiety and neural mechanisms underlying its influence are not well understood. Utilizing the socially monogamous prairie vole model, the present study investigated 1) the effect of voluntary exercise on isolation-induced anxiety-like behavior and 2) the role of central oxytocin (OT) in the relationship between social isolation and the benefits of exercise. Adult male and female prairie voles cohoused with a same-sex sibling were randomly assigned to 1) 8 weeks sedentary isolation (SI), 2) 8 weeks isolation with access to a running wheel in the final 4 weeks (RWI), or 3) paired control conditions. At the conclusion of the study, anxiety- and exploration-related behaviors were evaluated in a 20-minute open-field test (OFT). Brain tissue was evaluated for OT activation in the paraventricular nucleus (PVN). Preliminary behavioral analyses revealed significant sex-dependent differences in anxiety-related behaviors between the RWI condition and SI condition. In the OFT, RWI voles spent a significantly greater duration in the center of the arena compared to SI voles, suggesting a potential reduction in anxiety-like behavior, however this effect was driven by males. Preliminary histological results also revealed sex-dependent differences in OT neuron activation in the PVN. OT activation in RWI females was significantly lower than in SI females, shown via co-labeled OT and cFos, while no

differences in OT activation were observed between conditions among males. Results suggest that exercise may protect against behavioral indicators of anxiety associated with social isolation. OT's mechanistic role in this effect, however, remains somewhat ambiguous and requires more detailed investigation. Further research using animal models will provide additional opportunities to elucidate the mechanistic pathways through which exercise exerts therapeutic benefits in socially isolated individuals.

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Poster

PSTR085: Threat, Anxiety, and Avoidance in Animal Models

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Program #/Poster #: PSTR085.25/K34

Topic: B.07. Network Interactions

Title: Infralimbic prefrontal cortex and basal medial amygdala projections to bed nucleus of tria terminalis regulate innate and learned behaviors.

Authors: *V. E. RODRIGUEZ;
Northwestern Univ., Chicago, IL

Abstract: More than half of the US population has lived through at least one traumatic experience in their lifetime.While many will be able to overcome trauma, a subset of individuals will develop trauma-related andanxiety disorders. Research has shown that traumatic experiences disrupt circuits required toappropriately express fear (i.e., threat)memories and anxiety and lead to maladaptive behaviors inotherwise safe contexts.The bed nucleus of stria terminalis (BNST)is one of the major structures involved in mediating fearmemory, apprehension, and anxiety. Retrograde tracing experiments have shown that the BNST receivesinputs from the basomedial nucleus of the amygdala (BMA), which has been implicated as an inhibitorystructure for anxiety and fear responses. Additionally, the infralimbic subdivision of medial prefrontalcortex (IL)— a region implicated in reducing fear — also projects to BNST. Furthermore, the IL toBNST projection has been shown to suppress fear of uncertain threats. However, the interaction of thesecircuits in innate and learned defensive behaviors remains poorly understood.To characterize the role of BMA- anterior dorsal (ad)BNST and IL-adBNST projections on learned andinnate defensive behaviors, we used an optogenetic approach in combination with behavioral assays. Wefirst expressed the excitatory opsin channelrhodopsin (ChR2)in the BMA-adBNST pathway. Optogeneticactivation of BMA-adBNST during the elevated plus-maze (EPM), fear conditioning (FC), and predatorodor exposure increases exploration of open arms, reduces conditioned freezing, and innate freezingrespectively ($p<0.05$). Interestingly, optogenetic activation of IL-adBNST during the EPM, FC, andpredator odor exposure decreases exploration of open arms while reducing conditioned and innatefreezing ($p<0.05$).We are currently using an optogenetic approach to investigate the necessity of BMA-adBNST andIL-adBNST projections

for the regulation of fear and anxiety. Additionally, to disentangle how thesecircuits work together to orchestrate defensive behaviors in-vivo, we are using a dual-photometryapproach to simultaneously record activity from BMA-adBNST and IL-adBNST projection neuronsduring task performance. Conclusions from this experiment will further expand the role of BNST as animportant hub linking cortical and subcortical circuits in the regulation of behaviors underlying PTSD.

Disclosures: V.E. Rodriguez: None.

Poster

PSTR085: Threat, Anxiety, and Avoidance in Animal Models

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR085.26/L1

Topic: G.07. Post-Traumatic Stress Disorder

Support: VA BX004727-01

Title: Stress and cannabis use change stress responses by altering perineuronal nets in the ventral pallidum

Authors: *R. HODEBOURG[1], P. W. KALIVAS[2];
[1]Neurosci., Med. Univ. of South Carolina, Charleston, SC; [2]Neurosci. Res., Med. Univ. S Carolina, Charleston, SC

Abstract: The increasing legalization of cannabis and its high comorbidity with post-traumatic stress disorder (PTSD) necessitates a better understanding of the interaction between stress and cannabis in the brain. Using acute restraint stress combined with a rat cannabis self-administration paradigm, I recently found that cannabis use promotes two primary PTSD-like symptoms: avoidance coping behaviors and the generalization of stress-coping responses to a neutral stimulus (NS) not previously associated with stress exposure. However, the neuroadaptations underlying these changes are poorly understood. Recent studies demonstrated that perineuronal nets (PNNs), the highly condensed form of the extracellular matrix, are dysregulated in several brain regions after stressful events. Although the ventral pallidum (VP) is a brain region well characterized for its role in aversive behaviors, the effects of stress and cannabis on PNNs in this structure are unknown. First, we aimed to investigate the effects of acute stress and stress-conditioned stimulus (stress-CS) on PNNs in VP. To this end, rats were restraint stressed for 2h and simultaneously exposed to an odor that became the stress-CS. Control rats were exposed to the same odor in the home cage. 3 weeks after the stress, the effect of the CS or an NS was tested in a defensive burying task (DBT) for 15 min. The active (buying behavior) and avoidant coping strategies (immobility and escape behaviors) and the number of neurons surrounded by PNNs were quantified. The acute stress induced an enduring increase in the number of neurons surrounded by PNNs in the VP. Moreover, exposure to a stress-CS led to a decrease in PNNs, which was negatively correlated with the burying behavior, supporting an

important role of PNNs in coping strategies. To directly assess the impact of PNNs on stress responses, chondroitinase ABC was used to enzymatically degrade PNNs. We found that PNN removal in the VP mimics the effect of cannabis use by generalizing stress responses to the NS. This suggests that cannabis use may worsen PTSD symptoms by reducing PNNs in the VP. To test this hypothesis, 3 weeks after the acute stress, another cohort of rats self-administered cannabinoids (delta9-tetrahydrocannabinol+cannabidiol; THC+CBD) or vehicle for 10 days. After 10 days of withdrawal, coping strategies were evaluated in the DBT. As expected, cannabis withdrawal reduced the number of PNNs in the VP and generalized stress responses even in non-stressed rats. These data strongly point to the need to investigate how stress and cannabis affect PNNs, potentially contributing to the comorbidity between PTSD and cannabis use disorder.

Disclosures: R. Hodebourg: None. **P.W. Kalivas:** None.

Poster

PSTR085: Threat, Anxiety, and Avoidance in Animal Models

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR085.27/L2

Topic: G.06. Anxiety Disorders

Title: Sex-dependent effects of chronic oral cannabidiol exposure in rats on anxiety-like behavior

Authors: *C. R. MAESTAS-OLGUIN[1], T. CHANEL[2], A. MASIN[1], N. PENTKOWSKI[1]; [1]Univ. of New Mexico, Albuquerque, NM; [2]Psychology, Univ. of New Mexico, Tijeras, NM

Abstract: Three decades of waning political opposition combined with waxing positive sentiment from the public have culminated in recent legislative developments concerning the rescheduling of cannabis (i.e., marijuana) containing tetrahydrocannabinol (THC) under the Controlled Substances Act of 1970. These circumstances have fueled a rush of new consumer products designed for the maximal and, or specified delivery of cannabis derived compounds. While THC has received most of the attention due to its psychoactive properties and abundant natural production, over 600 compounds, including more than 100 compounds similar to THC, known as phytocannabinoids, have been identified in cannabis[1]. Of note, the second most abundantly produced compound, cannabidiol (CBD), has already been proven effective in treating two forms of severe early onset epilepsy[2]. Additionally, growing evidence supports an anxiolytic role of CBD[3-5]. However, few reports have directly explored possible sex-dependent variations in the proposed anxiolytic effects. The present study sought to characterize and compare the sex-dependent behavioral response of rats to seven consecutive days of low-dose (150mcg/dose), oral CBD exposure prior to a single trial within the elevated plus maze (EPM). Adult, naïve male (n = 14) and female (n = 14) Long-Evans hooded rats were randomly assigned to either “CBD” (LyfeBaak® full-spectrum hemp oil mixed with peanut butter) or “control” (peanut butter) conditions. Analysis of the data revealed a significant difference in average time spent in the open arm of the EPM. Further analysis revealed no significant main effect of sex or

condition on the duration of time spent in the open arm. However, a significant interaction between sex and condition was observed. Interestingly, seven days of consecutive, low-dose oral CBD exposure produced anxiogenic effects in female rats and anxiolytic effects in male rats, evidenced by a decrease and increase in open arm duration respectively, compared to controls. These findings add to the growing knowledge base regarding the therapeutic use of various cannabinoid formulations. In particular, these findings suggest that more attention should be paid to patient characteristics that could influence the efficacy of cannabinoid interventions.

Disclosures: C.R. Maestas-Olguin: None. **T. Chanel:** None. **A. Masin:** None. **N. Pentkowski:** None.

Poster

PSTR085: Threat, Anxiety, and Avoidance in Animal Models

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR085.28/L3

Topic: G.06. Anxiety Disorders

Title: The anxiolytic-like effect of Punica Granatum is dependent on stress condition

Authors: *E. ESTRADA-CAMARENA[1], N. VEGA[2], J. CHAN MONROY[2];
[1]Inst. Natl. Psiquiatria "Ramón de la Fuente", Cd de Mexico, Mexico; [2]Natl. Inst. of Psychiatry, México City, Mexico

Abstract: Anxiety is a normal behavior considered an adaptative and survival response which purpose is keep us away from danger, however when anxiety becomes excessive,and irrational is considered as a psychiatric disorder and have comorbidity with other conditions as depression and stress.Pharmacological treatment includes serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs) or benzodiazepines, and alternatives therapies, for example the use of functional food as *Punica Granatum* (PG) which has numerous properties, for example, antioxidant, antidepressant, and anxiolytic-like actions in murine models.
Anxiolytic properties of *Punica Granatum* have been evaluate as aqueous extract (AE-PG) in animals for reverse the anxiety-like behaviors, however, the anxiolytic effect of AE-PG it has not yet been evaluated as a preventive treatment.Because of that our objective is evaluated if AE-PG have an anxiolytic-like effect in mice without prior stress condition. For it, groups of independent female mice were administrated on sub chronic scheme with AE-PG, diazepam (positive control) and saline solution as negative control. After last administration, animals were evaluated in Elevated Plus Maze (EPM) and Splash Test (ST) to elucidate anxiolytic-like effect of the drugs.
Results shows that diazepam has anxiolytic-like effect in mice without prior stress, but the effect of AE-PG has in mice without prior stress induced anxiogenic-like effect. With these findings we can conclude that the anxiolytic-like effect of AE-PG is dependent on the previous setress condition in wich the animals are found.

Disclosures: E. Estrada-Camarena: None. **N. Vega:** None. **J. Chan monroy:** None.

Poster

PSTR085: Threat, Anxiety, and Avoidance in Animal Models

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR085.29/L4

Topic: G.06. Anxiety Disorders

Support: JSPS KAKENHI 22K06714

Title: Effects of Chotosan and Uncaria hook on LPS-induced anxiety-like behavior in mice

Authors: *Y. KITAMURA[1], Y. OKAWA[2], Y. IZUSHI[1], S. USHIO[3], Y. ZAMAMI[2], T. SENDO[2];
[1]Shujitsu Univ., Okayama, Japan; [2]Okayama Univ. Hosp., Okayama, Japan; [3]Fukuoka Univ., Fukuoka, Japan

Abstract: This study aimed to examine the effects of chotosan, a traditional Japanese herbal medicine, and its active component, uncaria hook, on anxiety-like behavior induced by systemic inflammation in mice. To induce systemic inflammation, mice were treated with lipopolysaccharide (LPS), a bacterial endotoxin. Prior to the LPS treatment, the mice received chotosan orally each day for 14 days. The anxiety-like behavior of the mice was then evaluated using the light-dark test 24 h after the LPS treatment. The repeated administration of chotosan prevented anxiety-like behavior in both the normal and LPS-treated mice. Similarly, uncaria hook suppressed LPS-induced anxiety-like behavior in the mice. LPS treatment significantly increased serotonin (5-HT)2A receptor mRNA expression in the frontal cortex. Conversely, chotosan significantly suppressed 5-HT2A receptor mRNA expression. In addition, the levels of brain-derived neurotrophic factor (BDNF) were decreased in the hippocampi of the LPS-treated mice. This effect of LPS was not seen after the administration of chotosan or uncaria hook. These findings indicate that chotosan exerts anxiolytic-like effects in the context of inflammation-induced anxiety, which may be mediated by inhibiting 5-HT2A receptor hyperfunction, in LPS-treated mice. Consequently, we postulate that chotosan may be effective for managing inflammation-induced anxiety-like behavior. (# Y Kitamura and Y Okawa contributed equally to this study.)

Disclosures: Y. Kitamura: None. **Y. Okawa:** None. **Y. Izushi:** None. **S. Ushio:** None. **Y. Zamami:** None. **T. Sendo:** None.

Poster

PSTR086: Drugs of Abuse: Cell Signaling, Circuitry, Learning, and Decision-Making

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR086.01/L5

Topic: G.09. Drugs of Abuse and Addiction

Support: Dickinson College Faculty Research Fund

Title: Effects of post-training dopaminergic and beta-adrenergic antagonism on sensitization

Authors: *A. S. RAUHUT[1], J. HENDERSON[1], H. HOLDAWAY[1], N. S. AL HAMADANI[2], O. ALI[2], N. S. NOTO[1], D. S. SALE[2];
[1]Psychology, [2]Neurosci., Dickinson Col., Carlisle, PA

Abstract: Memory consolidation processes contribute to conditioned hyperactivity and sensitization. However, the underlying neural systems that mediate memory consolidation, and their impact on conditioned hyperactivity and sensitization are poorly understood. The present experiments examined if antagonism of the dopaminergic and noradrenergic systems, specifically the dopaminergic D2 and beta-adrenergic receptors, respectively, disrupted memory consolidation and subsequently blocked the development of conditioned hyperactivity and sensitization. Following 4 weeks of acclimation, male, Swiss Webster mice received either a single injection (intraperitoneal, i.p.) of physiological saline (vehicle) or methamphetamine (2.0 mg/kg) prior to a single 30-minute locomotor activity session (Conditioning). Immediately or 2 hours after the conditioning session, mice received either an injection (i.p.) of physiological saline (vehicle) or the dopaminergic D2 receptor antagonist, haloperidol (40 μg/kg; Experiment 1) or physiological saline (vehicle), or the non-selective (β1/β2) receptor antagonist. propranolol (16 or 32 mg/kg; Experiment 2) or distilled water (vehicle), and then returned to their home cages. Following the conditioning session, tests for conditioned hyperactivity (CR Test) and behavioral sensitization (Methamphetamine Challenge Test) occurred after a delay of 6 and 7 days, respectively. An injection of physiological saline or methamphetamine (1.0 mg/kg) occurred on the CR Test and Methamphetamine Challenge Test, respectively. Distance traveled served as the dependent measures of locomotor activity. A single injection of methamphetamine produced robust conditioned hyperactivity and sensitization. Neither immediate post-injection of haloperidol nor propranolol disrupted conditioned hyperactivity but propranolol dose-dependently attenuated sensitization. Taken together, these results indicate that neither dopaminergic nor beta-adrenergic antagonism disrupted memory consolidation and subsequent conditioned hyperactivity whereas post-training antagonism of beta-adrenergic receptors disrupted development of sensitization through non-memory consolidation process(es).

Disclosures: A.S. Rauhut: None. **J. Henderson:** None. **H. Holdaway:** None. **N.S. Al Hamadani:** None. **O. Ali:** None. **N.S. Noto:** None. **D.S. Sale:** None.

Poster

PSTR086: Drugs of Abuse: Cell Signaling, Circuitry, Learning, and Decision-Making

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR086.02/L6

Topic: G.09. Drugs of Abuse and Addiction

Support: T32 Drug Abuse Training Program
McMahon Recruitment Package

Title: Function of the Nucleus Reuniens following meth-induced memory deficits in rats

Authors: *S. T. GOLDSMITH[1], M. D. SCOFIELD[2], L. L. MCMAHON[3];
[1]Med. Univ. of South Carolina, Charleston, SC; [2]Dept. of Anesthesiol., Med. Univ. of South Carolina, Charleston, SC; [3]Dept. of Neurosci., Med. Univ. of South Carolina, Charleston, SC

Abstract: Methamphetamine (meth) use causes neural inflammation and memory deficits in nearly 2/3rd of users that appear during abstinence. These memory deficits indicate treatment outcomes, necessitating studies to reveal the mechanisms behind this memory loss. Fortunately, this phenotypic response following meth use can be replicated in preclinical experimental models. In rats, meth impacts many forms of episodic memory, including memory for the location of objects called Object-in-Place (OiP) memory. OiP memory requires normal function of the thalamic brain region, the Nucleus Reuniens (NRe), which coordinates activity between the hippocampus and prefrontal cortex. However, how meth use impacts neuronal excitability or synaptic connectivity of principal neurons in NRe is unknown. We have confirmed previous literature that meth disrupts OiP performance. In these studies, meth-related memory deficits occur a week following severe meth use, as acute meth administration can increase memory performance. In ongoing studies, we continue our investigation using male and female Long Evans rats pre-tested on the OiP task to establish healthy function. They are subsequently treated with meth (four 4 mg/mL/kg, 2hr intervals) or saline. The NRe will be manipulated using DREADDs validated using whole-cell patch clamp electrophysiology. This experiment is to determine the role of the NRe in memory loss. We hypothesize excitatory activation of the NRe will restore performance on the OiP task following the meth-induced deficit. These data will be analyzed using 2-way ANOVA. Additionally, intrinsic excitability and synaptic connectivity of the NRe will be evaluated in the absence and presence of meth. These recordings for intrinsic membrane properties, sEPSCs, and sIPSCs will occur after 7 days of abstinence following meth to align with the period when these cognitive deficits appear. The data for synaptic functionality will be analyzed using students' T-tests. Preliminary data suggest that the NRe is negatively impacted following meth use. Since this brain region has never been studied in the context of methamphetamine use, further analysis will likely reveal nuance about the function of this brain region and meth abuse’s detrimental effects on memory. The NRe is a key region for understanding meth’s negative influence on memory, providing valuable insight into the function of this brain region.

Disclosures: S.T. Goldsmith: None. **M.D. Scofield:** None. **L.L. McMahon:** None.

Poster

PSTR086: Drugs of Abuse: Cell Signaling, Circuitry, Learning, and Decision-Making

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR086.03/L7

Topic: G.09. Drugs of Abuse and Addiction

Title: The Deferential Effects of the NMDA Receptor Antagonist MK-801 and the Beta-Blocker Propranolol on the Reconsolidation of Methamphetamine Associated Memories

Authors: *M. HANNA;
Vanguard Univ., Costa Mesa, CA

Abstract: A significant contributing factor to drug relapse is exposure to environmental stimuli that have been previously associated with drug administration. Exposure to such cues evokes memories of the effects of the drug and induces drug-seeking behavior. Drug-associated memories go through a process of consolidation wherein unstable memories are placed into a permanent state. When these memories are later triggered, they go through reconsolidation, in which a memory becomes temporarily unstable and liable to disruption before becoming stable again. Previous research has shown that consolidation and reconsolidation share similar mechanisms but differ in a few ways. It has been shown that consolidation requires the activation of the glutamate receptor NMDA to initiate a cascade of cellular processes that ultimately leads to the transcription and translation of new proteins needed for memory formation. Previous studies have also shown that beta-receptors play a role in consolidation. In this study, we examined whether the N-methyl-D-aspartate (NMDA) receptor and beta-adrenergic receptors play a role in the reconsolidation of drug-associated memories and whether blockage of the NMDA receptor can attenuate memories of methamphetamine-associated drug-cues. To examine these questions, we examined the effects of the NMDA Receptor Antagonist MK-801 and the Beta-Blocker propranolol in a methamphetamine-induced condition place preference task. Rats injected with the MK-801 before reactivation showed a significant decrease in drug-seeking behavior compared to rats injected with saline. On the other hand, administration of propranolol prior to the reactivation session did not decrease drug-seeking behavior.

Disclosures: M. Hanna: None.

Poster

PSTR086: Drugs of Abuse: Cell Signaling, Circuitry, Learning, and Decision-Making

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR086.04/L8

Topic: G.09. Drugs of Abuse and Addiction

Title: The Effects of an Antidepressant Dose of Ketamine on Distinct Processes of Implicit and Explicit Memory in Adult Rats

Authors: Z. SEN, B. YUKSEL, ***G. UNAL**;
Bogazici Univ., Istanbul, Turkey

Abstract: Ketamine, a non-competitive N-methyl-D-aspartate receptor antagonist, produces rapid antidepressant effects. The therapeutic effect, however, may be accompanied by different cognitive side effects and memory impairments. In this study, we assessed the impact of an antidepressant dose of ketamine (10 mg/kg) on distinct memory processes—acquisition, retrieval, and modulation—in both an implicit and an explicit task in 60 adult male Wistar rats. In one set of experiments, ketamine was administered intraperitoneally 30 minutes before the acquisition, retrieval, or extinction stages of cued fear conditioning, an amygdala-dependent implicit memory test. In the explicit memory experiment, rats were injected with ketamine 30 minutes before either the training, probe trial, or reversal training phases of the Morris water maze (MWM). We found that ketamine administration before the acquisition or retrieval stage impaired subsequent modulation of conditioned fear memory. In explicit memory, IP ketamine administration altered searching strategies in the probe trial of MWM, as indicated by fewer target quarter entries. In addition, administering ketamine before acquisition or reversal training phases significantly decreased escape latencies on the first day of reversal training, indicating transient ameliorative effects of ketamine. Overall, these results demonstrate that an antidepressant dose of ketamine could obstruct modulation of implicit memory while improving certain explicit memory processes. This reflects the different influences of ketamine on memory functions that primarily rely on the amygdala versus the hippocampus.

Disclosures: Z. Sen: None. **B. Yuksel:** None. **G. Unal:** None.

Poster

PSTR086: Drugs of Abuse: Cell Signaling, Circuitry, Learning, and Decision-Making

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR086.05/L9

Topic: H.08. Learning and Memory

Title: Effect of late gestational ingestion of combined cbd and thc on cerebellar morphology in the offspring of Wistar rats.

Authors: *D. O. TAIWO-OLA[1], I. A. SULEIMAN[2], P. D. SHALLIE[3], J. A. ARIYO[1], F. B. BAMIDELE[4];
[1]Dept. of Anat., Olabisi Onabanjo Univ., Ago Iwoye, Nigeria; [2]Dept. of Anat., Crescent Univ., Abeokuta, Nigeria; [3]Univ. of Missouri, Kansas City, MO; [4]Dept. of Anat., Olabisi Onabanjo Univ., Shagamu, Nigeria

Abstract: This study investigates the effects of late-gestational ingestion of combined CBD and THC on cerebellar morphology in Wistar rats. Twelve pregnant Wistar rats were divided into two groups of six: a control group and an experimental group. The experimental group received 150mg/kg body weight of CBD and THC from day 15 of gestational age until delivery. Neurodevelopmental data was analyzed using the GraphPad Prism software version 5.0. Comparisons between more than two groups were analyzed using ANOVA. The significance level was set at $P < 0.05$. Analysis revealed a significant decrease in fetal weights at birth in the

CBD and THC group compared to controls ($p < 0.01$). Distinct alterations in neurodevelopmental indices, including accelerated righting and posture in pups, were observed in the CBD and THC group. Photomicrographs showed notable morphological changes in the cerebellum, including vacuolization between the Purkinje cell layer and the molecular layer.

Disclosures: D.O. Taiwo-ola: None. **I.A. Suleiman:** None. **P.D. Shallie:** None. **J.A. Ariyo:** None. **F.B. Bamidele:** None.

Poster

PSTR086: Drugs of Abuse: Cell Signaling, Circuitry, Learning, and Decision-Making

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR086.06/L10

Topic: G.09. Drugs of Abuse and Addiction

Support: NIH Grant NIAAA 7R01AA024526 to JT
VA Grant 1I01BX005367

Title: The divergent effect of cannabinoids on cognition, addiction, and behavior

Authors: *B. MCGUFFIN[1], B. SCHWARTZ[1], L. J. WILLS[2], J. T. GASS[2];
[1]East Tennessee State Univ., Johnson City, TN; [2]Biomed. Sci., Quillen Col. of Med., Johnson City, TN

Abstract: Cannabis is the most widely used illicit drug, particularly in vulnerable populations such as veterans diagnosed with posttraumatic stress disorder (PTSD), adolescents, and chronic alcohol users. Indeed, patients diagnosed with cannabis use disorder (CUD) are 10x more likely to develop alcohol use disorder (AUD), and 6x more likely to develop PTSD. Cannabis contains two major phytocannabinoids, tetrahydrocannabinol (THC) and cannabidiol (CBD) that appear to have divergent effects. Therefore, we sought to better understand the relationships between cannabis use, psychiatric disease, and addiction. We first investigated the impact of combined alcohol and THC exposure on subsequent alcohol intake. THC exposure has been shown to negatively impact both physiological and behavioral outcomes through alterations in glutamatergic signaling, which are further exacerbated when used concomitantly with alcohol. Conversely, CBD is non-psychoactive and has been shown to produce therapeutic effects that include anxiolytic properties and treatment for addiction. Therefore, we investigated the use of CBD to reduce anxiety in a model of comorbid PTSD and AUD. We hypothesized that combined THC and alcohol exposure would exacerbate alcohol self-administration, and that CBD would recover deficits in extinction learning in a model of comorbid PTSD and AUD. To test our hypotheses, male Wistar rats were exposed to THC vapor followed by chronic intermittent ethanol exposure (CIE) to model alcohol dependence. Next, alcohol self-administration was measured with a Two-Bottle Choice (TBC) task and operant self-administration paradigm. Our results indicated that rats exposed to THC+CIE displayed significantly higher alcohol consumption in both the TBC and operant self-administration tasks and produced deficits in the

extinction of alcohol-seeking behavior. Importantly, treatment with the mGlu5 positive allosteric modulator, CDPPB (30mg/kg), recovered deficits in extinction learning of alcohol-seeking behavior. To test the efficacy of CBD as an anxiolytic, rats were exposed to restraint stress (RS) and CIE to model comorbid PTSD and AUD. Next, rats were tested in a conditioned fear task in which they learned to associate contextual information and a sound cue to a mild footshock followed by extinction training. Thirty minutes prior to each extinction session, rats were administered CBD (20mg/kg). While exposure to RS+CIE led to deficits in the ability to extinguish fear-related behaviors, treatment with CBD recovered these deficits in extinction learning. Together, these data suggest that THC and CBD have diverging effects on drug- and fear-related behaviors.

Disclosures: B. McGuffin: None. **B. Schwartz:** None. **L.J. Wills:** None. **J.T. Gass:** None.

Poster

PSTR086: Drugs of Abuse: Cell Signaling, Circuitry, Learning, and Decision-Making

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR086.07/L11

Topic: B.05. Synaptic Plasticity

Support: Robert J. and Nancy D Carney Institute for Brain Science Innovation Award
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IMSD: 5R25GM083270-11 (MPI)
Rhode Island Institutional Development Award (IDeA) Network of Biomedical Research Excellence from the National Institute of General Medical Sciences of the National Institutes of Health under grant number P20GM103430
Rhode Island Foundation Medical Research Fund 20210957

Title: Neural Dynamics Underlying the Formation and Retrieval of Alcohol Memories in Drosophila

Authors: *T. BROWN[1], K. R. KAUN[2], K. M. SCAPLEN[3];
[1]Brown Univ., PROVIDENCE, RI; [2]Neurosci., Brown Univ., Barrington, RI; [3]Neurosci., Bryant Univ., Smithfield, RI

Abstract: Alcohol Use Disorder (AUD) may arise from the gradual disruption of neural circuits that encode memory and reward. These neural circuits contain strong, inflexible memories that can generate problematic alcohol consumption. However, the cause of this inflexibility is poorly understood. Using *Drosophila melanogaster*, we take advantage of sophisticated genetic tools and well-mapped circuitry to investigate how memories for alcohol are encoded across memory

circuitry. Using *in vivo*, functional imaging of intrinsic mushroom body (MB) neurons, dopaminergic neurons projecting onto the MB, and downstream mushroom body output neurons (MBONs), we recorded how these circuits respond to acquisition and retrieval of alcohol memories. We expressed sensors for calcium (GCaMP7B), dopamine (GRAB-DA) or acetylcholine (GRAB-Ach) in cue-encoding intrinsic MB neurons and found that acquisition of alcohol memory potentiated responses at the axon terminals and resulted in the gradual recruitment of more cells in response to intoxication (n = 10). Additionally, we observed that dopaminergic transmission onto the terminals of the mushroom body increases during presentation of alcohol and an odor cue as opposed to an odor cue alone (n = 10). Presentation of a cue previously associated with alcohol resulted in a slight depression in calcium traces within cue-encoding intrinsic MB neurons (n = 16). These findings demonstrate that plasticity occurs at multiple points in a memory circuit during formation of alcohol memories, thus elucidating how these strong, inflexible alcohol memories are generated.

Disclosures: T. Brown: None. **K.R. Kaun:** None. **K.M. Scaplen:** None.

Poster

PSTR086: Drugs of Abuse: Cell Signaling, Circuitry, Learning, and Decision-Making

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR086.08/L12

Topic: H.03. Decision Making

Support: NIAAA P60 AA011605

Title: The impact of adolescent alcohol exposure on functional connectivity and immunhohistochemical markers associated with behavioral flexibility

Authors: *G. E. KIRKPATRICK[1], E. SULLIVAN[2], S. D. GARRISON[2], D. L. ROBINSON[3]; [1]Univ. of North Carolina-Chapel Hill, Chapel Hill, NC; [3]Bowles Ctr. for Alcohol Studies, [2]Univ. of North Carolina Chapel Hill, Chapel Hill, NC

Abstract: Adolescents often drink alcohol in a binge-like pattern, and this alcohol exposure can lead to reduced behavioral flexibility in adulthood. Behavioral flexibility is complexly regulated via the prefrontal cortex (PFC) exerting top-down control over subcortical areas. Additionally, adolescent intermittent ethanol (AIE) exposure alters MRI-based functional connectivity to the PFC and the anterior insular cortex (AIC), brain regions involved in cognition and behavioral flexibility. However, the molecular alterations driving this reduced connectivity are poorly understood. Perineuronal nets (PNNs), specialized extracellular matrix, preferentially ensheath parvalbumin-expressing (PV+) interneurons and modulate PV+ neuron activity to maintain excitatory/inhibitory balance within local neural circuits. We previously found that AIE exposure increased the number of PV+ neurons, PNNs, and co-expression of PV+ cells surrounded by PNNs in the rat AIC. To our knowledge, no study has examined immunohistological, functional connectivity, and behavioral changes following AIE exposure within the same subjects. To

address this, we performed immunofluorescent analysis of PV and PNN on a subset of rats from our prior MRI study. Methods: Sprague Dawley rats underwent AIE (5g/kg; male=4, female=5) or volume-matched water (CON; male=4, female=6) via gavage from postnatal day (P) 25-54 on a 2-day-ON/2-day-OFF regimen. In adulthood (>P100), rats underwent an attentional set shift task followed by resting-state functional MRI and transcardial perfusion. Immunofluorescence was performed in the PFC and AIC to visualize PV+ cells and PNNs. Results: Regarding behavioral flexibility, AIE rats showed no significant alterations to total trials to criterion during the initial acquisition but did make more active errors than CON rats ($p<0.05$). This effect persisted each test day during reacquisition of the prior day's contingency, as AIE-exposed rats made significantly more active errors than CON rats (RA1: $p<0.05$; RA2: $p<0.001$). During reversal 1 and 2, AIE-exposed rats took significantly more trials to reach criterion (RV1: $p<0.05$; RV2: $p<0.001$) and made more errors (RV1: $p<0.001$; RV2: $p<0.001$). Specifically, they made more perseverative errors (RV1: $p<0.001$; RV2: $p<0.05$) than CON rats, which is consistent with our previous studies. Ongoing connectivity and immunohistological analyses will determine within-subject how AIE impacts functional connectivity and PV+/ PNN measures in the AIC and the PFC. Together, these analyses will allow us to better elucidate how adolescent binge alcohol affects cellular and functional drivers of behavioral flexibility

Disclosures: G.E. Kirkpatrick: None. **E. Sullivan:** None. **S.D. Garrison:** None. **D.L. Robinson:** None.

Poster

PSTR086: Drugs of Abuse: Cell Signaling, Circuitry, Learning, and Decision-Making

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR086.09/L13

Topic: A.07. Developmental Disorders

Support: AA022534
5T32AA014127
AA015614

Title: Third Trimester Alcohol Exposure Results in Hippocampal-Retrosplenial Cortex Epileptiform Discharges

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Abstract: Third trimester alcohol exposure (TTAE) damages the hippocampal-diencephalic-cingulate (HDC), a critical circuit for learning and memory. Impairments in the function of this circuit are therefore speculated to drive deficits in learning, memory, and attention observed in individuals with prenatal alcohol exposure. Two main anatomical centers within the HDC network, the hippocampus and retro-splenial cortex (RSC), are thought to be key mediators of

memory consolidation during sleep. However, the impact of TTAE on memory consolidation during sleep in these brain areas has not been investigated. To do so, male and female TTAE and control (saline) mice were produced using a single day, double alcohol injection model (5 g/kg total) at postnatal day 7. After postnatal day 60, electrodes were implanted in the hippocampus and RSC. Following recovery, home cage electrophysiological recordings were collected in 24-hour epochs. Among the TTAE mice, we were extremely surprised to find frequent large amplitude events resembling epileptiform discharges (EDs) - a phenomenon that to our knowledge has never before been reported in any rodent model of prenatal alcohol exposure. Additionally, EDs occurred more frequently during sleep than awake behavioral states, and were observed in both the hippocampus and RSC. Interestingly, we were able to infer two different neuroanatomical sources and one source generated EDs that were preceded by high frequency oscillations in the RSC - a neural event important for long-term memory consolidation. These results identify and characterize HDC EDs as a potential mechanism for learning and memory impairments experienced by individuals exposed prenatally to alcohol which may be useful for developing therapeutic and supportive routes for this clinical population.

Disclosures: A. Myrick: None. **S. McKenzie:** None. **D.N. Linsenbardt:** None.

Poster

PSTR086: Drugs of Abuse: Cell Signaling, Circuitry, Learning, and Decision-Making

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR086.10/L14

Topic: G.09. Drugs of Abuse and Addiction

Support: (R01) 5R01DA049544
(SBIR) R44DA055420
(R21) R21AA028727

Title: Drug reactivation paired with non-muscle myosin II inhibition disrupts cocaine, heroin, and alcohol seeking

Authors: *S. PANDEY[1], E. J. YOUNG[1,2], L. KELLEY[3], A. B. HALL[1], M. SECCI[3], T. J. TEMPLETON-JAGER[3], S. DIARRA[3], G. RUMBAUGH[1], N. W. GILPIN[3], C. A. MILLER[1]; [1]The Herbert Wertheim UF Scripps Inst. for Biomed. Innovation & Technol., Jupiter, FL; [2]Myosin Therapeutics, Jupiter, FL; [3]Louisiana State Univ. Hlth. Sci. Ctr. Sch. of Med., New Orleans, LA

Abstract: Repeated exposure to drugs of abuse results in enduring drug-context associations that exert a powerful influence on the motivation to drug seek, even long into abstinence. At the cellular level, the synaptic structural plasticity supporting drug associations is maintained by the actin cytoskeleton, and our group has discovered that the molecular motor ATPase, non-muscle myosin IIB (NMIIB), is a direct regulator of synaptic actin polymerization and memory consolidation. We further discovered that inhibition of NMIIB even days after learning disrupts

methamphetamine (METH) seeking and association spine dynamics in a retrieval-independent manner, suggesting a dynamic memory consolidation window that uniquely extends well beyond drug exposure. Based on this discovery, our group has been developing MT-110, a first-in-class small molecule inhibitor of NMIIB (NMIIBi) for the treatment of METH use disorder. Interestingly, NMIIBi-mediated disruption of METH seeking is highly selective, as the same intervention has no such immediate and lasting effect on other drug associations. In the interest of potentially extending the utility of NMIIBi to other substance use disorders, we targeted reconsolidation, a brief period after retrieval of memory lability and updating. We and others have previously shown that drug associations are labile and vulnerable to disruption during this period. In line with most reconsolidation-focused studies, we have shown that NMIIBi paired with conditioned stimuli (CS) reactivation (i.e. exposure to cues or contexts) can disrupt other drug associations by weakening memory reconsolidation. However, a CS-based strategy has met with limited success in clinical studies because individuals with substance use disorder often have hundreds of associations that can trigger the motivation to drug seek. It is difficult for an individual to actively retrieve all these associations, some of which may be unconscious motivators. As an alternative, we sought to reactivate the full extent of these learned associations by using the unconditioned stimulus (US), i.e. administration of the drug itself at a subthreshold dose. Using conditioned place preference and self-administration models, we reactivated learned cocaine, heroin, and ethanol associations by administering subthreshold doses of the respective drugs (US) in the home cage, followed by NMIIBi. This resulted in a lasting reduction in cocaine and heroin seeking and alcohol drinking. Our findings support the therapeutic potential of NMIIBi, in combination with US-based reactivation, for a wide range of substance use disorders.

Disclosures: S. Pandey: None. **E.J. 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.; Myosin Therapeutics. **L. Kelley:** None. **A.B. Hall:** None. **M. Secci:** None. **T.J. Templeton-Jager:** None. **S. Diarra:** None. **G. Rumbaugh:** None. **N.W. Gilpin:** None. **C.A. Miller:** None.

Poster

PSTR086: Drugs of Abuse: Cell Signaling, Circuitry, Learning, and Decision-Making

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Topic: G.09. Drugs of Abuse and Addiction

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NIH Grant DA025646
WSU ADARP
Poncin Foundation Fund
WSU Alcohol and Drug Abuse Research Program

Title: Optogenetic inhibition of dorsal CA3 to CA1 circuit disrupts cocaine memory reconsolidation

Authors: *S. QI, J. RITCHIE, D. SOTO, A. PRUITT, D. REEVES, A. GREENWAY, R. A. FUCHS;
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Abstract: Destabilized long-term memories must be reconsolidated to maintain their strength over time. Interference with memory reconsolidation can weaken maladaptive memories in individuals with substance use disorders and reduce drug-seeking behavior in animal models of drug relapse. Therefore, it is a promising therapeutic approach for treating neuropsychiatric disorders characterized by strong, maladaptive memory. Previous research has demonstrated that the cornu ammonis 3 subregion of the dorsal hippocampus (dCA3) is necessary for maintaining the strength of cocaine memories. However, the contribution of dCA3 efferent circuits to memory reconsolidation has not been studied. The dCA3 sends direct monosynaptic inputs to the dCA1, and we postulated that this circuit critically modulates cocaine memory reconsolidation. To test this hypothesis, we used optogenetics to inhibit dCA3 terminals in the dCA1 after memory retrieval that was expected to initiate memory destabilization. To this end, rats received jugular catheter implants, bilateral infusions of AAV5-hSyn-eNpHR3.0-eYFP to express halorhodopsin in dCA3 neurons, and optic fiber implants aimed at the dCA1. After surgical recovery, the rats received cocaine self-administration and extinction training in two different environmental contexts. After training, the rats were re-exposed to the cocaine-predictive context to destabilize their cocaine memories. Immediately after this session, the rats received intermittent laser manipulation (Light-ON or Light-OFF) for one hour to inhibit the dCA3-dCA1 circuit during cocaine memory reconsolidation. At test, non-reinforced lever presses were measured in the extinction context and the cocaine-predictive context to assess the strength of extinction and cocaine memories, respectively. We found that optogenetic inhibition of the dCA3-dCA1 circuit immediately after memory retrieval reduced cocaine-seeking behavior selectively in the cocaine-predictive context compared to no inhibition. Conversely, optogenetic inhibition of the circuit six hours after memory retrieval (i.e. post-reconsolidation) failed to alter cocaine-seeking behavior compared to no inhibition. Thus far, these results suggest that monosynaptic input from the dCA3 to the dCA1 is necessary for maintaining the strength of cocaine memories.

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Poster

PSTR086: Drugs of Abuse: Cell Signaling, Circuitry, Learning, and Decision-Making

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Title: Dorsal raphe to basolateral amygdala corticotropin-releasing factor circuit regulates cocaine-memory reconsolidation in rats

Authors: D. A. SOTO[1], A. Y. PRUITT[1], J. L. RITCHIE[1], S. QI[1], S. E. SWATZELL[1], H. I. GRENZ[1], L. M. ARTIMENIA[1], S. K. COOKE[2], C. W. BERRIDGE[2], *R. A. FUCHS[3,4]; [1]Integrative Physiol. and Neurosci., Washington State Univ., Pullman, WA; [2]Psychology, Univ. of Wisconsin in Madison, Madison, WI; [3]Washington State Univ., Pullman, WA; [4]WSU Alcohol and Drug Abuse Research Program, Pullman, WA

Abstract: Retrieval can destabilize context-drug associative memory traces, requiring their reconsolidation into long-term memory stores for continued environmental stimulus control over drug-seeking behaviors. Disruption of labile cocaine memories or interference with their reconsolidation may be a viable therapeutic approach to prevent cue-induced relapse. Corticotropin-releasing factor (CRF) signaling in the basolateral amygdala (BLA) is critical for memory reconsolidation, but the source of CRF to the BLA is not known. Here, we investigated the role of a dorsal raphe (DR) → BLA CRF circuit in cocaine-memory reconsolidation. Sprague-Dawley rats (n = 4-10 per sex per group) were trained to lever press for cocaine infusions in a distinct environmental context. Lever responding was then extinguished in a different context. The rats were then briefly re-exposed to the cocaine-predictive environment to retrieve and destabilize cocaine memories and trigger their reconsolidation. In experiments 1-2, we examined the effects of chemogenetic DR → BLA CRF pathway inhibition on extinction and cocaine memory strength as indicated by lever pressing in the respective contexts at test. In experiment 3, we assessed the effects of the same manipulation on the expression of Zif268, a plasticity and activity related protein that has been shown to be critical for cocaine-memory reconsolidation in the BLA in other paradigms. In experiment 4, we characterized the cell types of BLA-projecting DR neurons that expressed c-Fos, a marker of neuronal activation, during memory reconsolidation. Chemogenetic inhibition of the DR → BLA CRF circuit during cocaine memory reconsolidation using the designer receptors exclusively activated by designer drugs (DREADDs) ligand, deschloroclozapine (DCZ; 0.1 mM, 0.5 uL/hemisphere), administered into the BLA reduced cocaine-memory strength as indicated by a cocaine-predictive context-, memory reactivation-, DREADD-, and DCZ-dependent decrease in lever pressing in males and females (Bonferroni's tests, ps < 0.05). The same manipulation also reduced Zif268 expression in DCZ-dependent manner (Dunnet's tests, ps < 0.05). Furthermore, the cell type analyses revealed that the BLA-projecting DR CRF cells activated during memory reconsolidation co-expressed the glutamatergic neuronal marker, vesicular glutamate transporter 3 (Bonferroni's tests, ps < 0.05). Together, these findings suggest that DR inputs to the BLA regulate cocaine-memory strength during reconsolidation, and this phenomenon may involve CRF and glutamate co-transmission in the BLA.

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Poster

PSTR086: Drugs of Abuse: Cell Signaling, Circuitry, Learning, and Decision-Making

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Program #/Poster #: PSTR086.13/L17

Topic: G.09. Drugs of Abuse and Addiction

Support: NIH Grant R01 135294

Title: Examining mechanisms of multiple memory encoding of cocaine- and fear-associated memories

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Abstract: Maladaptive memories, such as those associated with substance use disorder (SUD) or post-traumatic stress disorder (PTSD), are long-lasting and resistant to treatment. These memories link environmental stimuli (cues) with associated outcomes, such as drug effects or a threatening event(s). When the cues are encountered, the associative memories are recalled, which can lead to resumption of substance use or presentation of anxiety- or fear-like behaviors. These disorders are often comorbid. However, the interplay between them is understudied. To explore the brain regions contributing to expression of these memories, rats underwent cocaine self-administration followed by fear conditioning, while control groups underwent saline self-administration and no-shock exposure. Rats then underwent reactivation of the cocaine, fear, or both memories (control rats were placed in both contexts) and then were euthanized 90 minutes later to examine cFos expression. The number of cFos positive cells was counted in a number of reward and learning-related brain regions. For example, in the infralimbic medial prefrontal cortex, there was a decrease in cFos density between rats that underwent reactivation of a fear- and cocaine-associated memory compared to saline controls. Additionally, in the nucleus accumbens core, female rats that had the cocaine-associated memory reactivated had increased cFos density compared to all groups. The finding that reactivation of both memories led to different patterns of neural activation compared to each memory alone, suggested that rats receiving both conditioning paradigms have altered circuitry. Therefore, we next aimed to determine if fear conditioning after cocaine self-administration altered the expression of the cocaine or fear memory. To test this, rats were divided into groups that underwent fear conditioning either before or after cocaine self-administration. A control group underwent only cocaine self-administration. Rats displayed typical cocaine cue-induced reinstatement when fear conditioned before, but not after acquisition, suggesting that post cocaine fear conditioning interferes with subsequent cocaine seeking. Future experiments will replicate these findings and determine if cFos expression differences between groups correlate with differential levels of reinstatement. Examining the mechanisms underlying both cocaine- and fear-associated memories, and how they might interact, is not well explored. Determining unique or overlapping mechanisms could lead to novel therapeutic options.

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Poster

PSTR086: Drugs of Abuse: Cell Signaling, Circuitry, Learning, and Decision-Making

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR086.14/L18

Topic: G.09. Drugs of Abuse and Addiction

Support: R01AG072897
R21NS108128
R01AA025784

Title: Deep Analysis of in Vivo MiniScope Calcium Imaging Recordings in the Secondary Motor Cortex during Cocaine Self-Administration

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Abstract: Recent findings in our lab demonstrated that the risk of cocaine relapse is closely linked to the hyperexcitability of cortical pyramidal neurons in the secondary motor cortex (M2), noticeable 45 days after cocaine intravenous self-administration (IVSA). Our current study was designed to explore the underlying mechanisms of neuronal alterations in M2. Our hypothesis was that M2 neurons were affected directly by cocaine taking behaviors. This hypothesis was tested by monitoring neuronal activity in M2 using in *vivo* MiniScope Ca^{2+} imaging in C57BL/6J mice when they had access to cocaine IVSA as a reinforcement (RNFS) contingent to active lever press (ALP) but not to inactive lever press (ILP). We found significant increase of Ca^{2+} influx in M2 neurons in cocaine mice from the first 15 min to the last 15 min on the first IVSA day (i.e., Day 1), which were consistently enhanced throughout the 1-hr session on the last IVSA day (i.e., Day 5). Further analyses of Ca^{2+} transient activity right before each ALP or ILP identified less positively and more negatively responsive M2 neurons in cocaine mice, relative to saline mice, before ALP, whereas similar subpopulations with positive or negative responses were detected before ILP in saline *vs*. cocaine mice. Relative to saline injections, cocaine injections immediately reduced Ca^{2+} influx in a larger population of M2 neurons from the first 15 to the last 15 min on Day 1, which were consistently attenuated throughout the 1-hr IVSA session on Day 5. Finally, linear regression analyses were performed between the Ca^{2+} influx and the number of ALP, ILP or RNFS in each of the fifteen 30-sec blocks during the first or the last 15 min of the 1-hr IVSA session on Day 1 and Day 5. We found cumulative effects of ALP and RNFS, but not ILP, on Ca^{2+} influx, particularly in the first 15 min of the cocaine IVSA session on both Day 1 and Day 5. Different from reduced neuronal population positively associated with ALP, ILP and RNFS in saline mice, cocaine IVSA increased the proportion of M2 neurons positively associated with the ALP and RNFS, but not ILP. Interestingly, the M2 neurons

responsive to ALP and RNFS consisted of a significantly larger population than those responsive to ILP in cocaine mice after the first 15 min on Day 1 IVSA session, which was not observed in saline mice throughout the 5-day IVSA sessions. This study is the first to identify, in real time, the responses of neurons during drug-taking behaviors, which will provide critical insights into understanding the short-term and long-term effects of drug self-administration at the neuronal level, and guide future exploration and regulation of the experience-dependent brain and behavioral adaptations.

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Poster

PSTR086: Drugs of Abuse: Cell Signaling, Circuitry, Learning, and Decision-Making

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Topic: G.09. Drugs of Abuse and Addiction

Support: NIH Grant DA 040965
NIH Grant 055645
Good Samaritan Foundation of Legacy Health

Title: Ketamine combined with a novel retrieval session blocks cue-induced reinstatement of cocaine self-administration in rats

Authors: A. E. GONZALEZ[1], J. D. RAMOS[2], Z. ANDERSON[3], *B. A. SORG[3];
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Abstract: Strong drug-associated memories are highly resistant to disruption. Novel information introduced during memory retrieval could potentially weaken drug-associated memories, making them susceptible to interference by amnestic agents. Our previous work in the medial prefrontal cortex (mPFC) demonstrated that combining novel memory retrieval with the enzymatic disruption of perineuronal nets (PNNs), which surround the majority of parvalbumin (PV) neurons, decreased cue-induced reinstatement in cocaine self-administering rats. Ketamine in low doses acts via NMDA receptor antagonism preferentially in PV cells and has been shown to disrupt fear- and certain drug-associated memories. We tested whether ketamine administered with novel memory retrieval would decrease cocaine cue-induced reinstatement. Rats were trained to self-administer cocaine on a fixed-ratio 1 (FR1) schedule. After training, rats were given an intraperitoneal injection of saline or ketamine (6 mg/kg) 10 min prior to a cocaine-reinforced 30 min memory retrieval session. The retrieval session was either a familiar FR1 or a novel variable-ratio 5 (VR5) schedule. We also tested post-novel VR5 retrieval administration of saline or ketamine (6, 20 or 50 mg/kg, i.p.). The following day, rats were given a 30 min

extinction session followed immediately by a 30 min cocaine cue reinstatement. The combination of pre-retrieval ketamine and a novel VR5 retrieval session reduced cue reinstatement compared to FR1 ketamine and VR5 control groups, while post-retrieval ketamine did not impact reinstatement. We subsequently conducted intensity analysis of PNNs, PV, c-Fos, and Npas4 from the prelimbic mPFC of pre-retrieval groups 90 min post-cue reinstatement. The most pronounced effect was a reduction in PNN intensity after ketamine combined with novel VR5 retrieval, suggesting that a reduction in PNNs prior to retrieval may dampen the original cocaine-associated memory.

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Poster

PSTR086: Drugs of Abuse: Cell Signaling, Circuitry, Learning, and Decision-Making

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Topic: G.09. Drugs of Abuse and Addiction

Support: NIH DA 040965
DA 055645
Good Samaritan Foundation of Legacy Health

Title: Perineuronal net removal in the rat medial prefrontal cortex attenuates prefrontal-hippocampal coupling during cocaine cue acquisition

Authors: J. D. RAMOS[1], J. C. WINGERT[2], S. X. REYNOLDS[3], *A. E. GONZALEZ[3], B. A. SORG[4];
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Abstract: Environmental stimuli become paired with exposure to drugs of abuse and play an important role in the maintenance of drug memories. In the medial prefrontal cortex (mPFC), parvalbumin (PV) interneurons regulate pyramidal cells critical for cocaine memory consolidation. The majority of PV neurons are surrounded by a perineuronal net (PNN), an extracellular matrix structure essential for supporting fast firing rates and precise spike timing of PV neurons. These qualities of PV cells help generate oscillations and mediate coupling within and between brain regions, which play an important role in memory consolidation. Removal of PNNs with chondroitinase ABC (Ch-ABC) disrupts acquisition of cocaine memories, but it is not known why this occurs. After microinjection of either saline (control) or Ch-ABC into the mPFC of male Sprague Dawley rats, electrodes were implanted into the mPFC and hippocampal dorsal CA1. Rats were given intravenous infusions of saline paired with one cue light or cocaine paired with a second cue light over eight alternating days. On the last day, rats were presented both cue lights in a pseudo-randomized order. All rats exhibited event-related phase resetting in response to cue light presentation. In Veh-treated rats, phase-amplitude coupling between the mPFC and

CA1 was greater in response to the cocaine vs saline-paired cue lights. We are currently analyzing the responses in ABC-treated rats.

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Poster

PSTR086: Drugs of Abuse: Cell Signaling, Circuitry, Learning, and Decision-Making

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Topic: G.09. Drugs of Abuse and Addiction

Support: 1U01DA056003-01

Title: Multiomic Profiling of Cellular Responses to HIV Infection and Cocaine Use in the Mouse Brain

Authors: *R. LIU[1], D.-W. KIM[2], Y. GAO[1], K. SMITH[1], K. JAMES[1], T. PHAM[1], B. NGUY[1], J. GOLDY[3], A. CHAKKA[1], R. CHAKRABARTY[1], N. DEE[2], Z. YAO[2], C. VAN VELTHOVEN[1], H. ZENG[2];
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Abstract: There is a high prevalence of co-morbid conditions in people with substance use disorders (SUD), including an increased risk of HIV infection. Vice versa, HIV is a risk factor for SUD. This suggests important reciprocal interactions between HIV infection and SUD. However, the molecular and cellular mechanisms driving their interaction is not clear. In this study, we used the 10x Multiome platform to profile the transcriptomic and epigenomic changes in 10 brain regions (HIP, CTXsp, PL, LSX, STRd, STRv, MB, PAL, TH, HY), using both male and female mice subjected to either HIV infection, cocaine use, or both. Our findings reveal that most cell types did not show changes in proportion; rather, changes are reflected at the gene expression level. Using edgeR-based pseudo-bulk analysis, we observed that in a variety of neuronal populations, the cellular responses to HIV and cocaine are heavily influenced by sex. Among non-neuronal populations, endothelial cells showed the most significant changes in response to cocaine exposure, independent of HIV status or sex, as illustrated by enhanced activation of interleukin/interferon signaling pathways. Our current results highlight the complex interplay of sex in the response to HIV and cocaine and underscore potential inflammatory pathways activated by cocaine that may influence HIV pathology.

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Poster

PSTR086: Drugs of Abuse: Cell Signaling, Circuitry, Learning, and Decision-Making

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Topic: G.09. Drugs of Abuse and Addiction

Support: T32 DA007237

Title: The role of PKMζ in the prefrontal cortex in synaptic and behavioral plasticity in female and male mice

Authors: *A. KNIFFIN[1], E. ENGLISH[1], L. A. BRIAND[2];
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Abstract: Drugs of abuse activate the reward pathway and have long-term impacts on glutamate neurotransmission. Animals exposed to drugs of abuse exhibit alterations in glutamate transmission within the reward circuit, including alterations in glutamate receptor trafficking, disrupted glutamate homeostasis, and blunted long-term potentiation (LTP) and long-term depression (LTD). The constitutively active form of protein kinase C, PKMζ, is involved in the insertion of GluA2-containing AMPA receptors in the synapse and drugs of abuse including cocaine increase PKMζ expression. Studies in global PKMζ knockout mice indicate that PKMζ may be acting to dampen reward, as knockout mice consume more alcohol and engage in higher rates of cocaine seeking. Selective PKMζ knockdown in the nucleus accumbens (NAc) recapitulates this increase in cocaine taking and seeking in male animals only. Further, global PKMζ knockout leads to sex-specific effects on synaptic plasticity in the NAc, with knockout males exhibiting blunted LTD, and females exhibiting augmented LTD. The current studies aimed to determine if this sex-specific role for PKMζ was unique to the NAc or representative of more widespread mechanistic differences in the role of this kinase. We first examined whether global PKMζ knockout altered other forms of plasticity differently in male and female mice. Cocaine experience leads to disruptions in LTP within the prefrontal cortex. We found that drug naïve male and female PKMζ knockout mice exhibited blunted prefrontal LTP compared to wildtype controls. As decreased top-down control could mediate drug seeking behaviors, studies are underway to examine whether selective PKMζ knockdown in the PFC leads to augmented cocaine seeking in male and female mice. Taken together, these findings point toward regional differences in the role of PKMζ in glutamate trafficking in male and female mice.

Disclosures: A. Kniffin: None. **E. English:** None. **L.A. Briand:** None.

Poster

PSTR086: Drugs of Abuse: Cell Signaling, Circuitry, Learning, and Decision-Making

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR086.19/L23

Topic: G.09. Drugs of Abuse and Addiction

Support: R00 DA045758

Title: Sex Differences in Contextual Cocaine Seeking Behavior are Driven by Noradrenergic Signaling to the Dorsal Hippocampus

Authors: *A. KOHTZ, M. BERRY;
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Abstract: Individuals suffering from substance use disorders face relapse when triggered by environmental. or contextual, cues, suggesting that contextual memories associated with drugs of abuse hinder abstinence success. Women may encounter greater challenges maintaining abstinence; an effect recapitulated in rodent models. β-adrenergic receptors (β-ARs) have a long-standing implication in driving processes associated with contextual drug memories, and therefore may play a role in context-induced cravings. However, sex differences in the adrenergic system driving drug memories remain unknown. Herein, we tested the sex differences in the roles of dorsal hippocampus (dHPC) β-ARs in non-operant and operant cocaine memories using cocaine conditioned place preference (Pavlovian; CPP) and cocaine-seeking persistence during extinction from self-administration (operant; CSP) in male and female adult Sprague Dawley rats. We administered β-AR antagonists (Betaxolol (β1) and/or ICI 118,551 (β2)) to the dHPC prior to retrieval in both CPP and CSP. We then investigated sex differences in the projections of locus coeruleus norepinephrine (LC-NE) neurons to the dHPC during CSP using DREADDs. Our results show that intra-dPHC administration of both β1 and β2 antagonists attenuated Pavlovian conditioning in both sexes. However, CPP was attenuated in males with the administration of either antagonist, whereas in females, β1 antagonists impaired recall, whereas β2 impaired retention, of CPP expression. Notably, the involvement of β-ARs varied under operant conditions, as CSP was attenuated by β-AR antagonists in females only. Similarly, inhibition of LC-NE signaling to the dHPC using DREADDs attenuated operant cocaine-seeking solely in females. In summation, we observed significant sex differences in the role of dorsal hippocampus β-ARs in the encoding and expression of both Pavlovian and operant cocaine memories. Furthermore, these effects may be driven by sex differences in adrenergic tone between the locus coeruleus and dorsal hippocampus. Thus, the substantial sex differences in the retrieval and retention of cocaine memories may be driven in part by adrenergic signaling.
Financial Support: R00 DA045758 to ASK

Disclosures: A. Kohtz: None. **M. Berry:** None.

Poster

PSTR086: Drugs of Abuse: Cell Signaling, Circuitry, Learning, and Decision-Making

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR086.20/L24

Topic: G.09. Drugs of Abuse and Addiction

Support: NIDA

Title: Role of dopaminoceptive cells in the ventral hippocampus in cocaine action

Authors: *V. KONDEV[1], A. GODINO[2], B. T. KIPP[1], E. KAHN[3], R. FUTAMURA[4], A. M. MINIER-TORIBIO[2], A. LABANCA[5], T. MARKOVIC[6], E. J. NESTLER[4];
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Abstract: Dysfunctional dopamine (DA) signaling has been tied to several psychiatric disorders that involve disruption in reward learning or motivational behavior, including substance use disorder (SUD), depression, post-traumatic stress disorder, and anxiety. While significant work has been done to delineate a role for DA in corticostriatal circuits and the regulation of motivated behavior, very little is known about DA signaling and its downstream effects in other limbic brain regions, such as the ventral hippocampus (vHPC), despite recent evidence that the vHPC controls key aspects of drug-seeking and relapse behavior. Here, we use a combination of interdisciplinary neuroscience techniques, including fiber photometry, optogenetics, and single nuclei RNA-sequencing, to further delineate the role of dopaminoceptive cells within the vHPC that express either the dopamine receptor type 1 (D1) or type 2 (D2). We characterize anatomical projections of these two distinct dopaminoceptive ensembles as well as cocaine-induced changes in their molecular landscape, further supporting that these vHPC D1 and D2 cells represent distinct neuronal populations. Using cocaine conditioned place preference, we reveal that vHPC D1 cell activity *decreases* following entry to the cocaine-paired context after conditioning, with no effects seen in D2 populations. We are now studying the effect of optogenetic control over vHPC D1 and D2 neurons on place conditioning behavior and also extending this work to cocaine self-administration and relapse models. For example, we have established procedures to obtain fiber photometry recordings from vHPC D1 and D2 neurons during drug self-administration. Together, these studies broaden our understanding of the role of DA within the larger mesocorticolimbic system and reveal new neuronal and circuit mechanisms underlying how drugs of abuse promote strong associative learning processes and facilitate drug seeking and taking that characterize SUD.

Disclosures: V. Kondev: None. **A. Godino:** None. **B.T. Kipp:** None. **E. Kahn:** None. **R. Futamura:** None. **A.M. Minier-Toribio:** None. **A. LaBanca:** None. **T. Markovic:** None. **E.J. Nestler:** None.

Poster

PSTR086: Drugs of Abuse: Cell Signaling, Circuitry, Learning, and Decision-Making

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR086.21/L25

Topic: G.09. Drugs of Abuse and Addiction

Support: Canadian Institutes of Health Research (CIHR; PJT-189943)

Title: The impact of adolescent nicotine vaping exposure on cognition in mood and anxiety disorders

Authors: *M. YOUSSEF[1,2,3], M. SARIKAHYA[4,3], M. DEVUONO[4,3], M. MACHADO[4,3], M. JONES[4,3], E. PÉREZ-VALENZUELA[4,3], T. UZUNESER[4,3], M. DE FELICE[4,3], J. Y. KHOKHAR[4], W. J. RUSHLOW[4,3,5], S. R. LAVIOLETTE[4,3,6,5];
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Abstract: The transition from tobacco to vaping as the primary nicotine source, especially among adolescents, raises concerns for neurodevelopment. Traditional animal models inadequately represent vaping's complexities. Adolescent nicotine exposure (ANE) has emerged as a significant public health concern, given its potential implications for cognitive function and mental health. Mood and anxiety disorders often co-occur with cognitive impairments, which may be exacerbated by nicotine exposure during adolescence. Understanding the neurobiological mechanisms linking adolescent nicotine use to cognitive dysfunction in neuropsychiatric disorders is crucial for developing effective interventions. This study aims to determine the impact of nicotine vapour exposure in adolescent rats on cognition, neuronal spiking activity, and the expression of cognitive biomarkers associated with anxiety and depression within the prefrontal cortex and hippocampus. In this study, Adolescent male and female Sprague-Dawley rats were exposed to vaporized nicotine smoke three times a day for ten days. In adulthood, cognition will be assessed through behavioral assays, while prefrontal and hippocampal neuronal activity will be measured via electrophysiological recordings. Additionally, proteomic molecular analyses will quantify biomarker expression. Preliminary Results show that Nicotine-exposed rats showed increased locomotion and anxiety during ANE compared to controls. However, this effect is not seen following nicotine cessation during adulthood. Additional cognitive-related behavioural assays, prefrontal and hippocampal electrophysiological recordings, and proteomic analysis are underway to further examine ANE's effect on cognition. This study examines nicotine vapour's neurodevelopmental effects on cognition. By integrating behavioural, electrophysiological, and molecular analyses, it seeks to elucidate pathways that could potentially link adolescent nicotine use to cognitive dysfunction in neuropsychiatric disorders in adulthood.

Disclosures: M. Youssef: None. **M. Sarikahya:** None. **M. DeVuono:** None. **M. Machado:** None. **M. Jones:** None. **E. Pérez-Valenzuela:** None. **T. Uzuneser:** None. **M. De Felice:** None. **J.Y. Khokhar:** None. **W.J. Rushlow:** None. **S.R. Laviolette:** None.

Poster

PSTR086: Drugs of Abuse: Cell Signaling, Circuitry, Learning, and Decision-Making

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR086.22/L26

Topic: G.03. Motivation

Support: NIH NCT05623306
NIH R01MH124760-01A1

Title: Deep brain stimulation of the nucleus accumbens reduces cue-hyperreactivity electrophysiological marker associated with opioid craving

Authors: *Y. NHO[1], L. QIU[1], R. L. SEILHEIMER[1], A. TUFANOGLU[1], K. SCANGOS[1], A. CHILDRESS[1], C. H. HALPERN[1,2];
[1]Univ. of Pennsylvania, Philadelphia, PA; [2]Corporal Michael J. Crescenz Veterans Affairs Medical Center, Philadelphia, PA

Abstract: Drug cue hyperreactivity is a pathophysiological feature of substance use disorder and may predict relapse even after long periods of abstinence. We have previously shown that the presence of persistent cue-evoked BOLD fMRI response in the ventral striatum is predictive of a poorer outcome. In this case report, we demonstrate the feasibility of using a drug-cue paradigm to measure electrophysiological response to identify an electrophysiological marker of a cue hyperreactive state through an implanted deep brain stimulation electrode, as well as the persistence of the signal with repeated task administration over 6 days. A 26-year-old male with opioid use disorder received deep brain stimulation (DBS) treatment 4 years ago and achieved remission. A wound erosion prompted a temporary externalization of the DBS system, allowing an opportunity to investigate electrophysiological responses in the nucleus accumbens (NAc). An opioid video cue-reactivity task was performed using brief personalized videos to identify electrophysiological markers of cravings through the DBS electrode contacts. The task paradigm had three conditions: 1) watching a neutral video (“Neutral”), 2) passively watching a personalized opioid video (“Watch”), and 3) attempting to reduce the response to the opioid video (“Down”). The patient also reported craving intensity using a visual analog scale. We found that low-frequency band (1-8 Hz) power was significantly elevated in the NAc shell region (contacts 1-2) when the patient was provoked with drug-related cues (Watch), correlating with cravings severity. This was not present in any other electrode contact, nor when the patient inhibited his drug craving (Down). This biomarker was persistent across repeated task presentation within and between days, and the strength of the biomarker signal did not wane between the first and second half of the task. Delivery of electrical stimulation to the NAc shell for 10 minutes prior to administration of the task ameliorated this electrophysiological response and clinical ratings of cravings. We conclude that a distinct, persistent electrophysiological biomarker response can be reliably identified in the NAc for cue-hyperreactive cravings, and reduced with acute electrical stimulation to the region.

Disclosures: Y. Nho: None. **L. Qiu:** None. **R.L. Seilheimer:** None. **A. Tufanoglu:** None. **K. Scangos:** None. **A. Childress:** None. **C.H. Halpern:** None.

Poster

PSTR086: Drugs of Abuse: Cell Signaling, Circuitry, Learning, and Decision-Making

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR086.23/L27

Topic: G.09. Drugs of Abuse and Addiction

Title: Effects of Transcranial Direct Current Stimulation on Reconsolidation of Nicotine Addiction Memory: A tDCS-EEG Study

Authors: *P. WU;
Natl. Inst. On Drug Dependence, Peking Univ., Beijing, China

Abstract: Objective: To explore the effects of transcranial direct current stimulation (tDCS) in the dorsolateral prefrontal cortex (dlPFC) after unconditioned stimulus retrieval of nicotine addiction memory on nicotine craving and the underlying neuroelectrophysiological characteristics. Methods: Subjects were randomly divided into USR+tDCS group, USR+pseudo-stimulation group (USR+sham) and no retrieval (NoR)+tDCS group. The NoR+tDCS group received tDCS intervention directly, while USR+tDCS group and USR+sham group received tDCS stimulation and pseudo stimulation respectively after exposure to unconditioned stimulation (smoking 1/6 cigarettes) to activate addictive memory. Nicotine use and craving were evaluated before and after intervention, and the EEG was collected before, during and after tDCS stimulation. Results: The results showed that during the 1-month follow-up, the amount of daily smoking ($F(6,135) = 7.692$, $p < 0.001$) and smoking craving ($F(4,90) = 3.341$,$p < 0.05$) of USR+tDCS group were significantly decreased. In USR+tDCS group, the amplitudes of cue-induced P3 ($p < 0.05$) and slow response positive waves ($p < 0.05$) in cue response task after intervention were significantly lower than those before intervention, and the amplitudes of P3 ($r = 0.487$,$p < 0.05$) and SPW ($r = 0.516$,$p < 0.05$) after intervention were significantly correlated with the score of nicotine dependence after intervention. In addition, the whole brain delta and theta power in USR+tDCS group and noR+tDCS group were significantly higher than those before stimulation, and the delta ($p < 0.001$) and theta ($p < 0.001$) frequency band connectivity between dlPFC and occipital cortex were significantly higher than those before stimulation. The increase of power of delta and theta in USR+tDCS group was related to the improvement of withdrawal symptoms. After tDCS treatment, the power of dlPFC and theta of occipital cortex in USR+tDCS group were significantly higher than those before stimulation, and the connectivity of delta and theta between dlPFC and occipital cortex was significantly higher than that before stimulation. The power of theta band and the connectivity between dlPFC and occipital cortex in USR+tDCS group were significantly correlated with the score of nicotine dependence after intervention. Conclusion: USR combined with tDCS can disrupt the reconsolidation of nicotine addictive memory, reduce smoking amount and craving. This intervention may play a role by increasing the theta power of dlPFC and occipital cortex and increasing the connectivity of delta band and theta band between dlPFC and occipital cortex.

Disclosures: P. Wu: None.

Poster

PSTR087: Perception, Imagery, and Imagination I

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR087.01/L28

Topic: H.02. Perception and Imagery

Support: William Orr Dingwall Foundations of Language Fellowship
NIH Grant T32NS047987
NIH Grant R00MH117226

Title: On the relationship between distributed association networks and category-preferring visual streams in the inferotemporal cortex

Authors: *J. SALVO[1], N. L. ANDERSON[2], R. BRAGA[3];
[1]Northwestern Univ., Chicago, IL; [2]Neurol., Feinberg Sch. of Med., Northwestern Univ., Chicago, IL; [3]Neurol., Northwestern Univ., Chicago, IL

Abstract: The ventral visual stream in the inferotemporal cortex (ITC) comprises hierarchically organized visual regions involved in recognition. Within ITC, contrast-based approaches reveal regions responding preferentially to images containing scenes (Epstein et al., 1998), faces (Kanwisher et al., 1997), or text (Cohen et al., 2002). These regions are arranged as streams along the long axis of the ITC's posterior half. Posterior ITC also includes a broad region of the canonical dorsal attention network (dATN), an association network that is implicated in top-down visual attention (Corbetta, 1998) and can be defined using intrinsic ('resting-state') correlations. We asked whether the visual streams are confined to the canonical dATN, given the dATN's role in higher-order visual processing, or if the streams extend beyond the dATN, implying dATN involvement in earlier stages of visual processing.
We collected 3T data from 8 healthy adults across 8 MRI sessions, using a multi-echo sequence (Lynch et al., 2020). Participants performed tasks targeting different cognitive functions (language, theory of mind, mental imagery), and visual categories (scenes, faces, text). Eight runs per task allowed individualized definition of task-related regions. Large-scale networks were identified through functional connectivity using seed-based and data-driven clustering approaches (Braga & Buckner, 2017).
Text, faces, and scenes activated parallel streams of ITC regions, with text regions most lateral, scenes most medial, and faces in between. Face and scene streams clearly passed through the dATN, and the text stream did so in most participants, linking the dATN with mid-stage visual processing of multiple stimulus categories. All streams also extended anteriorly beyond the dATN boundaries and overlapped with different large-scale networks in more anterior ITC: text regions aligned with the core language network, scenes aligned with a mental scene construction network (Default network A; DN-A), and faces tentatively aligned with the social cognition network (DN-B). Our results suggest a conserved arrangement of parallel visual streams that pass through the dATN and terminate in distinct association networks that are functionally related to the content of each visual stream.

Disclosures: J. Salvo: None. **N.L. Anderson:** None. **R. Braga:** None.

Poster

PSTR087: Perception, Imagery, and Imagination I

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR087.02/L29

Topic: H.02. Perception and Imagery

Support: NEI Grant K99EY034169-01
NIMH Grant ZIAMH002588-29

Title: Dissociating layer-specific responses to perceived and imagined faces and places in the human ventral occipitotemporal cortex using VASO fMRI

Authors: *T. L. LI, J. SHAO, A. S. PERSICHETTI, S. AUDRAIN, L. HUBER, A. MARTIN; Natl. Inst. of Mental Hlth., Bethesda, MD

Abstract: Layer-specific fMRI promises to dissociate feedforward and feedback information across cortical laminae from V1 to downstream category-selective visual regions in the ventral occipitotemporal cortex (VOTC). However, using a cutting-edge functional MRI method called vascular space occupancy (VASO) to measure fMRI signals at submillimeter resolution comes with major methodological challenges. Thus, we introduce two methodological advances that allow us to measure layer-specific fMRI signals in VOTC. The first is a forward model that can predict the optimal flip angle regime for the VASO sequence in the brain region to be studied. The second is an anatomical segmentation routine that cleanly segments the cortical ribbon from white matter and cerebral spinal fluid for precise definition of cortical layers. We used this optimized VASO fMRI routine in a study on perceiving and imaging faces and places. Participants saw the names of famous faces and places followed by either a picture (perception), or a white frame (mental imagery) during separate task blocks. After independently localizing the fusiform face area and parahippocampal place area, we found preliminary evidence that mental imagery elicits the strongest responses in the superficial and deep layers of the corresponding category-selective region that receive feedback signals from higher-order brain regions but not in the middle layers that receive feedforward signals from early visual cortex. In contrast, viewing pictures of famous faces and places elicits the strongest responses in the middle (and superficial) layers. Thus, our methodological advances allow us to accurately dissociate feedforward and feedback information across layers of VOTC.

Disclosures: T.L. Li: None. **J. Shao:** None. **A.S. Persichetti:** None. **S. Audrain:** None. **L. Huber:** None. **A. Martin:** None.

Poster

PSTR087: Perception, Imagery, and Imagination I

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR087.03/L30

Topic: H.02. Perception and Imagery

Support: JST
CREST JPMJCR23P
japan

Title: The Effect of Acute Stress on Heartbeat Evoked Potential during a Stress Task

Authors: *D. SUGO, Y. TSUJI, S. SHIMADA;
Meiji Univ., Kawasaki, Japan

Abstract: A growing body of evidence indicates that the heartbeat evoked potential (HEP) reflected afferent signals from the cardiovascular system related to interoceptive processing. Recent research suggested a complex relationship between interoception and acute stress. However, the relation between HEP and acute stress has not been fully investigated. To examine this relationship, we measured electroencephalography (EEG) and electrocardiogram (ECG) during a mental arithmetic task as a stress task. Ten healthy volunteers (female:4, mean age 22 ± SD 0.87 years) participated in this study. EEG signals were recorded from 30 scalp sites, located according to extended international 10-20 system. ECG signals were recorded by lead II. Subject sat in a chair and rested for 5 minutes, and then performed a mental arithmetic task for 10 minutes. During the mental arithmetic task, subjects were instructed to continuously subtract 13 from 1022 and required to answer by pressing keys. All subjects completed the BDI-II questionnaire before the experiment. The R-R interval was calculated from the measured ECG data. Heart rate variability analyses in time-frequency domain were performed by wavelet transform. The LF/HF ratios during the rest and the mental arithmetic task were calculated by dividing the power in the LF band (0.04-0.15 Hz) by the power in the HF band (0.15-0.4 Hz) for each task. The HEP was obtained by EEG data time-locked to the R peak time. We selected time window that occurred after 400-600 ms from R wave based on reports of the HEP time window in which cardiac field artifacts decrease after ECG T wave. The time window was divided into 400-500 ms and 500-600 ms after the R wave because the cardiac cycle differs around 500 ms after the R wave. Previous studies have reported that HEP amplitudes at left temporal and lateral frontal regions correlated with stress-induced cardiac output changes in patients with established ventricular dysfunction. Thus, we calculated the Spearman's rank correlation coefficient between LF/HF ratio and mean HEP amplitude and between BDI-II score and mean HEP amplitude in the left temporal and lateral frontal regions. A significant positive correlation ($r = 0.64$, $p < 0.05$) was found between mean LF/HF ratio and mean HEP amplitude (400-500 ms after the R wave) in the left temporal region (TP7) during the mental arithmetic task. A significant correlation was also found between BDI-II score and mean HEP amplitude (500-600 ms after the R wave) during the mental arithmetic task (TP7: $r = 0.85$, $p < 0.01$). These results showed that HEP was associated with LF/HF ratio during task and BDI-II score. Therefore, HEP can be used as a biomarker of acute stress and depression.

Disclosures: D. Sugo: None. **Y. Tsuji:** None. **S. Shimada:** None.

Poster

PSTR087: Perception, Imagery, and Imagination I

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR087.04/L31

Topic: H.02. Perception and Imagery

Support: NSERC Postdoctoral Fellowship

Title: The neural representation of object expectations across space and time

Authors: *L. CAPLETTE, T. KURUMISAWA, H. BORGES, J. A. CORTES, N. B. TURK-BROWNE;
Yale Univ., New Haven, CT

Abstract: Visual perception is modulated by expectations resulting from prior knowledge. Despite great progress in recent decades, the neural mechanisms underlying this phenomenon, especially in the case of complex objects, remain unclear. In this ongoing project, we investigate how object expectations travel across the brain through time before and during the presentation of stimuli. In the main task, we presented participants with cues that predicted subsequent photographs of real-world objects with 58% validity. These cue-object associations were learned incidentally without explicit instructions. Participants were tasked with categorizing the objects as either animate or inanimate while their brain activity was recorded using magnetoencephalography (MEG). Shorter response times for valid trials suggest that participants learned the associations. Participants also completed a localizer run before the main task, in which they were shown object images individually. We performed source reconstruction on the MEG data and focused analyses on early visual cortex and high-level visual cortex as regions that might be modulated by object expectations, and on the hippocampus as a region that might generate object expectations based on associative learning. For every time point in the localizer, we trained multivariate decoding models in each region of interest (ROI). We then used these models to assess the representations of cues and objects at each time point during the main task. Early results show that representations of the presented objects (whether expected or unexpected) can be decoded from all ROIs shortly after their onset. Representations of expected (but not unexpected) objects are also evident in the visual cortex before onset, indicating a prediction, and late in the time course of invalid trials, possibly signaling a prediction error. Interestingly, representations defined from early and late time points of the localizer trials can be decoded during the main task, suggesting the presence of both low-level and high-level feature information. These results enrich our understanding of the neural mechanisms of expectations about real-world objects in space and time. As next steps, we will collect additional MEG data and acquire fMRI data with a similar experimental design to validate and extend our results through multi-modal MEG-fMRI data fusion.

Disclosures: L. Caplette: None. **T. Kurumisawa:** None. **H. Borges:** None. **J.A. Cortes:** None. **N.B. Turk-Browne:** None.

Poster

PSTR087: Perception, Imagery, and Imagination I

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR087.05/L32

Topic: H.02. Perception and Imagery

Support: NSF Career Award 2144700

Title: Anterior shift between perception and memory is specific to scenes

Authors: *D. PRASAD, A. D. STEEL, C. E. ROBERTSON;
Dartmouth Col., Hanover, NH

Abstract: Classic models of reinstatement posit that visual recall reactivates the same category-selective brain regions as visual perception, but recent research has shown that visual recall for places consistently recruits brain regions just anterior to canonical scene-selective cortex (Steel et al., 2021). Is this anterior shift between perception and recall unique to scenes, or does it also occur for other visual categories (e.g., faces, body parts, objects)? We address this question by examining shifts in recall relative to perception across several canonical visual categories. Participants (N=18) took part in two fMRI paradigms designed to functionally localize category-selective regions during visual memory recall and visual perception. Before the scan, participants provided a list of personally familiar faces, places, objects, and body parts, in addition to a list of famous faces (5 stimuli per category; 25 stimuli total). Participants underwent 6 runs of a classic visual localizer task designed to functionally define brain areas involved in perception of different visual categories (e.g., parahippocampal place area (PPA) for places, fusiform face area (FFA) for faces, extrastriate body area (EBA) for bodies, and the lateral occipital complex (LOC) for objects, etc.). On each trial of the visual memory localizer , participants were instructed to vividly recall a famous face or a personally familiar face, place, object, or body part for 10 seconds after a brief visual cue (5 exemplars per category, 25 trials per run, 6 runs total). We defined the PPA, FFA, and EBA in individuals by contrasting place, face, and body-activity respectively against activity during object trials. The LOC was identified by contrasting intact versus scrambled objects. For each contrast we restricted our region of interest (ROIs) using an established parcellation for category-selective perceptual regions (Julien et al., 2012), thresholded at $p \leq 0.001$. To assess the anterior shift of each category, we compared the center of mass of these ROIs with activity during visual memory recall, using the same contrasts. Initial results identified category-specific clusters of memory activation for all stimulus conditions (face, places, objects, and bodies). Importantly, only place memory elicited a consistent anterior shift for memory relative to perceptual activity. This implies that the anterior shift in activity between perception and recall is unique to scene processing. More broadly, this suggests that the mechanism of scene processing may differ from other visual categories such that it requires distinct, but adjacent regions for perception and visual memory.

Disclosures: D. Prasad: None. **A.D. Steel:** None. **C.E. Robertson:** None.

Poster

PSTR087: Perception, Imagery, and Imagination I

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR087.06/L33

Topic: H.02. Perception and Imagery

Support: 2123781 NSF Expedition in Computing: Mind In Vitro to Mattia Gazzola

Title: Network modularity explains long-range temporal dependencies in perception

Authors: *M. IRANI[1], R. O. BIDO MEDINA[2], M. K. EGAN[3], R. YANG[4], L. A. PRITSCHET[5], E. WINTER-NELSON[6], W. HELLER[7], T. ALDERSON[8], S. SADAGHIANI[9]; [1]Univ. of Illinois, Champaign, IL; [2]Neurosci., Univ. of Illinois At Urbana Champaign, Champaign, IL; [3]Univ. of Illinois, Urbana-Champaign, Champaign, IL; [4]Univ. of Illinois Urbana-Champaign, Urbana, IL; [5]Psychological and Brain Sci., Univ. of California, Santa Barbara, Santa Barbara, CA; [6]Ctr. for Vital Longevity, Univ. of Texas at Dallas, Dallas, TX; [7]Univ. of Illinois, Urbana Champaign, Urbana, IL; [8]UIUC, Urbana, IL; [9]Psychology, Univ. of Illinois, Urbana-Champaign, Urbana, IL

Abstract: To deal with uncertainty from real-world sensory information, we alternate among perceptual interpretations that help us generate a coherent experience of the outside world. Under ambiguous settings, perception goes through continuous and spontaneous alternations relying on a balance between flexible states that allow sensitivity to momentary changes in external drive, and stable states that provide robustness and consistency with the history of previous decisions. Time series generated by sequences of perceptual decisions in made under ambiguous sensory detection tasks exhibit dynamics with long-range temporal correlations (LRTC) and scale invariance, two features that are exhibited by complex systems. However, whether this behavior extends to higher-order perception is still limited and the underlying neural features that give rise to these behavioral dynamics are not entirely known. Here we used an emotional valence perception task, where subjects (N=38) were instructed to indicate whether an emotionally ambiguous face image was perceived as sad or neutral. The threshold at which the image appeared emotionally ambiguous was determined prior to the experiment in each subject. Subjects also performed an object perception task, where they viewed the Rubin's vase-face ambiguous figure and were indicated on each trial whether they perceived a face or a vase. We then assessed the temporal structure of the time series in terms of its scale-free properties using Detrended Fluctuation Analysis (DFA) and autocorrelation. Our results show that, under ambiguity, subjects generate perceptual sequences with long-range temporal correlations and scale invariance with decay rates significantly different than our null model. We hypothesized that, as other complex system, a balance between modularity and integration in the architecture of neural networks is a necessary feature driving the neural activity that shapes long-range temporal dependencies and scale-invariant behavioral dynamics. We therefore trained a recurrent neural network model on an analogous perceptual decision task and tested it on trials presented continuously. We built on a previously published training method that constrained the network weights and induced modularity in the network. Our preliminary results show that intermediate levels of modular connectivity maximize long-range temporal correlations in the outcomes of the

network. This evidence supports the view that behavioral dynamics emerge out of the interplay between integration and segregation of brain networks.

Disclosures: M. Irani: None. **R.O. Bido Medina:** None. **M.K. Egan:** None. **R. Yang:** None. **L.A. Pritschet:** None. **E. Winter-Nelson:** None. **W. Heller:** None. **T. alderson:** None. **S. Sadaghiani:** None.

Poster

PSTR087: Perception, Imagery, and Imagination I

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR087.07/L34

Topic: H.02. Perception and Imagery

Support: NIH Grant R01EY032125

Title: Planar Cortical Magnification Measurement with Optimal Transport and Topological Smoothing

Authors: *Y. XIONG[1], Z.-L. LU[2], Y. WANG[1];
[1]SCAI, Arizona State Univ., Tempe, AZ; [2]New York Univ. Ctr. For Neural Sci., New York, NY

Abstract: The human visual system displays non-uniform spatial resolution and neuronal processing resources across the visual field, a phenomenon often characterized by the cortical magnification factor (CMF), a widely used metric reflecting the relationship between brain anatomy and human vision. However, conventional approaches to quantifying CMF using retinotopic maps derived from BOLD functional magnetic resonance imaging (fMRI) encounter significant limitations due to the inherent low signal-to-noise ratio of fMRI data and violations of topological relationships in retinotopic maps.In this study, we propose a novel pipeline for estimating planar CMF from population receptive field (pRF) solutions. The pipeline involves first projecting the 3D cortical pRF solutions onto a 2D planar disk, employing optimal transport techniques to preserve local cortical surface areas during projection. It then applies topological smoothing to ensure preservation of the correct topology in the retinotopic map. Subsequently, a 2D planar CMF measurement is derived from the projected retinotopic map on the planar disk using the 1-ring patch method.Applying this pipeline to the Human Connectome Project (HCP) 7T dataset, we unveiled previously unobserved CMF patterns across the visual field and demonstrated interindividual differences among the 181 subjects. Based on their CMF patterns, we categorized the subjects into five major clusters. Our findings provide novel insights into visual information processing in the human brain and may have implications for individual differences in visual behavior.

Disclosures: Y. Xiong: A. Employment/Salary (full or part-time):; asu. **Z. Lu:** A. Employment/Salary (full or part-time):; nyu. **Y. Wang:** A. Employment/Salary (full or part-time):; asu.

Poster

PSTR087: Perception, Imagery, and Imagination I

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR087.08/L35

Topic: H.02. Perception and Imagery

Support: NIH Grant R01EY034436

Title: Decoupling feature and timescale hierarchies in visual cortex

Authors: *Z. HIRSCHSTEIN[1], M. ALY[2], C. BALDASSANO[1];
[1]Columbia Univ., New York, NY; [2]Univ. of California, Berkeley, Berkeley, CA

Abstract: In our experience of the natural world, the complexity of visual features varies along with the timescale at which they are stable. Higher-level visual features, like objects and scenes, are reliably stable over longer durations than the lower-level features that constitute them, such as textures and lines. This inherent coupling of features and timescales in the natural world makes it challenging to identify which property drives hierarchical organization in the visual system: later visual areas are sensitive to both higher-order features and longer timescales; earlier visual areas are sensitive to both lower-order features and shorter timescales. Here, we develop a novel approach to decouple visual features and the timescales at which they are stable, allowing us to determine whether a given brain region's activity is primarily determined by particular visual features (regardless of the timescale of their stability) or by an inherently preferred timescale (regardless of visual features). To that end, we employed a Stable Diffusion-based image generation framework to develop a novel, naturalistic set of 1615 images in which four feature-level categories (scene/object/texture/lines) are independently manipulable. This framework enables us to create videos in which high-level features (scenes and objects) can be stable while their lower-level constituents (textures and lines) change quickly, mirroring dynamics of the natural world; and, critically, it also enables us to invert this natural coupling by generating videos in which high-level features change quickly while lower-level features remain stable. To validate our approach, we used state-of-the-art image processing models to confirm that higher-level features are represented similarly regardless of their lower-level constituent features and, conversely, that lower-level features are represented similarly regardless of the higher-level objects/scenes to which they contribute. As a second validation, we confirmed that human observers (n=3) can readily (94.8% ± 0.2SD mean accuracy) and rapidly (mean: 3073ms ± 1776SD) categorize the lower- and higher-order features in our generated images. In an upcoming fMRI study, we will present participants with generated videos that follow both the natural structure of the visual world and our inverted-timescale structure. This will allow us to determine whether features vs. timescales preferentially drive activity across the visual system. Such insights will have implications for theories of cortical organization, by demonstrating whether features or timescales are a more critical organizing principle of visual cortex.

Disclosures: Z. Hirschstein: None. **M. Aly:** None. **C. Baldassano:** None.

Poster

PSTR087: Perception, Imagery, and Imagination I

Location: MCP Hall A

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Program #/Poster #: PSTR087.09/L36

Topic: H.02. Perception and Imagery

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Title: Event-related EEG microstates complexity indicates specific brain functional network connectivity in the aesthetic process of depression

Authors: *X. MA[1], W. LI[2];
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Abstract: The aesthetic experience, viewed as a daily pursuit involving the observation of external objects, is widely acknowledged to yield sensory satisfaction or pleasure, constituting a fundamental aspect of human nature. Prevailing perspectives suggest that visual aesthetic information is initially captured by the retina, transmitted to the brain, and subsequently influences brain function. These alterations in brain activity have the potential to evoke associations in individuals, thereby inducing changes in their psychology, emotions, and other cognitive dimensions. In numerous studies, depressed individuals have exhibited aberrant and negative aesthetic preferences, yet research on the neural networks involved in the aesthetic processing of depressed patients remains limited. In our study, we recruited 30 Major Depressive Disorder (MDD) patients and 30 healthy controls, from whom EEG signals were acquired. Subsequently, micro-state features were extracted, and regression analysis of EEG microstate parameters revealed that these parameters could explain 90% of the observed variability. Additionally, computational analysis identified a time window reflecting varying levels of micro-state feature complexity. Within this 5-second interval, a significant alteration in brain functional network connectivity was observed. The significance of this study extends to its potential implications for guiding interventions aimed at modulating the functional brain networks implicated in depression. By elucidating the distinct functional brain connections observed during aesthetic processing in depressed individuals, this research offers insights that could inform strategies for modulating neural circuitry associated with depression, and the potential to

use diverse modalities of aesthetic therapy hold promise for ameliorating negative emotions and enhancing cognitive functions.

Disclosures: X. Ma: None. **W. Li:** None.

Poster

PSTR087: Perception, Imagery, and Imagination I

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR087.10/Web Only

Topic: H.02. Perception and Imagery

Support: National Science and Technology Innovation 2030 Major Program (2022ZD0204802)
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Title: Non-feature-specific elevated responses and feature-specific backward replay in human brain induced by visual sequence exposure

Authors: *T. HE;
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Abstract: The ability of cortical circuits to adapt in response to experience is a fundamental property of the brain. After exposure to a moving dot sequence, flashing a dot as cue at the starting point of the sequence can induce successive elevated responses even in the absence of the sequence. This cue-triggered elevated responses have been demonstrated to play a crucial role in predicting future events in dynamic environments. However, temporal sequences we are exposed usually contain rich feature information. It remains unknown whether the elevated responses are feature specific and, more crucially, how the brain encodes this sequence information. To address these questions, participants were exposed to a predefined sequence of four motion directions for about 30 min and subsequently presented with the start or end motion direction of the sequence as a cue. Surprisingly, we found that the cue-triggered elevated responses were not specific to a particular motion direction. Interestingly, the motion direction information was spontaneously reactivated and the motion sequence was backward replayed in a time-compressed manner. These effects were marginally significant even with brief exposure. Notably, when presenting the second or third motion direction of the sequence as a cue, no replay events were observed. Further analyses revealed that activity in the medial temporal lobe (MTL) preceded the ripple power increase in visual cortex at the replay onset, implying a coordinated relationship between the activities in the MTL and visual cortex. Together, we demonstrate that visual sequence exposure could induce two-fold brain plasticity that may simultaneously serve for different functional purposes. The non-feature-specific elevated

responses may facilitate general processing of upcoming stimuli, whereas the feature-specific backward replay may underpin the visual sequence learning process.

Disclosures: T. He: None.

Poster

PSTR087: Perception, Imagery, and Imagination I

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR087.11/L37

Topic: H.02. Perception and Imagery

Title: Neural Basis of Number Sense in Zebrafish

Authors: P. LUU[1], A. NADTOCHIY[2], M. ZANON[1], S. E. FRASER[3], ***T. V. TRUONG**[1]; [1]USC, Los Angeles, CA; [2]Quantitative and Computat. Biol., USC, Los Angeles, CA; [3]Mol. & Computat. Biol., USC, Los Angeles, CA

Abstract: Number sense, or the ability to discriminate between the numbers of objects in a set, is an essential cognitive function for animals in nature to execute a variety of tasks, such as avoiding predators, finding food, mating, and other group behaviors. In humans, number sense forms the basis for more advanced mathematical abilities and is important for general success in modern society. Despite decades of research, it is still not known where the neurons responsible for number sense are throughout the brain, and how they change as a function of development. Here, we leveraged the small and transparent larval zebrafish (*Danio rerio*), optimized a 2-photon fluorescence light sheet microscopy platform, and developed a custom data analysis pipeline, to image the functional activity of nearly all the neurons across the whole-brain, at single-neuron resolution, to identify comprehensively the neurons that are active as the live zebrafish processed visual number stimulus.
We found thousands of number-responsive neurons in zebrafish larvae starting at 3 days old or days post-fertilization (dpf). These neurons, numbering at ~ 1-2% of all neurons, are present throughout the brain, though with the majority in the forebrain and midbrain. In 3 dpf zebrafish, we identified neurons tuned to 1 and 2 objects. For zebrafishes at 5 and 7 dpf, neurons tuned to 3, 4, and 5 objects begin to appear. Using the underlying neuronal activity of the zebrafish, we trained a supervised classification model to predict the number of objects seen by the animals. We found that the model can make correct predictions significantly better than chance, with an increased prediction accuracy with age. We also we examined the effect of alcohol on number-tuned neurons, observing a decrease in 1-tuned neurons in the forebrain (cognitive region), but no change in the midbrain (sensory region). This suggests alcohol impairs cognitive rather than the sensory capacity of number sense, as have been shown in human behavioral research. Overall, our work establishes larval zebrafish as the platform for future numerosity research, toward understanding its nature, development, and malleability.

Disclosures: P. Luu: None. **A. Nadtochiy:** None. **M. Zanon:** None. **S.E. Fraser:** None. **T.V. Truong:** None.

Poster

PSTR087: Perception, Imagery, and Imagination I

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR087.12/M1

Topic: H.02. Perception and Imagery

Title: Effects of social cues on trust in social media content

Authors: *G. LAU[1], Z. ZHAO[1], S. SUN[1], N. NG[1,2], B. NG[2], H. XU[1];
[1]Psychology, [2]Linguistics and Multilingual Studies, Nanyang Technological Univ., Singapore, Singapore

Abstract: How do people trust speakers and information on social media? Previous studies found that social cues influenced trustworthiness of facial images. However, the effects of social cues (emotion and attire), display mode (hologram), and communication modes (video, text, and audio) on trust in social media remain unclear. We examined how these factors affect trust evaluations in three studies. In the first study, we manipulated communication mode (audio, text, video, and its combinations) and content veracity (real and fake). Participants (n = 31) viewed 20 TikTok videos (5 communication modes * 2 content veracities * 2 genders) in random order and rated trust (from 0 - 100, least to most trustworthy) in speaker and content. Using repeated measures ANOVA, we did not find any significant effect of communication mode on trust in news content or speaker (p's > 0.05). However, gender of the speaker ($F(1, 30) = 13.43$, $p = 0.001$) and content veracity ($F(1, 30) = 79.08$, $p < 0.001$) significantly influenced news content trust; female speakers ($F(1, 30) = 14.65$, $p = 0.001$) who delivered real news ($F(1, 30) = 79.08$, $p < 0.001$) were perceived as more trustworthy. In the second study, we examined the effects of facial emotions (neutral, happy, and angry), attires (casual and uniforms), and news veracities (no news, real, ambiguous, and fake). Thirty participants viewed 384 composite images of individuals (3 emotions * 4 attires * 2 genders * 4 ethnicities * 4 news veracities) in random order and rated trustworthiness. Individuals who appeared happy (ANOVA, $F(1.33, 30.59) = 21.79$, $p < 0.001$) and wore uniforms ($F(1.93, 44.44) = 15.22$, $p < 0.001$) were perceived as more trustworthy. Both emotion ($F(1.15, 29.94) = 4.40$, $p = 0.04$) and attire of the speaker ($F(1.78, 46.28) = 5.53$, $p = 0.009$) influenced news content trust. To investigate whether hologram provides a more realistic experience to influence trust, we manipulated display modes (monitor and hologram) with social cues in the third study. Participants (n = 32) viewed 192 composite videos of individuals reporting news items (2 display modes * 3 emotions * 4 attires * 2 genders * 4 content veracities) in random order and rated trust. Similar to the results of study two, we found that emotion and attire significantly influenced both speaker and news content trust. However, there was no significant effect of display mode on trust in speaker or news content (p's > 0.05). We found that emotion and attire consistently foster trust perceptions in social media,

for static images and dynamic videos. The current studies provide insights into the effect of social cues on trust in social media and fake news detection.

Disclosures: G. Lau: None. **Z. Zhao:** None. **S. Sun:** None. **N. Ng:** None. **B. Ng:** None. **H. Xu:** None.

Poster

PSTR088: Distributed Neural Mechanisms of Cognition

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR088.01/M2

Topic: H.05. Working Memory

Support: CONACyT fellowship no. 788978 (No.CVU: 919723).
CONACyT grant CB255462.
DGAPA-PAPIIT UNAM grant IN207923

Title: Functional connectivity variability of resting states networks according to racial identity

Authors: *D. ATILANO-BARBOSA, F. A. BARRIOS;
Univ. Nacional Autónoma de México, Queretaro, Mexico

Abstract: ***Introduction*** Functional magnetic resonance studies (fMRI) related to identify resting states networks are fundamental to characterize human brain variability. African Americans persons has recurrently been excluded from neuroscience research, in contrast with Whites persons which are overrepresented. In this sense, the purpose of this study was to identify functional connectivity differences between Afroamerican and Whites populations to understand human brain functional variability that may be linked to historical inequalities and social privileges between racial groups. ***Method*** We analyzed rs-fMRI high resolution T2* sequences from the Human Connectome Project (HCP) database. T2* raw functional sequences (2 x 2 x 2 mm voxel size, TR =0.72) of participants identified as African-Americans (n=53) and Whites (n=56) were used to identified functional connectivity differences between ROIs related to Default Mode, SensoriMotor, Visual, Salience / Cingulo-Opercular, DorsalAttention , FrontoParietal / Central Executive, Language and Cerebellar resting state networks. Preprocessing stages, denoising and ROI to ROI functional connectivity analysis were implemented from the default preprocessing pipeline of CONN toolbox (V18b, Functional connectivity toolbox, NITRC). Pearson correlation coefficients were calculated within each subject in MNI space taking the time course of the ROIs (ROI-to-ROI analysis). The resultant correlation coefficient maps were converted to normally distributed scores using Fisher transform to implement a second-level analysis, in which, a two-sample t-test was performed. A Network Connectivity Analysis with 5000 permutations was implemented for the connectivity maps with a cluster threshold level of $p<0.05$ corrected for False Discovery Rate (FDR) ***Results*** Differences on functional connectivity between ROIs of the Default Mode (LP: Lateral Parietal), DorsalAttention (FEF: frontal eyes field, IPS: Intraparietal sulcus), FrontoParietal /

Central Executive (LPFC: lateral prefrontal cortex, PPC: Posterior Parietal Cortex), SensoriMotor (lateral portion) and Cerebellar (posterior region) resting state network were identified between racial identity groups.
Conclusion Brain functional connectivity results may indicate differences on network brain processing related to attention and executive functions between racial identities groups. In this sense, the results are fundamental for the comprehension of human brain morphometric diversity, the reduction of generalization bias based on majority populations and to design personalized clinical brain diagnosis for racial minorities.

Disclosures: D. Atilano-Barbosa: None. **F.A. Barrios:** None.

Poster

PSTR088: Distributed Neural Mechanisms of Cognition

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Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR088.02/M3

Topic: H.05. Working Memory

Support: Wellcome Trust 104571/Z/14/Z
James S. McDonnell Foundation Award 220020448
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Vidi Grant 14721

Title: Behavioural and neural correlates of shifting between external and internal attention

Authors: *D. GRESCH[1], S. E. P. BOETTCHER[1], F. VAN EDE[2], A. NOBRE[3];
[1]Univ. of Oxford, Oxford, United Kingdom; [2]Vrije Univ. Amsterdam, Amsterdam, Netherlands; [3]Yale Univ., New Haven, CT

Abstract: During natural behaviour, our attention is in constant flux, rapidly transitioning between information available in the external environment and internal representations stored in memory. However, as past research has primarily investigated external and internal attention in isolation, relatively little is known regarding the dynamic interplay between these attentional domains. Here, we developed a combined perceptual and working-memory task in which participants could be presented with two consecutive cues, sequentially guiding attention between encoded contents, upcoming sensory information, or both. Critically, the second cue could redirect attention to an item within the same domain as the first cue (internal-to-internal or external-to-external shift), or to an item in the alternative domain (external-to-internal or internal-to-external shift), allowing attentional shifts both within and between perception and working memory to be systematically investigated. Across three behavioural studies, we observed larger costs when shifting attention between versus within domains. Strikingly, these costs persisted even when participants were given more time to complete the attentional shift and when the necessity to spatially shift attention was removed. Next, we employed our design in a magnetoencephalography study, aiming to identify the neural signatures of within- and between-

domain shifts via multivariate decoding. Brain activity associated with between-domain shifts was broadly distributed, highly dynamic, and predictive of behavioural performance. Intriguingly, within- and between-domain shifts did not differ during the early attentional orienting stage. This was evidenced by alpha lateralisation, which showed similar time courses when cues redirected attention to the same versus the alternative domain. Moreover, the current findings suggest that neural states associated with a given domain lingered and influenced subsequent shifts of attention within versus between domains. In sum, our studies provide first insights into the behavioural and neural signatures that govern attentional shifts between perception and working memory.

Disclosures: D. Gresch: None. **S.E.P. Boettcher:** None. **F. van Ede:** None. **A. Nobre:** None.

Poster

PSTR088: Distributed Neural Mechanisms of Cognition

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR088.03/M4

Topic: H.05. Working Memory

Support: NIMH R01MH132171

Title: A Neural Circuit model of Working Memory representations using Laplace Neural Manifolds

Authors: *A. SARKAR[1], C. WANG[1], S. ZUO[2], M. W. HOWARD[1];
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Abstract: We have an internal experience of time passing - the present slowly recedes into the past, as if on an internal timeline which organizes what happened when. A wealth of data from cognitive psychology confirms this intuition. It is an open question how populations of neurons can support this representation. Inspired by cognitive models of working memory (WM) we describe a hypothesis for constructing neural representations encoding what happened when. The neurons show distributed mixed selectivity, having separable receptive fields (RFs) for stimuli and time, forming two-dimensional sheets indexing ‘what’ X ‘when’, which we call Laplace Neural Manifolds. The temporal representation in the Laplace Neural Manifold uses two connected populations with different RF. One set of neurons computes the Laplace transform of events unfolding in time. Another set of downstream neurons approximates the inversion of the Laplace transform. The two populations closely mirror neurons found in the medial temporal lobe implicated in maintaining an internal record of the past - the former resembling exponentially decaying cells called temporal context cells, and the latter resembling sequentially firing cells called time cells. Laplace Neural Manifold for time can be implemented at the circuit level using continuous attractor networks. The attractor moves smoothly over time along a what X when grid. The attractor in the Laplace space appears as an edge; the attractor for the inverse space appears as a bump. As events recede into the past, the attractors move as a function of log

time. We study these populations for two WM tasks, oculomotor delayed response (ODR) and vibrotactile delayed discrimination (VDD), where the task variables are arranged on a circle and a line, respectively. Due to their design, the overall population covariance matrices neatly decouple into stimulus and time covariances respectively, and the cumulative dimensionality of the neural trajectories grows logarithmically with elapsed time. State space population analyses of Laplace neurons resemble stable stimulus-specific subspaces observed in PFC neural data. Inverse Laplace neurons, due to their localized receptive fields in time, exhibit rotational dynamics in state space. This work provides a map for going from more abstract cognitive models of WM to a circuit-level implementation using continuous attractor neural networks, and places constraints on the types of neural dynamics that support working memory.

Disclosures: A. Sarkar: None. **C. Wang:** None. **S. Zuo:** None. **M.W. Howard:** None.

Poster

PSTR088: Distributed Neural Mechanisms of Cognition

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Program #/Poster #: PSTR088.04/M5

Topic: H.05. Working Memory

Support: NIH Grant 1R01MH131678-01A1

Title: Neural transformations supporting the representation of context and priority in visual working memory

Authors: *J. M. FULVIO[1], B. R. POSTLE[2];
[1]Univ. of Wisconsin - Madison, Madison, WI; [2]Psychology and Psychiatry, Univ. of Wisconsin–Madison, Madison, WI

Abstract: How does the brain keep future-relevant information accessible while preventing it from interfering with other items in working memory (WM) and with ongoing behavior? Recent simulations with recurrent neural networks (RNNs) have provided mechanistic insights into the neural transformations that support visual WM performance by demonstrating that distinct items are held in separate "context-encoded" subspaces that undergo priority-related transformations according to the status assigned by an external cue (i.e., 'relevant now' vs. 'possibly relevant later'). Here we employed time-resolved representational similarity analysis (RSA) of human electroencephalography (EEG) data to track these representational dynamics in human WM performance. Sixteen subjects performed a double serial retrocuing (DSR) task in which two gratings were presented serially, followed by a retrocue indicating the item to be recalled ("1" or "2;" 100% valid cues, each with 50% probability), followed by a second retrocue and a second recall test. In RNNs the presentation of the second item in the memory set prompts the first item to rotate into a new representational subspace, suggesting that order in WM may be encoded chronologically (not ordinally). With EEG, RSA of voltages suggested a similar scheme, with the representational format of the second sample grating ('S2') being more similar to the initial

format of the first sample grating ('S1') than was the contemporaneous format of S1. Interestingly, dynamics in RSA timecourses suggested that encoding of S2 entailed a "tug of war" between S2 and S1 for occupancy of the "initial S1 subspace," with the representational geometries of the two items moving in and out of the "initial S1 subspace" at a rate of ~15Hz. Future analyses will assess timelocked dynamics in the beta band of the spectrally-transformed EEG data. For prioritization, RSA revealed rapid shifts in the representational geometry of the two items in WM, timelocked to retrocue onset, a pattern consistent with rapid priority-based stratification of representational subspaces observed in RNNs. Furthermore, a similar pattern of rapid transformation was observed timelocked to the recall response, consistent with the 'reset' of priority status observed in RNNs.

Disclosures: J.M. Fulvio: None. **B.R. Postle:** None.

Poster

PSTR088: Distributed Neural Mechanisms of Cognition

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Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR088.05/M6

Topic: H.05. Working Memory

Support: NIH Grant ROIMH087214
ONR Grant N00014-12-1-0972

Title: Visual working memory load persists during the comparison phase

Authors: *C. ZHAO, T. ADEKOYA, E. AWH, E. K. VOGEL;
Univ. of Chicago, Chicago, IL

Abstract: Working memory is often measured by presenting arrays of visual items to be remembered over a short delay that must be compared with a test display. Extensive work has elucidated the neural mechanisms that support the encoding and maintenance periods of these tasks. Though, little is still understood about the comparison process itself. For example, the contralateral delay activity (CDA) is a sustained EEG component that provides a sensitive measure of the current working memory load during the retention period. However, it is not clear whether this activity continues to track the full working memory load during the comparison phase of the task or if it is reduced to just the one item from the array that is being tested. In Experiment 1, we used a change localization task with 2-item and 4-item arrays of colors. At test, subjects had to report which item changed. We observed that the response-phase CDA for set size 4 was significantly larger than the CDA for set size 2. In Experiment 2 we used a single-probe change detection design, in which only a single item from the original array was shown at test. Despite only a single item shown on the screen, we again observed that the response-phase CDA for set size 4 was still significantly larger than the CDA for set size 2. Our results suggest that the working memory load during test reflects the load from all of the items from the array that were stored.

Disclosures: C. Zhao: None. **T. Adekoya:** None. **E. Awh:** None. **E.K. Vogel:** None.

Poster

PSTR088: Distributed Neural Mechanisms of Cognition

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Program #/Poster #: PSTR088.06/M7

Topic: H.05. Working Memory

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Alfred P Sloan Research Fellowship
Nvidia Hardware Grant
UCSB Academic Senate Grant

Title: Working memory for visual features does not necessarily encode bound spatial information

Authors: *D. THAYER[1], Y. LI[2], T. C. SPRAGUE[2];
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Abstract: Models of working memory (WM) state that anterior regions of human cortex engage posterior regions to maintain information in the absence of sensory input due to the high feature selectivity throughout many posterior areas, like visual cortex (Curtis & D'Esposito, 2003; Postle, 2006). This 'sensory recruitment hypothesis' has been supported by many studies using multivariate analysis techniques coupled with spatial WM tasks, where regions throughout the visual hierarchy contain robust representations of a memorized location (e.g., Sprague et al., 2014; Curtis & Sprague, 2021). Since the sensory recruitment hypothesis predicts WM representations would be maintained via neural populations with specialized tuning, then regions with known selectivity for non-spatial features, like color (hV4/VO1/VO2) and motion (TO1/TO2), should be recruited to remember color- and motion-specific information, respectively. Furthermore, it has been proposed that when a specific feature value is remembered, the location corresponding to that stimulus feature is maintained in memory as well (Schneegans & Bays, 2017; Foster et al, 2017), while others suggest that features are maintained in a spatially global format (Ester et al., 2009). To test whether feature-selective sensory regions maintained bound spatial and feature information or global representations, we had participants perform a visual WM task, where they were shown a colorful moving dot stimulus at a random peripheral location on each trial. Participants were immediately postcued to remember either the color or motion of the dot stimulus, or in a baseline condition instructed to remember nothing. After a brief delay, participants reported the specific feature value they remembered using a response dot array at the position of the sample stimulus. We used an inverted encoding model within each feature-selective region to reconstruct spatial maps using multivariate activation patterns. Each map contained a robust representation of the stimulus location at memory encoding and memory report, with stronger representations when the remembered feature

matched a region's feature preference, but there was no evidence of a spatial memory representation maintained throughout the delay period. This indicates that maintaining features in WM may not result in obligatory activation of corresponding spatial locations during memory maintenance, and suggests that delay-period sensory activation patterns may be a result of an active 'reformatting' of information, rather than a sustained activation of previously-stimulated populations (e.g., Kwak & Curtis, 2022; Duan & Curtis, 2024).

Disclosures: D. Thayer: None. **Y. Li:** None. **T.C. Sprague:** None.

Poster

PSTR088: Distributed Neural Mechanisms of Cognition

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Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR088.07/M8

Topic: H.05. Working Memory

Support: NIMH (R01MH123686)
NINDS (R01NS127785)

Title: Compromised Persistent Firing in Posterior Parietal Cortex Pyramidal Cells Following Repeated Multimodal Stress: Implications for Working Memory.

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Abstract: Stress is known to impede cognitive functions including working memory, a temporary memory storage that serves as a mental platform for ongoing activities and thus supports cognitive functions like planning and decision-making. Sustained action potential firing after a brief stimulus is thought to underlie working memory. Studies reported that persistent firing is mediated by an interconnected local microcircuit and cell intrinsic mechanisms. The posterior parietal cortex (PPC) is an essential cognitive hub that plays a crucial role in attention, decision-making, and working memory. Our previous studies reported circuit-specific loss of input to the PPC and impaired visuo-spatial working memory in an adolescent mouse model of repeated multimodal stress (aRMS). However, how stress exposure alters physiological mechanisms of working memory remains unclear. We used whole-cell patch-clamp electrophysiology to record sustained action potential firing in layer 5 pyramidal cells (PCs) of the PPC from mice exposed to aRMS for 1hr/day for 10 days and age-matched controls. Evaluation of intrinsic properties in PCs showed no significant differences between control and aRMS groups. However, the persistent firing duration in response to increasing duration of depolarizing current injections was significantly reduced after aRMS compared to controls. In the presence of glutamate blockers, the persistent activity duration is diminished substantially in controls, suggesting that excitatory synaptic connections are essential in mediating persistent activity. While the amplitude of stimulus-evoked AMPA and NMDA-mediated currents in PCs

showed no apparent differences, the decay phase of NMDA-mediated currents was significantly slower in aRMS mice. We evaluated local monosynaptic connections between excitatory PCs to test whether reduced persistent activity is compromised due to reduced recurrent connections. From our rabies virus-based transsynaptic tracing, we observed that local monosynaptic connections were preserved and unaffected by aRMS. In PC-PC paired recordings, using peak-scaled non-stationary fluctuation analysis, we observed a moderate increase in single channel current at PC-PC synapses and a moderate decrease in the number of channels open at peak response in aRMS mice. In summary, our results suggest that aRMS induced compensatory changes at excitatory synapses between local PCs. However, the significant reduction in persistent firing in PCs following aRMS suggests that overall compensatory mechanisms are still inefficient at restoring persistent activity to normal conditions and may contribute to working memory deficits.

Disclosures: A. Proddutur: None. **D.J. Rindner:** None. **K. Beier:** None. **G. Lur:** None.

Poster

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Topic: H.05. Working Memory

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Title: Sensory and working memory representations are separated in low-dimensional state space of the human early visual cortex

Authors: *S. KIM[1], J. LEE[1], H. GU[2], H. LEE[1], J. LIM[1], H.-J. LEE[1], D.-G. YOO[1], M. CHOE[1], S.-H. LEE[1];
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Abstract: Studies on working memory in the early visual cortex suggest that its representation corresponds to perception (Harrison and Tong, 2009; Serences et al., 2009). The early visual cortex has specialized structures like columnar organization and retinotopic properties that help with sensory processing and might also play a role in working memory (Yacoub et al., 2008; Larsson and Heeger, 2006; Ryu and Lee, 2018; Ryu and Lee, 2024). However, working memory prioritizes task-relevant aspects of sensory events over every detail, raising questions about the suitability of sensory code for representing working memory. Recent findings also highlight differences between working memory and sensory encoding (Kwak and Curtis, 2022), suggesting a need for further exploration. Thus, we designed a task to separate sensory and

working memory representations and check their compatibility. Inside an MRI scanner, fifty human individuals viewed an oriented grating for 1.5 seconds and then later had to recall its orientation after a long delay (16.5 seconds). We extracted multivoxel activity patterns at two widely separated time points—one right after stimulus onset (encoding phase) and the other at the end of the delay (maintenance phase). Using demixed principal component analysis (dPCA), we identified stimulus-specific principal components (PCs) to construct a 3D state space in which a 2D circular manifold of orientation information is embedded. To determine the extent to which the 3D state space can be applied to other phases, we examined the projection of manifold during the encoding phase onto the 2D manifold plane of the maintenance phase, and vice versa. We found that the size of the cross-projected areas was very small, which indicates lower generalizability between sensory and working-memory representations. We then tested whether the voxels contributing to the PCs were shared between the encoding and maintenance phases. We found that the voxels contributing to the PCs for the encoding phase substantially differed from those for the maintenance phase, which indicates that distinct neural populations support sensory and working memory codes. Lastly, we found that whereas the voxels' orientation preferences during the encoding phase were nicely aligned with their radial position, those during the maintenance phase did not, which suggests that the working memory representation, unlike the sensory representation, does not reflect the functional architecture constrained by visual input structure. Our findings suggest that working memory representations in the early visual cortex differ from those in sensory representation, relying on distinct neural substrates.

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Poster

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Topic: H.05. Working Memory

Support: DFG Grant 465409366

Title: Visual cortex TMS causally affects working memory in a topographic and task-specific manner

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Abstract: When maintaining visual information in visual working memory (VWM), neuroimaging has consistently shown that early visual areas represent the memorized items. However, it is a matter of current debate if this information is actually relevant for the maintenance of visual information. Transcranial magnetic stimulation (TMS) studies have presented incongruent results, revealing both, disruption, and enhancement in performance, especially during the encoding part of VWM. Here, we report results from two experiments in which we applied TMS over the visual cortex during the maintenance period of a dual VWM task. Participants were asked to remember either the category or the orientation of a composite image, while TMS was applied over visual cortex. TMS stimulation location was defined prior to the experiments by phosphene induction, and visual stimuli were presented exactly at the perceived phosphene location. Our results revealed retinotopically specific TMS effects long into the retention time of the orientation task, but not the category task. This is evidence that visual areas are involved in the maintenance of VWM items in a retinotopic and task-specific manner.

Disclosures: P.R. Grassi: None. **E. Artner:** None. **B. Stöckle:** None. **A. Bartels:** None.

Poster

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Program #/Poster #: PSTR088.10/M11

Topic: H.05. Working Memory

Title: Within-subject comparison across neurological lesion cases reveals the functional relevance of the medial temporal lobe in visual short-term memory precision

Authors: *S. THAKURDESAI[1], O. E. FRUCHET[2], S. N. JACKSON[2], R. CHATTERJEE[2], S. INATI[2], K. A. ZAGHLOUL[2], W. XIE[1];
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Abstract: Classic case-control studies on brain lesions suggest that the medial temporal lobe (MTL) is minimally involved in visual short-term memory (VSTM), particularly in tasks involving simple stimulus features such as colors and orientation gratings. However, recent studies with direct recordings from the MTL indicate its pivotal role in VSTM representations. It is hypothesized that the MTL's pattern separation function may assist in reducing mnemonic interference during short retention intervals, thereby supporting the quality of VSTM. The absence of significant findings in previous case-control comparisons could be attributed to either less sensitive task measures or complications arising from individual differences. To address these potential confounds, we investigated whether MTL lesion affects participants' performance in a color recall VSTM task among 43 neurological cases, both before and after neurosurgery. Among these cases, 15 had lesions in the MTL, including the hippocampus, while the remaining 28 either had no lesion or lesions in brain regions other than the MTL (e.g., insula, prefrontal cortex, temporal pole), sparing the hippocampus. We measured participants' recall variability and overall recall likelihood in the color recall VSTM task across different measurement time

points. When comparing the pre- and post-lesion task performance within participants, we find that MTL lesion leads to a significant increase in recall variability, suggesting a reduction in VSTM precision after MTL resection. However, MTL lesion does not affect overall recall likelihood. In contrast, cases with non-MTL lesions or no lesion show no consistent changes in either recall variability or overall recall likelihood. This suggests that the MTL, especially the hippocampus, plays a crucial role in determining the quality of VSTM. Future research incorporating neuroanatomical imaging data may further elucidate the lesion-symptom mapping in these neurological cases.

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Poster

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Topic: H.05. Working Memory

Support: NIH Grant R01DC107979
NIH Grant RF1NS127129
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NYU Training Program in Computational Neuroscience

Title: Circuit and synaptic mechanisms supporting a working memory circuit for navigation

Authors: *A. J. LANZ[1], N. D. KATHMAN[2], E. HAO[2], B. ERMENTROUT[3], K. I. NAGEL[2]; [1]Neurosci., [2]NYU Langone Med. Ctr., New York, NY; [3]Univ. of Pittsburgh, Pittsburgh, PA

Abstract: Working memory is a fundamental building block of cognition and is thought to arise from recurrent interactions between neurons. In previous work, we showed that a population of local neurons in the *Drosophila* navigation center is a substrate for working memory during navigation; these neurons exhibit a bump of activity in response to odor that can outlast the stimulus and is associated with persistent heading, while loss of this activity reduces persistent upwind heading following odor encounters. Here we combine connectomics, synaptic physiology, and computational modeling to determine the circuit and synaptic basis of this persistent bump activity. First, using connectomics, we show that these local neurons are embedded in a recurrent network resembling a ring attractor. Next, using patch-clamp electrophysiology, we find that persistent activity requires recurrent feedback - stimulating an upstream olfactory neuron produces long-lasting excitation in local neurons that disappears after blocking local neuron synaptic output. We further find that stimulating one of the recurrent partners produces long-lasting excitation that quickens when serotonin signaling is blocked, suggesting slow metabotropic signaling contributes to persistence duration. Finally, we show that persistent activity in local neurons is gated by inhibition and identify two inhibitory neurons that

robustly inhibit our local neurons and undergo strong synaptic depression. Based on these data, we construct a dynamical model of this circuit. If the recurrent excitation uses fast synaptic transmission, we find that persistence in the network is fragile and only occurs for a narrow band of excitation and inhibition weights. In contrast, incorporating slow metabotropic signaling into our recurrent network generates robust persistence where the duration can be tuned through small modulations of excitatory and inhibitory weights. Ongoing works seeks to test our computational model using *in vivo* imaging from recurrent partners and manipulations of these neurons during odor-guided navigation behavior. Together, our data and model provide insight into how synaptic dynamics within an attractor-like network can produce a robust and tunable working memory signal for navigation.

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Poster

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Topic: H.05. Working Memory

Support: NIH Grant EY025872

Title: Mnemonic maneuvers: Voxel population codes in visual cortex multi-task to support distractor resistance in working memory

Authors: *J. W. WENNBERG[1], K. C. ADAM[2], J. SERENCES[3];
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Abstract: A defining feature of working memory is that information can be held “in mind” once the visual stimulus is no longer present, and is quite robust to the presence of distractors (Kamitani & Tong, 2005; LaRocque et al., 2012; Rademaker et al., 2019). While some studies suggest that distractor resistance is due to an offloading of mnemonic information from visual cortex to frontoparietal cortex (Xu, 2021; Mendoza-Hallyday & Trujillo, 2014), an alternative is that memory codes are transformed within early visual areas so that mnemonic and sensory information do not interfere (Libby & Buschman, 2021). In the present fMRI study, we tested the hypothesis that visual cortical areas may “multi-task” to support mnemonic information in the presence of distractors. Participants (N = 7) completed one spatial working memory task where they remembered the angular spatial location of a flickering checkerboard circle. On half of the trials, the screen was blank during the delay period. On the other half, identical checkerboard circles flickered around the screen. We trained a circular ridge regression model to decode spatial position, and we tested the model on held out data to obtain within-condition and cross-condition classification accuracy for distractor present and distractor absent trials. If memory

representations are offloaded to parietal cortex during distractions, we expect an asymmetry of decoding, with high classification accuracy when training on distractor absent trials but no success when training on distractor present data. Alternatively, a rotational shift in the memory representation would produce a cross-over interaction when training a model with and without distractors. We observed a crossover interaction as early as V1: When training the model on distractor absent trials, decoding was significantly better when testing the model on distractor absent trials than distractor present trials. The same pattern was observed when training the model on trials with distractors—classification was better when testing the model on distractor present trials than distractor absent trials. Together, these results suggest that voxel-level population codes flexibly rotate to support high fidelity storage of mnemonic information even in the presence of distractors.

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Poster

PSTR088: Distributed Neural Mechanisms of Cognition

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Topic: H.05. Working Memory

Support: NEI Grant EY033064

Title: Memory guided saccades in marmosets: behavior and electrophysiology in the prefontal and posterior parietal cortex

Authors: *S. AHMAD[1], A. HUK[2,3];
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Abstract: Persistent neural activity is considered the physiological hallmark of working memory, but the detailed mechanisms that support it have been difficult to study in primates. Marmosets present an exciting opportunity to deploy modern neural recording techniques to test the circuit-level assumptions predicted by computational theories of persistent activity. However, it remains unclear whether marmosets can be trained to perform memory-guided saccades (MGS) and whether they have cortical areas functionally analogous to those studied in macaques. We developed a method for training marmosets to perform memory-guided saccades, a task traditionally used to study working memory in macaques. Neural activity was measured from two cortical areas known to exhibit persistent activity: the prefrontal cortex (PFC) and posterior parietal cortex (PPC), using high-density Neuropixels probes while the marmosets performed memory-guided saccades. Two marmosets were successfully trained to perform the MGS task, with neural activity recorded from one of them. Marmosets were able to perform a significant number of trials per session (averaging 740 trials per session). They successfully completed trials at levels acceptable for physiological study, with delay periods of up to 1000 ms

(15-25% trials with <1 s saccade latency). The marmosets exhibited accurate eye movements, with saccadic endpoint errors of less than 4 degrees of visual angle relative to the true target location. Neurophysiological recordings allowed us to characterize the basic properties of neural activity within marmoset oculomotor brain areas during MGS. Preliminary data collected in our lab suggests functionally analogous signals to those observed in macaque oculomotor brain areas, including single neurons exhibiting persistent activity. Marmosets can be trained to perform MGS and serve as an important experimental bridge between rodents and primates in the study of persistent activity. The large-scale nature of recordings available in this species allows us to perform rigorous tests of computational models of persistent activity and contribute more detailed functional descriptions of these cortical circuits in primates.

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Poster

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Topic: H.04. Executive Functions

Support: NIH Grant R01 MH128177
NIH Grant P30 DA048742

Title: Hierarchical temporal dynamics across humans and macaques

Authors: *T. ERICKSON, G. DELGADO SALAZAR, A. M. MANEA, J. ZIMMERMANN; Dept. of Neurosci., Univ. of Minnesota, Twin Cities, MN

Abstract: Hierarchical temporal dynamics are a core computational neuronal feature subserving flexible behavior and cognition. Despite this, studies examining these scales of neural processing across human and animal models are lacking. We conducted a comparative analysis of neural timescales between humans and macaques to quantitatively assess functional homologies. Timescales of baseline neuronal activity vary throughout the brain, ranging from fast in sensory areas to slower in association areas. These intrinsic neural timescales (INTs) provide a temporal framework for input integration across brain areas. Traditionally, INTs were studied using invasive electrophysiology, unsuitable for revealing whole-brain dynamics and challenging to collect in humans. Alternatively, fMRI offers whole-brain coverage, cross-species analyses, and larger sample sizes. We used human (N=172) high-field (7T) and anesthetized macaque (N=29) ultra-high field (10.5T) resting-state fMRI data. Overall, INTs were slower in humans than in macaques. We posit the slower human INTs reflect cognitive engagement, contrasting with the anesthetized state of macaques. Despite variations in absolute values, the relative position of brain regions within the INT hierarchy remained consistent across species. We observed a consistent gradient across regions and specific network levels, such as occipital and temporal lobes (fastest) to parietal (intermediate) and frontal (slowest). In the visual system, V1 exhibited

the shortest timescales, followed by V2, V3, V4, and V6 with progressively slower timescales. In motor areas, INTs progressively slowed from M1 to PMd, PMv and (pre-)SMA. We noted a ventral-dorsal INT hierarchy in the PFC, with similarities and differences across species. In both, the medial wall of the PFC INTs became progressively slower from area 25, to OFC, areas 32 and 24. However, in humans, VLPFC and DLPFC were at the top of the hierarchy, while in macaques it was area 24. Visual, motor and prefrontal hierarchy closely follow an increase in representational complexity, progressively more abstract representations and higher-order control is accompanied by slower timescales. We demonstrate INTs hierarchies remain consistent across species at the whole brain and specific network level.

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Poster

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National Bio-Resource Project "Japanese Monkeys" of MEXT

Title: Multiscale chemogenetic dissection of fronto-temporal top-down regulation for object memory in macaques

Authors: *T. HIRABAYASHI[1], Y. NAGAI[1], Y. HORI[1], Y. HORI[1], K. OYAMA[1], K. MIMURA[1], N. MIYAKAWA[1], H. IWAOKI[1], K.-I. INOUE[2], T. SUHARA[1], M. TAKADA[2], M. HIGUCHI[1], T. MINAMIMOTO[1];
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Abstract: Visual object memory is a fundamental element of our various cognitive abilities, and the underlying neural mechanisms have been extensively examined especially in the anterior ventral temporal cortex (aVTC), the final stage of visual object processing in primates. However, both the large-scale network in which this region is embedded and the neuron-level dynamics of top-down regulation it receives for object memory remains elusive. By combining whole-brain functional imaging during the performance of a short-term visual object memory task and at rest, we identified the orbitofrontal cortex (OFC) node in two macaques as a critical partner of the aVTC node, forming the ventral fronto-temporal network for object memory. Focal chemogenetic silencing of the identified OFC node impaired visual object memory in a delay length-dependent manner, in association with a downregulation of memory-related activity in both the local OFC and remote aVTC nodes at the macro-scale. Subsequent single-unit recordings in the same macaques during the same task identified a cluster of neurons showing stimulus-selective cue and delay activity at the aVTC activation site. Stimulus-selective activity during the delay, but not cue, period diminished by OFC silencing, suggesting that OFC top-down modulation enhanced stimulus-selective mnemonic signal in individual aVTC neurons while leaving bottom-up perceptual signal unchanged at the micro-scale. Furthermore, similar mnemonic signal-specific difference was also observed between correct and mnemonic error trials before silencing, suggesting that the observed OFC top-down modulation is behaviorally relevant. Together, these multifaceted but convergent results provide a multiscale causal understanding of dynamic top-down regulation of the aVTC along the ventral fronto-temporal network underpinning short-term visual object memory in primates (Hirabayashi, et al., Nature Commun. accepted in principle).

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Poster

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Program #/Poster #: PSTR088.16/

Topic: H.08. Learning and Memory

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National Natural Science Foundation of China (31872776)
National Key R&D Program of China (2018YFA0701402)

Title: Organization of ipsilateral and contralateral connections within the macaque ventrolateral prefrontal cortex

Authors: *D. HU[1], H. LI[1], T. TAKAHATA[3], H. TANIGAWA[2];
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[3]Ctr. for the Evolutionary Origins of Human Behavior, Kyoto Univ., Inuyama, Japan

Abstract: The ventrolateral prefrontal cortex (VLPFC), located in the inferior frontal gyrus, shows diverse connectivity within the cortex and with other cortices. Understanding these connections is crucial for gaining insight into the higher-order information processing that occurs in the prefrontal cortex (PFC). Although previous studies have revealed the inter-areal anatomical connectivity of the VLPFC, connectivity at the submillimeter level within the VLPFC has not been fully investigated. This study aims to reveal the neuronal connectivity patterns within the VLPFC of the ipsilateral and contralateral hemispheres in each cortical layer using anatomical tracing methods. Four different types of retrograde tracers, including CTB-488, CTB-555, CTB-647, and BDA, were injected into the architectonic areas 8r and 45A of the VLPFC, roughly based on sulcal landmarks, in four monkeys, with each tracer separated by at least 3 mm. Perfusion was performed after three weeks of survival. The PFC tissues in both hemispheres were flattened, frozen, and cut into tangential sections at a thickness of 40 µm. Nissl staining was performed on a series of sections for laminar classification. All necessary sections were scanned by bright-field or dark-field fluorescence microscopy to verify the signals. The results show that all tracers were successfully injected into the intended sites, with small injection sites approximately 50 µm in diameter. Abundant retrogradely labeled cells were found around the injection sites, spreading as far as 9 mm from the injection sites and tending to form clusters of a certain size (~400 µm in diameter) in the tangential plane. In addition, tracer labeling was observed from the supragranular to the infragranular layer and was consistent along the vertical direction. Furthermore, in the contralateral VLPFC, cells labeled with different tracers were distributed in clusters (300-800 µm in diameter) while maintaining the positional relationship of the injection sites, indicating topographical transcallosal connections. Our results reveal the specific distribution patterns of connectivity within the VLPFC at the submillimeter level, providing a new anatomical framework for understanding the organization of this cortex.

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Poster

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Topic: H.03. Decision Making

Support: R01MH130608
T32NS115705

Title: Distinct combinations of cortical and subcortical afferents to sgACC and pgACC: within-animal studies in macaque monkeys

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Abstract: In humans and non-human primates, the anterior cingulate cortex (ACC) can be divided into distinct functional subregions. The subgenual ACC (sgACC, BA 25/14c) is thought to play an important role in sustaining emotional arousal and processing negative emotion. In contrast, the perigenual ACC (pgACC, BA 32/24b) is thought to be a "cognitive" area and is implicated in social decision-making and conflict monitoring. Comparison of the networks supporting these functional differences has relied on neuroimaging or on single injections of neuronal tracers in different animals. We examined combinations of cortical and subcortical inputs to the sgACC and pgACC both within and across animals to better understand these functional differences. We paired injections of retrograde neuronal tracers into sgACC and pgACC in the same macaque monkey (n=4 pairs) and mapped labeled neurons in the prefrontal cortex (PFC), thalamus, and brainstem. Analysis of PFC afferent networks revealed mainly segregated combinatorial inputs to sgACC and pgACC. Inputs to sgACC largely arise in areas 14c, 32, 13a, and Iam, while inputs to pgACC largely arise in areas 9, 46, 10m, 11m, 13m/l, and 12o/l. Importantly, specific patterns of sgACC inputs were highly sensitive to the rostrocaudal location of the sgACC injection site, whereas inputs to pgACC sites were more uniform. The pgACC (areas 32/24b) sends "top-down" inputs to sgACC (area 25), with few return projections. Thalamic inputs were also segregated with inputs to sgACC primarily originating from midline thalamus (paraventricular nucleus, PVT), involved in arousal. In contrast, pgACC received inputs mainly from thalamic nuclei involved in memory and spatial processing: anterodorsal (AD), anteroventral (AV), medial ventral anterior (VAM), and lateral ventral anterior (VAL) thalamic nuclei. Both sgACC and pgACC received smaller inputs from the mediodorsal (MD) and pulvinar (Pul) nuclei. In the brainstem, periaqueductal gray (PAG) inputs to sgACC arose from the lateral column (associated with "fight or flight" response), whereas inputs to pgACC arose from the ventrolateral column (linked with defensive behavior such as freezing). Taken together, these findings support that sgACC and pgACC act as distinct functional hubs. Inputs from the "autonomic brain" such as midline thalamus, insular cortex, and lateral PAG may support sgACC's key role in the arousal network. In contrast, inputs to pgACC from areas important for contextual processing (anterior thalamus) and executive function (dlPFC) may be important for its role in decision making and goal-directed action.

Disclosures: D.C. Myers: None. **J.L. Fudge:** None.

Poster

PSTR088: Distributed Neural Mechanisms of Cognition

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR088.18/M18

Topic: H.04. Executive Functions

Support: Allen Institute

Title: Brain-wide map of activity during sensory task switching

Authors: E. G. MCBRIDE[1], S. AKELLA[3], S. D. GALE[4], *C. BENNETT[1], B. HARDCASTLE[1], H. CABASCO[2], J. KUYAT[5], A. SRIDHAR[1], V. LAFEHR[1], A. AMAYA[1], C. MOCHIZUKI[1], C. GRASSO[1], W. HAN[1], B. OUELLETTE[1], K. S. NGUYEN[1], R. NAIDOO[1], J. SWAPP[1], A. WILLIFORD[1], P. A. GROBLEWSKI[4], S. R. OLSEN[1];
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Abstract: Animals must flexibly control their behavioral responses to sensory stimuli based on goals and environmental context. To characterize neural activity during dynamic sensorimotor routing, we made Neuropixels recordings from >20k units distributed over >50 cortical and subcortical regions during a multi-modal task switching paradigm in mice. The task requires mice to selectively respond to either visual or auditory stimuli in blocks of trials. After block switches, mice rapidly shift the modality to which they respond. Standard reinforcement learning (RL) does not capture these fast-switching dynamics, but adding a context belief state to the RL model leads to better correspondence with mouse behavior. A linear decoding model reveals that task context (visual-rewarded versus auditory-rewarded blocks) is represented across many areas of the brain during inter-trial activity, most strongly in frontal cortical and midbrain areas. Behavioral errors are correlated with a decrease in model confidence during the preceding inter-trial interval, and rewarded hit trials are followed by an increase in model confidence. In line with these results, fitting single neuron activity with a generalized linear model reveals that context encoding is significantly higher in expert mice. In early sensory areas, the encoding of sensory stimuli is modulated by context. In midbrain and prefrontal cortical areas, functional diversity of single neurons is greater than in sensory cortical areas, reflecting mixed encoding of context, movements, and sensory variables.

Disclosures: E.G. McBride: None. **S. Akella:** None. **S.D. Gale:** None. **C. Bennett:** None. **B. Hardcastle:** None. **H. Cabasco:** None. **J. Kuyat:** None. **A. Sridhar:** None. **V. LaFehr:** None. **A. Amaya:** None. **C. Mochizuki:** None. **C. Grasso:** None. **W. Han:** None. **B. Ouellette:** None. **K.S. Nguyen:** None. **R. Naidoo:** None. **J. Swapp:** None. **A. Williford:** None. **P.A. Groblewski:** None. **S.R. Olsen:** None.

Poster

PSTR088: Distributed Neural Mechanisms of Cognition

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR088.19/M19

Topic: H.05. Working Memory

Support: DFG Grant GR 2024/11-1

Title: Low dimensional embeddings bridge sensory representation to motor execution

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Abstract: In our everyday experience we iteratively sample information, maintain it in our working memory (WM), and select the relevant piece of it to inform our future actions. Understanding how this cascade unfolds remains one of the most fascinating riddles in neuroscience. One way in which this has been addressed non-invasively in humans is the study of electromagnetic brain dynamics with high temporally resolved methods such as EEG or MEG, which offered countless breakthroughs in the last decades. Key examples are some recent works (Van Ede et al. 2019; Boettcher et al. 2021) which undermined the intuitive idea of these steps being strictly sequential, and showing that the selection of relevant information from WM happens simultaneously with the response preparation.
Yet the study of electromagnetic brain dynamics, without adequate transformations, has multiple pitfalls: We need to make sense of dozens -or hundreds- of highly correlated sensors whose signal is highly variable between individuals. All these issues can obfuscate our understanding of multiplexed constructs like WM.
In this work, we addressed this issue by leveraging recent developments in non-linear manifold learning (Jazayeri et al. 2021; Mitchell-Heggs et al. 2023). In an MEG experiment, we had human participants perform an established task linking individual memory items to actions (Van Ede et al. 2019). By adopting a novel supervised decomposition method (Schneider, Lee & Mathis, 2023) we extracted some low-dimensional latent spaces highly informative of the relevant axes of our WM task, that is, information selection and motor preparation, replicating the original findings of simultaneity between the two. Crucially, these spaces showed generalization across participants. Further, we used Frechet distance to rank the dimensions of these spaces according to their informativeness along these axes, finding dimensions highly selective for motor preparation or information selection, alongside dimensions encoding information at a more abstract level, but orthogonal to visuomotor component such as left/right lateralization of both target location and motor response.
The present findings provide a powerful framework for exploring the temporal dynamics of WM together with the possibility to generalize these dynamics across different participants and tasks.

Disclosures: E. Balestrieri: None. **J. Fehring:** None. **C. Stier:** None. **N. Chalas:** None. **D. Kluger:** None. **J. Gross:** None.

Poster

PSTR088: Distributed Neural Mechanisms of Cognition

Location: MCP Hall A

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Program #/Poster #: PSTR088.20/M20

Topic: H.05. Working Memory

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McDonnell Center for Systems Neuroscience
Fondazione Neuron

Title: Electrophysiological Effect of Transcutaneous Auricular Vagus Nerve Stimulation (taVNS) during Spatial Working Memory in Intracranially-Monitored Epilepsy Patients

Authors: *T. TAN[1], G. TAN[2,4,5,6], J. T. WILLIE[7,8,6,4,5], E. C. LEUTHARDT[1,4,5,3,6], P. BRUNNER[9,4,5,3,6];
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Abstract: The auricular branch of the vagus nerve projects to brain areas involved in arousal and memory functions, such as the locus coeruleus, hippocampus, and amygdala. This anatomical connection underpins the potential of transcutaneous auricular vagus nerve stimulation (taVNS) to enhance cognitive functions. While previous literature highlights the efficacy of taVNS in enhancing working memory among healthy individuals, its impact on the electrophysiology in the human brain remains largely unknown. This study seeks to bridge this gap by examining the electrophysiological effect of taVNS during a spatial working memory task in patients implanted with stereoelectroencephalographic (SEEG) electrodes.The subjects in this study performed a spatial working memory task across various levels of difficulty. They were required to memorize the locations of red dots briefly displayed on a grid and later identify whether a single dot shown was part of the original array. To maximize cognitive load, we titrated the difficulty of the task so that subjects were only able to respond correctly to 80% of the trials. Specifically, we adjusted task complexity by modifying the grid size and the delay period between encoding and retrieval phases, with larger grids and longer delays intended to increase cognitive load. The primary measures of task performance were accuracy and reaction time. We validated the task by analyzing how performance metrics correlated with the introduced complexities. Specifically, larger grids and longer delays increased reaction time and decreased the accuracy during the spatial working memory task.Additionally, we studied the effects of taVNS on intracranial electrophysiology by administering vibrotactile stimulation to the auricular branch of the vagus nerve during half of the trials. We present the behavioral verification of the working memory task and the effect of taVNS on intracranial electrophysiology during different levels of cognitive load.

Disclosures: T. Tan: None. **G. Tan:** None. **J.T. Willie:** None. **E.C. Leuthardt:** None. **P. Brunner:** None.

Poster

PSTR088: Distributed Neural Mechanisms of Cognition

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR088.21/M22

Topic: H.06. Social Cognition

Title: The role of the primary motor cortex in propositional deductive reasoning: a TMS study

Authors: *S. FRESNOZA;
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Abstract: Reasoning is an essential human ability that underlies effective problem-solving, decision-making, and judgment. However, the underlying cognitive process and specific brain areas subserving our reasoning ability are not yet fully understood and are still under debate. Neuroimaging studies that contrasted the two main reasoning types, deductive and inductive, showed left inferior frontal gyrus (IFG) activation akin to greater engagement of syntactical processing for the former and the left dorsolateral prefrontal cortex (DLPFC) for the latter due to its dependency on background knowledge. A meta-analysis of neuroimaging studies further decomposed the deductive reasoning neural network into three subsystems: the left IFG and left basal ganglia for categorical arguments (e.g., “All As are Bs. All Bs are Cs. Therefore, all As are Cs”.), left posterior parietal cortex (PPC), left primary motor cortex (M1), and medial frontal gyrus for propositional arguments (e.g., “If there is an A, then there is a B. There is an A. Therefore, there is a B.”), and bilateral PPC and right middle frontal gyrus for relational arguments (e.g., “A is to the left of B. B is to the left of C. Therefore, A is to the left of C”.). The present study explores the role of the left M1 in propositional deductive reasoning using transcranial magnetic stimulation (TMS). Thirty young male participants underwent left motor cortex single- and double-pulse TMS at rest (baseline) and during deductive reasoning to compare differences in corticospinal and intracortical (short-interval intracortical inhibition (SICI) and intracortical facilitation (ICF)) excitability under different argument types. Results showed that propositional arguments only modulated corticospinal excitability (decreased). Propositional arguments also increased and decreased SICI and ICF, respectively. No changes in ICF and SICI were observed when reasoning with relational and categorical arguments. The result was consistent with the hypothesis that inhibition is increased in the motor cortex during propositional deductive reasoning to prevent overt motor output.

Disclosures: S. Fresnoza: None.

Poster

PSTR088: Distributed Neural Mechanisms of Cognition

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR088.22/M23

Topic: H.04. Executive Functions

Title: Local neural population geometry is associated with dynamic engagement of brain-wide networks

Authors: *C. MACDOWELL[1], A. ARDALAN[2], A. G. LIBBY[3], C. I. JAHN[3], S. TAFAZOLI[3], T. BUSCHMAN[1];
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Abstract: Cognition is flexible, allowing behavior to change on a moment-by-moment basis. Such flexibility is thought to rely on the brain's ability to route information through different networks of brain regions in order to perform different cognitive computations such as sensory processing, motor actions, and decision making. The mechanisms that determine how neural activity flows between brain regions remain unclear. One hypothesis is that the geometry of neural representations changes on a moment-to-moment basis, allowing a region to dynamically move in and out of "view" of a broader network in order to selectively engage that network to support a specific cognitive process. To begin to test this hypothesis, we combined large-scale electrophysiology and widefield calcium imaging as mice engaged in spontaneous behaviors. We then used reduced rank regression modeling to uncover the functional interactions between neural populations distributed across the brain. We found that neural activity in each brain region could be partitioned into multi-dimensional subspaces that were correlated with unique cortex-wide 'shared subspace networks'. For example, the predominant subspace of most brain regions involved a broad network that spanned the majority of the cortex and was closely associated with arousal state and motor activity. Other subspaces engaged canonical cortical networks, such as the lateral cortical and visual networks. We found that neural representations within a brain region dynamically aligned to different subspace networks. How well the neural representation within a region aligned with a subspace network predicted moment-by-moment changes in the way neural activity propagated across brain areas. Altogether, our results support a geometric model of cognitive control in which changing neural representations to align with a specific shared subspace of neural activity across regions propagates that information to the broader network.

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Poster

PSTR088: Distributed Neural Mechanisms of Cognition

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR088.23/M24

Topic: H.04. Executive Functions

Title: Behavioral evidence for context belief states during task switching in mice

Authors: S. D. GALE[1], C. BENNETT[2], E. G. MCBRIDE[2], B. HARDCASTLE[3], H. CABASCO[3], J. KUYAT[4], ***S. OLSEN**[2,5];
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Abstract: Animals leverage contextual information from their environment to execute flexible and adaptive behaviors. In this study, we devised a multimodal task-switching paradigm for mice, requiring them to alternate between auditory and visual discrimination tasks. Initially, mice were trained separately on a visual discrimination task (orientation discrimination) and an auditory discrimination task (AM noise discrimination) (n = 18 mice). Subsequently, they were trained in an audio-visual context-switching task, where they had to respond to visual or auditory stimuli based on the context of the current trial block. We observed that, following context-switching training—but not during initial training—mice exhibited cross-modal inference, using their knowledge of one modality's reward status to deduce the reward status of the other modality without direct experience. To understand the underlying processes, we applied reinforcement learning (RL) models to the mouse data, comparing basic Q-learning models with more complex models that incorporate a context belief state. Our findings indicate that while Q-learning accurately describes mouse behavior during initial training, models with a context belief state better capture behavior post task-switch learning, including the observed cross-modal inference. In these models, prediction errors are used to update the context belief and stimulus-action values. However, analysis of model parameters revealed that task-switch learning predominantly involved changes to the context belief update rate and the stability of the context belief in the absence of feedback. In contrast, the stimulus-action learning rate was slow and stimulus-action values were stable. These results show that a learned flexible context belief state in combination with stable stimulus-action values are critical for capturing the task-switching performance observed in mice. Currently, we are employing multi-regional Neuropixels recordings to track brain-wide spiking activity as mice perform this task, aiming to identify the neuronal networks that support context-based task-switching.

Disclosures: S.D. Gale: None. **C. Bennett:** None. **E.G. McBride:** None. **B. Hardcastle:** None. **H. Cabasco:** None. **J. Kuyat:** None. **S. Olsen:** None.

Poster

PSTR088: Distributed Neural Mechanisms of Cognition

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR088.24/M25

Topic: H.06. Social Cognition

Support: NIH T32GM008620
N00014-24-1-2014
BCS-1941216

Title: Depression-like Behavior is Associated with Defects in the Primary Hippocampal Circuit

Authors: *C. C. YANG[1], J. LAUTERBORN[2], B. PRUESS[3], C. M. GALL[4], G. LYNCH[5], B. G. GUNN[3];
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Abstract: Numerous studies have established a connection between the hippocampus and clinical depression but the circuits and mechanisms underlying this relationship are poorly understood. Here we report that single housing (7-10 days) of young adult (2-4 mo) male mice reliably produces multiple behavioral features associated with depression including reduced interactions in the 3-chamber sociability task, despair-like behavior in the Tail Suspension and Forced Swim paradigms, and aberrant responses to palatable foods. Single housed animals were maintained in the same colony as group housed controls and explicit stressors were not included in the study. Using a novel brain slice preparation that enables recordings of spike responses in the CA1 output stage to stimulation of lateral perforant path (LPP) input, we assessed the effects of single housing on frequency-dependent signal transformations across the entire hippocampal circuit. While signal throughput following LPP activation at theta frequencies (5Hz) was unaffected by housing condition, there was a near complete disruption of low pass filtering of signals arriving at beta (>20Hz) and higher frequencies in the single cage group. Filtering of beta frequency throughput was mediated by an unusual feedforward inhibitory arrangement within field CA3. We accordingly propose that behavioral depression is associated with surprisingly discrete changes to a CA3 network, resulting in a reduced capacity to process high frequency signals across the multiple stages of the hippocampus. We are currently testing 1) the prediction that these disturbances are accompanied by impairments to episodic memory (as occurs with clinical depression), and 2) the causal possibility that the circuit defect also contributes to the depression-like changes produced by single housing.

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Poster

PSTR088: Distributed Neural Mechanisms of Cognition

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR088.25/M26

Topic: H.01. Attention

Title: Triangulating neural correlates of consciousness

Authors: *N. FISH[1], A. SCHURGER[2];
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Abstract: For decades the desire to understand the brain basis of subjective experience has been a major goal of neuroscience. Pioneering efforts by Christof Koch and Francis Crick resulted in the idea of neural correlates of consciousness (NCCs) which can be defined as the "minimal neural mechanisms that are together necessary and sufficient for experiencing any conscious percept." Previous approaches at identifying NCCs, such as backward masking, have seemed to successfully identify many candidate NCCs, but have had difficulty in distinguishing manipulation-specific effects from general features of subjective experience that would be required of a "necessary and sufficient" correlate. This project introduces a method of "triangulation" which should more accurately identify universally applicable NCCs. Our approach contrasts three distinct visual perception manipulations - backward masking, dichoptic color fusion, and inattentional blindness - all within the same experimental framework. By comparing electroencephalography (EEG) responses to seen and unseen visual stimuli across three different manipulations in the same subjects, we are able to focus on overlapping neural correlates. The identification of these common features will help to isolate those NCCs that are consistent across all three experimental paradigms. By employing machine learning to the analysis of EEG data, the triangulation method represents a significant advance in identifying the neural correlates of conscious visual experience.

Disclosures: N. Fish: None. **A. Schurger:** None.

Poster

PSTR088: Distributed Neural Mechanisms of Cognition

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR088.26/M27

Topic: H.05. Working Memory

Support: NSF Grant 2050833

Title: Oculomotor and EEG signals index unique aspects of covert spatial attention.

Authors: *E. ESTER, D. VALDEZ IZQUIERDO;
Univ. of Nevada, Reno, Reno, NV

Abstract: Covert spatial attention is associated with modulations of neural signals and gaze position (i.e., microsaccades). However, studies examining interrelations these measures have reported mixed evidence, with some suggesting that neural and oculomotor measures of attention are strongly linked (e.g., Lowet et al., Neuron, 2018) and others suggesting a more tenuous link (e.g., Liu et al., Nat Comms, 2022). Here, we sought further clarity on this relationship by leveraging a well-characterized phenomenon: competition between top-down and bottom-up attention signals. We recorded EEG and high-fidelity gaze position data while participants performed a WM recall task. Participants remembered the orientations of two colored bars over a brief delay; a subsequent color cue instructed participants to recall the orientation of bar by adjusting a central probe stimulus. During 50% of experimental blocks the color of the

retrospective cue instructed participants which stimulus to recall (pro-cue blocks) while during the remaining 50% of blocks the retrospective cue instructed which stimulus to ignore (anti-cue blocks). Following earlier work, we reasoned that during pro-cue blocks top-down and bottom-up selection mechanisms are aligned, whereas during anti-cue blocks they conflict. Thus, we expected poorer memory performance during anti- vs. pro-cue blocks. We then examined whether EEG and oculomotor measures of covert spatial attention tracked performance differences across pro- and anti-cue blocks. Behavioral analyses revealed faster response times and lower recall errors during pro- vs. anti-cue blocks, and this effect was closely tracked by a well-characterized EEG measure of covert spatial attention, lateralized occipitoparietal alpha-band (8-12 Hz) activity. Analyses of concurrent gaze position recordings revealed a small but robust bias in horizontal gaze position towards the location of the task-relevant memory item shortly after the appearance of the retrospective cue. However, the latencies of these biases were similar across the pro- and anti-cue tasks. Our findings therefore further support a nuanced relationship between electrophysiological and oculomotor signals of covert spatial attention.

Disclosures: E. Ester: None. **D. Valdez Izquierdo:** None.

Poster

PSTR088: Distributed Neural Mechanisms of Cognition

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Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR088.27/M28

Topic: H.05. Working Memory

Support: R01EY028746
R01MH129042

Title: Maintenance suppression unleashes new associative memory formation from proactive interference

Authors: *Z. ZHANG, J. A. LEWIS-PEACOCK;
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Abstract: Sequential encoding of information in working memory can produce integrated associative memories, but it can also produce interference amongst the elements that can lead to memory distortions or forgetting. Despite its significance, the neural mechanisms responsible for releasing memories from proactive interference remain elusive. We investigated whether instructed suppression during the middle of sequential encoding could reduce proactive interference and thus enhance the encoding of the final item in the sequence. In an fMRI study, 18 participants (15 females) completed an ABC associative memory task, with images A (object), B (face or scene), and C (scene or face) presented sequentially. Participants were told to associate each A item with the next two items that followed. Our key manipulation pertained to the B items: following encoding of B, participants were instructed either to maintain B (i.e., keep B in mind and link it with A) or to suppress B (i.e., push B out of mind and don’t link it with A).

A baseline condition omitted the presentation of B altogether. All trials concluded with a C item that was to be linked with the preceding A item. Following a single exposure to each image sequence, memory for AB and AC associations was tested in a cued recall task. Memory cues (A images) prompted participants to recall image associates (B and C) and select the correct associate from four equally familiar probes. We hypothesized that suppression would impair AB memory and enhance AC memory, and this is precisely what we found. These findings suggest that the suppression of B items reduced proactive interference on forming AC associations. In the brain, maintenance suppression cues elicited distributed activations in frontal-parietal regions, consistent with our prior findings. Utilizing representational similarity analysis, we compared individual activation maps of the suppression operation to the group-averaged suppression map and correlated these to behavioral outcomes. Participants demonstrating more normative suppression patterns tended to forget more AB pairs. We also used multivariate pattern analysis in the ventral temporal cortex to decode the retrieval of items B and C during the memory test. Following A cues from maintenance trials, proactive interference was observed by the existence of stronger activation for item B than C. This pattern was reversed for A cues from suppression trials, indicating a reduction in proactive interference, with stronger activation for item C than B. These findings elucidate that an active memory suppression mechanism confers benefits for forming new memory associations by reducing proactive interference.

Disclosures: Z. Zhang: None. **J.A. Lewis-Peacock:** None.

Poster

PSTR089: Circuits and Neural Mechanisms of Social Cognition I

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR089.01/M29

Topic: H.06. Social Cognition

Support: NARSAD Young Investigator Grant 30029

Title: Lateral entorhinal cortex representations of social stimuli

Authors: *D. D. LESPERANCE[1], J. A. MARTINEZ CABRAL[2], L. POSANI[3], S. FUSI[4], S. A. SIEGELBAUM[5], J. LOPEZ-ROJAS[2];
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Abstract: Remembering others is an essential part of social interactions and a key to survival. This capacity, called social recognition memory, is of particular importance for an animal's ability to navigate relationships in complex societies and supports many critical aspects of an animal's life, such as maternal care, mate selection, the ability to collaborate within a group and defend resources from strangers. The hippocampus (HC), known for its contributions to spatial

and contextual memory, has also been implicated in social recognition memory in both humans and rodents. Our recent research highlights the crucial role of lateral entorhinal cortical (LEC) inputs to HC, and in particular to the HC CA2 region, in social memory. However the specific nature of the social information relayed by the LEC remains unclear. Here we expressed a calcium sensor in LEC superficial neurons projecting to dorsal HC to record neural activity in this population as the mice explored two conspecifics confined to wire cup cages in opposite corners of a rectangular arena during a series of 5 min trials. The positions of the mice were swapped in successive trials to disentangle spatial (cup position), social (mouse identity), and temporal (trial number) information. We found that LEC neurons contain significant information about the identity of explored conspecifics. Thus, a linear classifier trained on LEC neuronal activity was able to decode significantly above chance the identity of the animal being explored, independently of their degree of familiarity. In addition LEC activity could distinguish temporal and spatial information during exploration. However, spatial information (location of the conspecifics in the arena) was decoded with much less precision than social identity or trial information. These results emphasize the unique contribution of LEC neurons to social cognition and establish a foundation for further investigation into the neural circuits that underlie social recognition memory in health and disease.

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Poster

PSTR089: Circuits and Neural Mechanisms of Social Cognition I

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR089.02/M30

Topic: H.06. Social Cognition

Support: NARSAD Young Investigator Grant 30029

Title: Medial entorhinal cortex representations during social/spatial exploration

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Abstract: The hippocampus (HC), traditionally associated with spatial and contextual memory, has recently been shown to play an essential role in social memory. However, in its mnemonic role, the HC relies heavily on external inputs, particularly from the entorhinal cortex (EC), its primary source of multimodal sensory information. The EC comprises two main subdivisions: the medial (MEC) and lateral EC (LEC), which are proposed to play complementary functions.

Compared with our detailed understanding of how the MEC encodes spatial information in concert with the HC, we currently lack clarity on how the EC, through its functional interactions with the HC, and in particular the CA2 region of HC, contributes to social memory. Our recent data show that LEC, but not MEC, plays a critical role in social memory through its inputs to CA2. Moreover, in a companion abstract we show that LEC neural activity contains significant information on both social identity and the passage of time during social/spatial exploration, with a weaker representation of spatial position of the social stimuli. Here we examine whether and how MEC may represent social, temporal and spatial information during this task. As the CA2 region encodes both social and spatial information and integrates information from LEC and MEC, we hypothesized that MEC may provide information about the location of the social stimuli but not social identity. Here we expressed a calcium sensor in MEC superficial neurons projecting to dorsal HC to record neural activity in this population as the mice engaged in multiple trials of social/spatial exploration with a pair of stimulus mice confined to wire cup cages. We probed the information contained within MEC representations by asking whether a linear classifier could decode stimulus mouse identity, position, or the passage of time (trial number). We found that MEC neuron activity failed to decode social identity significantly above chance levels during exploration of either novel or familiar conspecifics. However, spatial information was highly represented in MEC neural activity, along, to a lesser degree, with temporal information. These findings underscore the distinctive functions of MEC and LEC in processing different aspects of episodic stimuli, providing insights into how these two regions may collaboratively contribute to the complex representation of episodic information in downstream HC regions.

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Poster

PSTR089: Circuits and Neural Mechanisms of Social Cognition I

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR089.03/M31

Topic: H.06. Social Cognition

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NIH U19 NS107616

Title: Functional Reorganization in the mPFC-BLA-A1 Circuit of Mice following Acute Oxytocin Administration

Authors: *D. JUNG[1,2], J. KIM[3], H.-B. HAN[4], R. C. FROEMKE[5], J. CHOI[6];
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Abstract: Oxytocin, a neuropeptide central to maternal behavior, has been shown to enhance sensory processing and increase the salience of important cues such as infant crying (Valtcheva and Issa et al., Nature 2023). However, little is known about the mesoscopic neural dynamics underlying these effects or whether oxytocin-induced changes in social brain circuitry vary depending on the task or occur from resting-state conditions. To address this gap, we examined the effects on intraperitoneal administration of oxytocin on mouse local field potentials (LFPs) during three conditions: during resting-state, playback of pup distress calls, and maternal behavior. Our results revealed that oxytocin induced an immediate and sustained decrease in broad band power across all recorded regions: the medial prefrontal cortex (mPFC), basolateral amygdala (BLA), and auditory cortex (A1). Despite this overall decrease, we observed an increase in functional connectivity, particularly in the theta band (2-5 Hz) in BLA and gamma power (30-40 Hz) in mPFC. Moreover, during playback of pup distress calls, event-related potential (ERP) analysis revealed differential modulation of regions, with increased ERPs in A1 but decreased ERP amplitudes in BLA. These results suggest that oxytocin may decrease local neuronal firing rates while reconfiguring neural circuits, potentially enhancing information transfer efficiency, by modulating mPFC and BLA activity in response to social cues.

Disclosures: D. Jung: A. Employment/Salary (full or part-time):; Korea Institute of Science and Technology. **J. Kim:** None. **H. Han:** None. **R.C. Froemke:** None. **J. Choi:** A. Employment/Salary (full or part-time):; Korea Institute of Science and Technology.

Poster

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Program #/Poster #: PSTR089.04/M32

Topic: H.06. Social Cognition

Support: KIST intramural grant 2N74510
KIST intramural grant 2E32901

Title: Length distinguishes the significance of syllables in mouse ultrasonic communication

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Abstract: Although more and more studies suggest important role of ultrasonic vocalization (USV) in mouse social communication, it has been unclear which feature of USV syllables acts as a distinctive feature that differentiate the significance of syllables in their communication. Previously defined syllable classes failed in showing clear behavioral relevance. In search of a syllable property that provides a criteria for behaviorally, physically and neurologically

meaningful division of mouse social signals, current study took a multimodal approach where courtship behavior was monitored while measuring breathing and brain signals. Over 20,000 syllables were detected from 18 male-female encounters. First looking at the distributions of syllable acoustic properties, syllable length exhibited a bimodal distribution, while other distributions were unimodal. Dimensionality reduction analyses showed that syllables are separable into two groups when their position and spectrotemporal modulation within the breathing cycle were taken into account. We therefore classified the detected syllables as either 'long' or 'short.' Physiologically, only syllables in the long class were found to linearly extend the length of exhalation, suggesting active suppression of inhalation during the production of long syllables. In terms of behavioral context, long syllables prominently occurred during close, face-to-face interaction. In order to monitor real-time brain activity during social communication, the CBRAIN telemetry system was utilized to measure the LFP activities from nucleus accumbens (NAc) of male and female mice. Frequency of beta (24-32 Hz) bursts in both sexes highly increased during social interaction, especially during vocalization. In addition, beta burst activity was positively correlated with the occurrence rate of long syllables. Finally, information theoretic measures suggest increased information flow between male and female LFP signals during vocal communication, followed by behavioral consequences such as increased probability of approaching and mating. This study suggests that mice are able to employ distinct vocal units, distinguished by their length, to signify social intent. Furthermore, ultrasonic communication is found to facilitate fast information transmission between the brains of social partners.

Disclosures: G. Lee: None. **K. Lee:** None. **J. Lee:** None. **J. Choi:** None.

Poster

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Support: KIST intramural grant (2N74510)
KIST intramural grant (2E32901)
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Title: Collective foraging dynamics in mice: unraveling the link between neural activity in the emergence of workers and freeriders

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Abstract: This study investigates the foraging behaviors of mice cohabiting with a predatory robot, exploring how individual differences arise during collective action for public goods. We designed a naturalistic foraging paradigm allowing the mouse to decide whether to work or freeride to obtain a snack from the robot, and conducted 50 to 162 trials spanning five to fourteen consecutive days in five different groups (five to ten mice per group). In a solitary foraging condition, mice did not show any individual difference in acting latencies, however, mice acted differently with the others in a group condition: Some mice acted as a worker by succeeding the food retrieval, some participated but did not work, and some neither work nor participated in the foraging. We referred these mice as worker, participant, and freerider, respectively. As the trials were repeated, we observed that the worker's job was concentrated on a single mouse, showing an increase in the working rate from 19.8% to 69.6% after one week. Conversely, the freeriding ratios increased for all participating mice, with the freeriding rate rising from 39.3% to 60.6% after one week. The work imbalance was estimated based on work contribution and food consumption, showing the Gini coefficient of 0.53 ± 0.06. Tube, open field, elevated plus maze, and Y-maze tests showed that all top-tier workers were from middle class and the work contribution did not alter the social dominance. We investigated the neural activities of individual mice using our recently developed CBRAIN telemetry (Kim et al., Sci Adv, 2020) recording the medial prefrontal cortex (mPFC), nucleus accumbens (NAc), and basolateral amygdala (BLA). Spectral power analysis revealed a significant elevation in the β band (24—32 Hz) in workers compared to others, while a significant decrease in γ band (70—90 Hz) of working mice compared to participating mice. We further analyzed the dynamic network constructed by co-occurring oscillatory bursts. We observed that working is associated with frequent occurrences of local β BLA, β PFC — β NAc, and β PFC — β NAc— β BLA, and freeriding mice showed a high rate of γ PFC compared to workers and participants. A directed phase lagging index showed that in the worker's brain, the β bursts drive from PFC to BLA. In summary, our novel behavioral paradigms provide an opportunity to study collective actions in groups of mice. We found that imbalances in group distribution can occur, and that the β network and flow within the mPFC-NAc-BLA underlie the individually distinct behaviors observed.

Disclosures: J. Lee: None. **G. Lee:** None. **S. Kim:** None. **J. Choi:** None.

Poster

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Support: NIH grant MH100029
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NIH grant MH086633
NIH grant U54 HD079124
Emory National Primate Research Center Base Grant OD P51OD011132

Title: The effects of maternal care quality on social development of rhesus monkeys and its underlying neurobiology

Authors: *B. NATENZON[1], S. SEEWALD[1], Z. KOVACS-BALINT[1], S. E. SAAVEDRA[1], T. JONESTELLER[1], E. R. SIEBERT[1], R. VLASOVA[2], M. A. STYNER[2], J. RAPER[1], J. BACHEVALIER[1], M. SANCHEZ[1];
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Abstract: Rhesus monkeys (RM) serve as a non-human primate model to understand typical and atypical social development in humans, including neurobiological mechanisms of Autism Spectrum Disorder social deficits. Our previous studies focusing on the development of social brain networks in infant RM up to 24wks (equivalent to 2yrs in humans) indicated that the social affiliation and attention networks experience significant structural growth in parallel to an increase in exploration, independence from the mother and social play. Here, we investigated how early maternal care (birth-12wks) shapes social competency during the juvenile period (1yr of age) and its underlying neurobiological mechanisms. T1 and T2-weighted structural MRI scans were acquired in 13 juvenile rhesus at 1yr of age to examine maturation of regions in the of social salience and affiliation/reward neural networks, including the amygdala (Amy), anterior cingulate cortex (ACC), insula (INS) and nucleus accumbens (NAcc). Spearman correlations examined associations between maternal care during infancy and juvenile social behavior and maturation of social brain regions. Maternal care was examined through focal observations with species-specific ethograms and an Instrument of Macaque Maternal Care (IMMC). Juvenile social behavior was also measured using focal observations/ethograms (main behaviors studied: contact, proximity, social vs. solitary play, anxiety behaviors) and the juvenile macaque Social Responsiveness Scale (jmSRS). Mother-infant contact at 2wks was associated with increased juvenile social contact (rho= 0.580, p= 0.048), reduced impairments in social interactions/play (jmSRS rho= -0.629, p= 0.028), and reduced repetitive/stereotypic and odd behaviors (jmSRS rho= -0.606, p= 0.037). Maternal responsivity at 4wks showed a trend towards positive correlation with ACC size (rho= 0.564, p= 0.056) and was also negatively correlated with juvenile atypical/awkward social communication/responses (rho= -0.581, p= 0.047). A consistent trend towards positive correlation was found between mother-infant contact at 12wks and right ACC volume (rho= 0.538, p= 0.058). Our study shows that early positive maternal care predicts competent social behaviors and structural maturation of social brain networks in juvenile rhesus, particularly the ACC. This is consistent with reports in the literature indicating a strong role of the ACC in social interactions, social decision-making and during encoding social reward. We are currently analyzing the associations between maternal care and the developmental trajectory of social affiliation brain areas from birth up to 1yr of age.

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Poster

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Title: Developmental trajectories of brain social attentional networks in infant rhesus monkeys: A structural MRI study

Authors: S. GINSBERG[1], Z. A. KOVACS-BALINT[1], S. SAAVEDRA[1], C. DE HOYOS, Jr.[1], B. NATENZON[1], R. VLASOVA[2], M. A. STYNER[2], *M. SANCHEZ[1], J. BACHEVALIER[1]; [1]Emory Univ., Atlanta, GA; [2]Univ. of North Carolina at Chapel Hill, Chapel Hill, NC

Abstract: Attention to social visual cues is critical for primates to navigate in the complex structures of their societies. This cognitive skill emerges early in life and refines from childhood to adolescence, but the maturation of brain networks mediating these skills is still poorly understood. We used a translational nonhuman primate (NHP) model to map volumetric changes in cortical areas of the primary and extrastriate visual cortex (V1, V3), and those along the ventral attentional pathway mediating covert visual attention -temporal parietal junction (TPJ) and ventrolateral prefrontal cortex (vlPFC)-, and the dorsal attentional pathway mediating overt attention -the lateral inferior parietal area (LIP) and frontal eye field (FEF)-. Seventeen newborn male rhesus macaques (*Macaca mulatta*) living with their mothers in large social groups received T1- and T2-weighted structural MRI scans longitudinally between 2-24 weeks of age (~ first 2 years in humans). When corrected for individual differences in intracranial volume, most cortical areas showed significant volume increases across ages for left and right hemispheres: Age effects for visual areas V1 ($F_{(5,70)}$=16.768; p=7.342E-11; $F_{5,70}$=15.820; p=2.113E-10), and V3 ($F_{5,70}$=12.233; p=1.561E-8; $F_{5,70}$=2.651; p=0.030), for posterior areas of the attentional pathways TPJ ($F_{5,70}$=10.208; p=2.25E-7, $F_{5,70}$=7.378; p=1.32E-5) and LIP ($F_{5,70}$=28.234; p=1.51E-15; $F_{5,70}$=3.883; p=0.004), but not for the anterior areas vlPFC (p=0.298, p=0.207) or FEF (p=0.140, p=0.182). Also, most of the cortical areas showed a sharp volume increase from Week 2 to Weeks 6-8 in both hemispheres (Bonferroni tests for L and R: p=1.89E-7, p=2.77E-6 for V1; p=1.25E-4, p=0.003 for V3; p=4.53E-4, p=0.04 for TPJ and p=0.036, p=0.01 for LIP), but not for the most anterior areas (p=0.298, p=0.207 for vlPFC ; p=0.140, p=0.182 for FEF). These cortical maturational changes parallel those reported in earlier histological (Rakic et al., 1986. *Science*: 232), electrophysiological (Rodman et al., 1993, *J Neurophysiol*: 70), neuroimaging (Kovacs-Balint et al., 2021, *Dev Cog Neurosci*: 48) and metabolic (Distler et al., 1996, *Cereb Cort*: 6) studies and may support the early emergence of attention to social visual cues in primate infancy in parallel with the emergence of social engagement milestones. Similarities between cortical growth reported in infant monkeys and that in human infants (Knickmeyer et al., 2008, *J Neurosci*: 28; Gilmore et al., 2012, *Cereb Cort*: 22) provide foundational information necessary to build NHP models of human neurodevelopmental

disorders that present with disruption of attention to social cues, such as Autism Spectrum Disorder.

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Poster

PSTR089: Circuits and Neural Mechanisms of Social Cognition I

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR089.08/M36

Topic: H.06. Social Cognition

Title: Empathic deficits in a rat model of schizophrenia

Authors: *R. TACHIHARA[1,2], M. TOYOSHIMA[1,3], T. XIONG[1,2], K. IGARASHI[1,2], M. HORI[1,3], K. YAMADA[1,3];
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Abstract: Schizophrenia is a serious psychiatric disorder accompanied by social dysfunctions, including loss of empathic abilities. Despite its severity, there is no effective treatment for social dysfunctions due to incomplete understanding of their pathological mechanisms. Here, we aim to gain insight into those mechanisms by using a rat model of schizophrenia. Sprague-Dawley rat pups were used as subjects. To establish the schizophrenia model, they were subcutaneously injected with either saline (Control) or MK-801 (Low: 0.2 mg/kg; High: 0.4 mg/kg) twice per day from postnatal day (PND) 7 to 20. A behavioral test for the assessment of emotion-discrimination abilities was conducted from PND 56. The subjects were exposed to two conspecifics, one of which was distressed and the other was non-distressed, then approaching behaviors toward each conspecific were measured. Rats in the Control and MK-Low groups demonstrated a preference for distressed conspecifics over the non-distressed ones, whereas the MK-High group exhibited no preference. These results suggest that emotion-discrimination abilities are impaired in the MK-High group.Since the causal relationships between abnormal phenotypes and cortical hyperexcitability are reported in animal models of schizophrenia, emotion-discrimination deficits observed here would also be attributed to the overexcitability in the brain. To verify this hypothesis, we observed the effects of diazepam, an anxiolytic agent with efficacy in inhibition of the central nervous system, on emotion discrimination. Consistently, the MK-High group did not approach the distressed conspecific after a vehicle treatment. However, following the diazepam treatment, they approached the distressed conspecific, suggesting that diazepam ameliorates emotion-discrimination deficits of the High group. Subsequently, we examined whether DREADDs inhibition of pyramidal neurons in the prelimbic cortex (PrL), a brain region deeply involved in social cognition, alleviates emotion-discrimination deficits in the model rats. The MK-High group with the PrL inhibition tended to

approach the distressed conspecifics, which could implicate that cortical overexcitability led to empathic deficits. Our data potentially support the hypothesis that negative symptoms of schizophrenia are due to cortical overexcitability. We are now observing abnormal behavioral expressions toward a distressed conspecific in the one-on-one social interaction in the MK model and will examine whether the cortical overexcitability also contributes to these behavioral abnormalities through diazepam treatments and DREADD inhibitions of the PrL.

Disclosures: R. Tachihara: None. **M. Toyoshima:** None. **T. Xiong:** None. **K. Igarashi:** None. **M. Hori:** None. **K. Yamada:** None.

Poster

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Topic: H.06. Social Cognition

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Title: Empathy for Nausea in Rats: Behavioral and Neural Mechanisms of Social Affective Responses to Distressed Conspecifics Treated with Lithium Chloride

Authors: *M. TOYOSHIMA, R. TACHIHARA, T. XIONG, A. CHIBA, P. DURVE, M. HORI, K. YAMADA;
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Abstract: Empathy is defined as the ability to understand and share the feelings of another. It involves cognitive processes influenced by the affective states of others and an individual's response to another's sentiments. Empathy-like behaviors, such as emotional contagion, empathic concern, and consolation, have been observed across various mammalian species, including rodents. Notably, distinct facial expression patterns associated with emotional states like fear, pain, and nausea have been demonstrated in mice. Furthermore, rodents tend to avoid fear-expressed conspecifics, yet approach those in pain, with different neural circuits regulating these emotional contagions. These observations suggest that behavioral and neural responses in empathic contexts vary based on the distressed states of oneself and others. However, compared to empathy for fear or pain, behavioral and neural responses to the nauseous state of others remain unexplored. We have established that rats exhibit empathy-like behaviors toward sex-matched unfamiliar conspecifics injected with the emetogenic agent lithium chloride (LiCl). Our initial experiment confirmed that rats preferentially approach LiCl-treated conspecifics over those treated with saline, indicating that rats can recognize and respond to the nauseous state in others. In the one-on-one social interaction paradigm, rats frequently engaged in sniffing and grooming the head region of LiCl-treated conspecifics more than those in the saline control group, suggesting a characteristic response to the others' nauseous states. These behaviors seem

to be achieved through olfactory signals, as rats consistently preferred the body odors of distressed conspecifics. According to immunostaining, clear differences in Fos expressions in the prefrontal cortex have not been found between rats encountering saline- and LiCl-treated partners. Our current studies are focusing on the involvement of specific brain regions and cell types in empathy-like behaviors, as well as social preference and consolable allogrooming behaviors toward opposite-sex distressed conspecifics.

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Poster

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Topic: H.06. Social Cognition

Support: Endowed Scholar Program: UT System
National Institute of Mental Health Grant R01MH120134
National Institute of Mental Health Grant R01MH125916

Title: Roles of mediodorsal thalamus on observational fear-responding activity in anterior cingulate cortex

Authors: *K. RAMESH[1], I. R. NAIR[1], J. I. TERRANOVA[2], N. YAMAMOTO[3], S. K. OGAWA[4], T. KITAMURA[4];
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Abstract: The ability to vicariously experience another's fearful situation, a process called observational fear (OF), is critical for survival in nature. It has been shown that the anterior cingulate cortex (ACC) and basolateral amygdala (BLA) are crucial for the expression of OF. A subset of neurons in the anterior cingulate cortex represents emotional mirror neuron-like activity; these neurons fire when observing aversive shock in the demonstrator and also when directly experiencing shock. Our previous study demonstrated that optogenetic inhibition of ACC-BLA pathways during shock moments suppresses OF. These results suggest that shock-responding activity in ACC neurons may be crucial for OF. However, the neural circuit mechanisms underlying the generation of shock-responding activity remain unknown. Previous studies showed that the mediodorsal thalamus (MD) is crucial for OF, and MD neurons project to the ACC. Therefore, we hypothesize that the MD-ACC projection facilitates the shock-responding activity in the ACC, which could trigger OF. To test this hypothesis, we expressed GCaMP6f in the ACC and eNpHR3.0-mCherry in the MD using AAV infection and implanted a GRIN lens into the ACC to monitor calcium activity in the ACC during OF. Our preliminary

data showed that a subset of ACC neurons are activated during the shock moment or immediately after shock. We also observed that optogenetic inhibition of the MD-ACC projection partially affected the activity of these shock-responding neurons. Our data suggests that the MD-ACC projection may play a role in OF-related activity in ACC neurons, which could facilitate the OF response.

Disclosures: K. Ramesh: None. **I.R. Nair:** None. **J.I. Terranova:** None. **N. Yamamoto:** None. **S.K. Ogawa:** None. **T. Kitamura:** None.

Poster

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Topic: H.06. Social Cognition

Support: Endowed Scholar Program: UT System
National Institute of Mental Health, R01MH120134
National Institute of Mental Health, R01MH125916

Title: Egocentric Coding of Geometric Features in the Anterior Cingulate Cortex

Authors: *I. R. NAIR[1], K. RAMESH[1], S. K. OGAWA[1,2], T. KITAMURA[1,2,3];
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Abstract: Animals perform action as a motor output in the self-perspective. For this to happen, the allocentric spatial map is transformed into an egocentric spatial map, and is then used by the animals to perform motor action by the secondary motor cortex (M2). Retrosplenial Cortex (RSC) is implicated in the transformation of allocentric to egocentric framework. However, it remains unclear how the information in the egocentric map is transformed for action. Anatomical studies have shown that Anterior Cingulate Cortex (ACC) receives input from RSC and is projected to M2 and is responsive to objects and social cues. These results suggest that ACC could be the site for map to action transformation. Therefore, we hypothesize that ACC could encode a wide variety of geometric features in egocentric fashion. To study the representational schema of the ACC, we expressed GCaMP6f in the ACC neurons using AAV infection and implanted a GRIN lens to monitor calcium activity in the ACC during spatial navigation. Our preliminary data showed that a subset of ACC neurons encode border, convex and concave corners, doors to the compartment, object and social cue. We also observed that a majority of such geometry-encoding cells exhibits egocentric response. Our data suggests that the ACC is potentially acting as a gateway to successful motor output by representing geometric features on the environment and the objects in an egocentric fashion, much like a contour map which provides a ‘birds eye view’ of the space to the animal.

Disclosures: I.R. Nair: None. **K. Ramesh:** None. **S.K. Ogawa:** None. **T. Kitamura:** None.

Poster

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Alfred P. Sloan Foundation, Sloan Research Fellowship FG-2019-11758

Title: Strategic turn-taking is supported by multi-timescale cortical computations in primates

Authors: *S. AHMADI, K. HAROUSH;
Stanford Univ., Stanford, CA

Abstract: Key to building and maintaining long-term relationships is the ability to coordinate conflicting individual preferences over repeated interactions to attain goals favorable to both parties. Such turn taking is a primary building block of social bonds and our societies, and its disruption is detrimental for relationships and is prevalent across mental health disorders. Despite their importance, the underlying neuronal mechanism for such long-timescale flexible strategic decision making remains unknown. Here, we designed a novel neurophysiology task that assesses for the first time strategic coordination of conflicting individual preferences, drawing on the iterated battle of the sexes (iBOS) game. Under the iBOS payoff matrix, in consecutive trials, monkeys can work together to coordinate on a player's distinct preference, which is inherently suboptimal to the other player, or both receive the least possible reward if they miscoordinate. Thus, both players can achieve high reward by a series of alternating coordinated choices on each player's preferred option. We hypothesized that such turn taking involves computations on at least three timescales. First, players should predict each of the opponent's choices to be able to coordinate. Second, players should track the recent outcomes to anticipate or bargain for turn-switching. Third, across hundreds of interactions, players should track the cumulative outcome of prior interactions to adapt to any inequities as they arise. We recorded hundreds of neurons in the dorsal anterior cingulate cortex (dACC) while pairs of rhesus macaques played iBOS. Monkeys systematically took turns to coordinate choices in significantly long trial sequences. Neuronal activity accurately predicted behavior on multiple timescales: First, on instantaneous timescale of single trials, dACC neurons preferentially distinguished between the two conflicting coordinated outcomes than other task variables. Second, on minutes-long timescale, we found "bout-counter" neurons that tracked the number of interactions within the current turn and other neurons that predicted when a turn terminated, thus

linking neural activity with behavior. Third, on the hours-long timescale, many neurons closely tracked the difference between the players' total payoff over hundreds of trials, integrating all past interactions. Remarkably, when dACC tracking precision diminished, monkeys were more likely to default to their preferred choice. Our results are the first demonstration of neural computations tracking multiple behavioral history timescales to resolve conflicting social preferences by turn taking in non-human primates.

Disclosures: S. Ahmadi: None. **K. Haroush:** None.

Poster

PSTR089: Circuits and Neural Mechanisms of Social Cognition I

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR089.13/N1

Topic: H.06. Social Cognition

Support: ZIAMH002498

Title: Investigation of the Fasciola Cinereum, absent in BTBR mice, and comparison with hippocampal area CA2

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Abstract: The arginine vasopressin 1b receptor (Avpr1b) plays an important role in social behaviors including social learning, memory, and aggression, and is known to be a specific marker for the cornu ammonis area 2 (CA2) regions of the hippocampus. The fasciola cinereum (FC) is an anatomical region in which Avpr1b expressing neurons are prominent, but the functional roles of the FC have yet to be investigated. Surprisingly, the FC is absent in the inbred BTBR T+tf/J (BTBR) mouse strain used to study core behavioral deficits of autism. Here, we characterized and compare transcriptomic expression profiles using single nuclei RNA sequencing and identify 7 different subpopulations and heterogeneity within the dCA2 and FC. *Mef2c*, involved in autism spectrum disorder, is more highly expressed in the FC. Using Hiplex *in situ* hybridization, we examined the neuroanatomical locations of these subpopulations in the proximal and distal regions of the hippocampus. Anterograde tracing of Avpr1b neurons specific for the FC showed projections to the induseum griseum, dCA2, lacunosum molecular layer of CA1, dorsal fornix, septofibrial nuclei, and intermediate lateral septum (iLS). In contrast to the dCA2, inhibition of Avpr1b neurons in the FC by the inhibitory DREADD system during behavior testing does not impair social memory. We performed single nuclei RNA sequencing in dCA2 region and compared between BTBR and WT mice. We found that transcriptomic profiles of dCA2 neurons between BTBR and WT mice are very similar as they did not form any unique clusters, yet we found there were differentially expressed genes between the dCA2s of BTBR and WT mice. Overall, this is a comprehensive study of the comparison of Avpr1b neuronal

subpopulations between the FC and dCA2.The fact that FC is absent in BTBR mice, a mouse model for autism spectrum disorder, suggests that the FC may play a role in understanding neuropsychiatric disease.

Disclosures: S. Lee: None. **S. Williams:** None. **W.S. Young:** None.

Poster

PSTR089: Circuits and Neural Mechanisms of Social Cognition I

Location: MCP Hall A

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Topic: H.06. Social Cognition

Support: Simons Collaboration on Plasticity and the Aging Brain
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Brain & Behavior Research Foundation Young Investigator Award
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Title: Adult hippocampal neurogenesis reconfigures CA3/CA2 inhibitory microcircuitry and network properties to enhance social recognition memory.

Authors: A. CHUNG[1,2,3,4], ***J. B. ALIPIO**[2,3,4], L. M. EVANS[2,3,4], M. GHOSH[5], S. M. MILLER[2,3,4], T. D. GOODE[2,3,4], O. J. AHMED[6], A. SAHAY[2,3,4];
[1]Bio and Brain Engin., Korea Advanced Inst. for Sci. and Technol., Deajeon, Korea, Republic of; [2]Massachusetts Gen. Hospital, Harvard Med. Sch., Boston, MA; [3]Harvard Stem Cell Inst., Cambridge, MA; [4]BROAD Inst. of Harvard and MIT, Cambridge, MA; [5]Psychology, [6]Dept. of Psychology, Univ. of Michigan, Ann Arbor, MI

Abstract: Social recognition memory is critical for adaptive social behavior. Social experiences are thought to be encoded in dentate gyrus-CA3/CA2 hippocampal circuits and consolidated in hippocampal-prefrontal networks. The dentate gyrus is host to the generation of adult-born dentate granule cells (abDGCs) throughout life. Prior work has implicated abDGCs in learning and memory; however, the circuit and network mechanisms by which abDGCs contribute to social recognition memory are poorly understood. Here, we demonstrate that genetic expansion of an age-matched population of 4-week-old abDGCs in adult mice improves social recognition memory in a social memory interference task. Genetic expansion of 4-week-old abDGCs increased parvalbumin inhibitory interneuron (PV IN) perisomatic contacts onto CA3/CA2. Chemogenetic inhibition of INs in CA3/CA2 during social cue encoding, impaired social recognition in mice with expanded reservoir of abDGCs. Conversely, selective chemogenetic activation of PV INs in CA3/CA2 in wild-type mice was sufficient to decrease memory

interference and enhance social recognition memory. To determine how genetic expansion of abDGCs influence DG-CA3/CA2 inhibitory microcircuitry, we conducted *ex vivo* patch-clamp recordings of spontaneous synaptic events and optically evoked transmission from adult mice with or without 4- and 8-week-old abDGC expansion. Genetic expansion of 4-week-old abDGCs increased the frequency of excitatory vesicle release upon CA3/CA2 PV INs and increased the frequency of inhibitory vesicle release upon CA3/CA2 pyramidal neurons. Opto-evoked transmission along the mossy fiber pathway revealed an increase in feed-forward inhibition onto CA2 pyramidal neurons. To understand how abDGC-dependent changes in inhibitory circuitry affects DG-CA2-CA1 network properties, we recorded *in vivo* local field potentials using multi-channel linear microelectrode arrays in DG, CA1, and CA2 before and after genetic expansion of abDGC population. Mice with a genetically expanded population of abDGCs exhibited increased CA1 sharp-wave ripple (SWR) power and reduced DG gamma range (30-100Hz) oscillatory neural activity during non-REM sleep. These findings provide insights into how young, abDGCs in the dentate gyrus reconfigure inhibitory circuitry and network properties to enhance social information processing.

Disclosures: A. Chung: None. **J.B. Alipio:** None. **L.M. Evans:** None. **M. Ghosh:** None. **S.M. Miller:** None. **T.D. Goode:** None. **O.J. Ahmed:** None. **A. Sahay:** None.

Poster

PSTR089: Circuits and Neural Mechanisms of Social Cognition I

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR089.15/N3

Topic: H.06. Social Cognition

Support: The Owens Family Foundation

Title: Microglial-mediated perineuronal net accumulation in the hippocampal CA2 region coincides with social memory impairments

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[1]Neurosci., [2]Univ. of Virginia, Charlottesville, VA; [3]Neurosci., Univ. of Virginia Neurosci. Program, Charlottesville, VA

Abstract: Social memory abilities are necessary for healthy social relationships and adaptive social interactions, with its dysfunction being a feature of many different disorders. While often overlooked, rodent studies indicate that the hippocampal CA2 region and its connecting regions form a unique circuit that is critical for social memory. One structural distinction of the CA2 is that it has a high abundance of perineuronal nets (PNNs), condensed extracellular matrix structures that ensheath particular neurons and regulate their plasticity. Our previous work showed that CA2 PNN disruption impaired social memory, and restoring CA2 PNN levels in a mouse model of social dysfunction improved social memory. While this suggests that PNNs may serve as a potential therapeutic target for social memory, the specific cellular and molecular

processes that regulate CA2 PNNs are unknown. Microglia, the brain's resident macrophages, participate in the structural remodeling of the extracellular matrix, including PNNs. In the current work, we fed mice pexidartinib (PLX3397) to pharmacologically inhibit colony-stimulating factor 1 receptor, effectively depleting microglia. In mice lacking microglia, we observed social memory impairments such that they were unable to distinguish between novel and familiar conspecifics. Although we did not find differences in the chondroitin sulfate proteoglycan aggrecan, an essential PNN component, we observed increased intensity of *Wisteria floribunda agglutinin* (WFA), which labels the glycosaminoglycan chains attached to chondroitin sulfate proteoglycans, in the CA2 after microglial depletion. This indicates that microglial elimination causes an accumulation of some, but not all, PNN components. Using WFA, we then examined PNNs in other hippocampal regions implicated in social memory and found no overt changes in mice lacking microglia, suggesting that the CA2 may be more vulnerable to microglial-mediated PNN remodeling. Next, we investigated whether repopulation of microglia reverses CA2 PNN accumulation. After cessation of the PLX3397 diet, we found that restoration of microglial numbers coincided with a reduction of WFA+ PNN intensity in the CA2 to control levels. Ongoing studies are exploring whether alterations in microglial reactivity mediate PNN abundance.

Disclosures: S. Lee: None. **B. Sanchez:** None. **E.C. Cope:** None.

Poster

PSTR089: Circuits and Neural Mechanisms of Social Cognition I

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Program #/Poster #: PSTR089.16/N4

Topic: H.06. Social Cognition

Support: NIMH 1R01 MH118631-01

Title: Parvalbumin+ interneurons in hippocampal area CA2 mediate associations between social experience and place

Authors: *R. S. CLEIN, S. H. WANG, E. GOULD;
Princeton Univ., Princeton, NJ

Abstract: The CA2 region of the hippocampus is essential for processing social information and updating existing representations about an animal's social environment. While previous work examining CA2 involvement in social information processing has largely focused on pyramidal cells (e.g., Hitti & Siegelbaum, 2014), CA2 contains a high proportion of parvalbumin positive (PV+) interneurons (Botcher et al., 2014), which have been less well-studied. Across the hippocampus, PV+ cells regulate neuronal activity in support of network oscillations and mnemonic function by modulating temporal coding of contextual information (Cardin, 2018). However, the role of PV+ cells in linking novel contextual information with social experiences remains unknown. To that end, we used chemogenetic, behavioral, and histological approaches

to investigate the role of PV+ cells in processing social experiences. Adult male and female Pvalb-IRES-Cre mice received bilateral injections of either control virus or inhibitory DREADD virus targeting the dorsal CA2. Viral-mediated inhibition of CA2 PV+ cells after CNO treatment was verified with CA2-specific immunolabeling and staining for phosphorylation of pyruvate dehydrogenase, an inverse activity marker (Yang et al., 2024). To assess the behavioral effects of PV+ inhibition, we administered a battery of behavioral tests after either CNO or vehicle administration to probe non-social memory, social novelty preference, and both long and short-term social recognition. While CA2-targeted PV+ inhibition did not disrupt long-term (24 hour) non-social memory, Gi-DREADD mice treated with CNO (Gi+CNO mice) had impaired long-term social recognition memory. After serial exposures to novel and familiar mice separated by short (10 minute) inter-trial-intervals, Gi+CNO mice also exhibited blunted responses to novel mice. We also implemented a social place preference paradigm to directly assess the contribution of PV+ activity in binding social stimuli with other environmental features. While control mice exhibited a preference for a chamber paired with social stimuli after four days of training, Gi+CNO mice had no such preference, suggesting that Gi+CNO mice are unable to associate social experiences with place. Taken together, our findings suggest that CA2 PV+ interneuron activity mediates long-term social recognition and social place preference. Ongoing and future investigation will probe the mechanistic underpinnings of CA2 PV+ interneuron involvement in the encoding, consolidation, and retrieval of context-dependent social memories.

Disclosures: R.S. Clein: None. **S.H. Wang:** None. **E. Gould:** None.

Poster

PSTR089: Circuits and Neural Mechanisms of Social Cognition I

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Program #/Poster #: PSTR089.17/N5

Topic: H.06. Social Cognition

Support: R01AG083841

Title: Chronic unpredictable stress-induced impairment of short and long-term social recognition memory is mediated by the ventral hippocampus-medial PFC pathway

Authors: *M. MALEK[1,2], Y. LEI[3], X.-Y. LU[3];
[1]Dept. of Neurosci. and Regenerative Med., Augusta, GA; [2]Medical College of Georgia At Augusta University, Augusta, GA; [3]Med. Col. of Georgia At Augusta Univ., Augusta, GA

Abstract: Social interaction plays a crucial role in fostering connections, promoting empathy, and enhancing well-being. Conversely, chronic stress exposure attenuates social motivation and disrupts social interactions across a spectrum of sociability tests. Rodents exhibit the ability to discern between individual social targets, demonstrated by their preference for exploring novel individuals over familiar ones, a phenomenon termed social recognition or social memory. To investigate both short- and long-term social memory in mice, we developed a novel social

paradigm. Utilizing this paradigm, we examined the role of the ventral hippocampus (vHIP)-medial prefrontal cortex (mPFC) pathway in regulating social recognition under basal and chronic stress conditions. Our findings indicate that chronic unpredictable stress (CUS) impairs both short- and long-term social memory. The combination of Cre-dependent DREADDs with the retrograde viral vector Cav2-Cre injected in an output region permits projection-specific circuit manipulation. We injected retrograde CAV2-Cre into the mPFC and Cre-dependent hM3D(Gq) or hM4D(Gi) into the vHIP to specifically target the vHIP-mPFC pathway. Activation of the vHIP (CA1)-mPFC circuit was able to reverse CUS-induced impairment in social memory without affecting novel object recognition, locomotor activity, or anxiety levels. On the other hand, inhibition of the vHIP (CA1)-mPFC circuit impaired social memory in non-stressed mice without significant effects on novel object recognition, spatial memory, locomotion, and anxiety behaviors. These results suggest that chronic stress-induced impairment in short- and long-term social memory is mediated by suppressing the activity of the vHIP (CA1)-mPFC circuit.

Disclosures: M. Malek: None. **Y. Lei:** None. **X. Lu:** None.

Poster

PSTR089: Circuits and Neural Mechanisms of Social Cognition I

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Program #/Poster #: PSTR089.18/N6

Topic: H.06. Social Cognition

Support: CBP Grant 2021ZD0202802
NSFC Grant 81961128024

Title: Post-weaning social isolation impairs the orbitofrontal cortical circuit subserving contagious pain < consolation in mice

Authors: *Y. GONG[1], M.-G. LIU[2], T.-L. XU[1,3];
[1]Dept. of Anat. and Physiol., Shanghai Jiao Tong Univ. Sch. of Med., Shanghai, China; [2]Inst. of Mental Hlth. and Drug Discovery, Oujiang Lab., Wenzhou, China; [3]Songjiang Res. Institute, Songjiang Hospital, Shanghai Jiao Tong Univ. Sch. of Med., Shanghai, China

Abstract: Empathy is an evolutionary behavior associated with the ability to feel, recognize, understand and share the affective states of others. The formation and expression of empathic behaviors are particularly vulnerable to several environmental insults, such as early life adversity. However, the neural mechanisms still remain poorly understood. In this study, we used a variety of techniques, including behavioral testing, immunohistochemistry, chemogenetics, *in vivo* fiber photometry, and whole-cell patch-clamp, to investigate whether post-weaning social isolation (SI) affects empathic behaviors and the underlying neural mechanisms. Here, we report that SI causes significant empathic deficits in terms of either contagious pain or other-directed consolation, such as allogrooming and allolicking, when the

mice are allowed to interact with the cagemates experiencing severe pain. Distress-induced empathic behaviors lead to activation of the orbitofrontal cortex (OFC) pyramidal neurons and the input from ventromedial thalamus (VM), while SI induces profound hypoexcitability of OFC neurons and blunted synaptic transmission of the VM→OFC circuit. Chemogenetic inhibition of either OFC pyramidal neurons or VM→OFC circuit attenuated emotional contagion of pain and consolation in group-housed mice, whereas chemogenetically enhancing the excitability of OFC or VM→OFC circuit rescued the impaired empathic behaviors in SI mice. Taken together, our findings reveal an important neural mechanism underlying SI-induced empathic deficits and provide a viable therapeutic strategy for treating neuropsychiatric disorders associated with the deterioration of empathy.

Disclosures: Y. Gong: None. **M. Liu:** None. **T. Xu:** None.

Poster

PSTR089: Circuits and Neural Mechanisms of Social Cognition I

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Topic: H.06. Social Cognition

Support: Key Program of Natural Science Foundation of Zhejiang Province (LZ20C090001)
National Natural Science Foundation of China (32271090)

Title: Neural and behavioral correlates of the external-internal structures of social working memory

Authors: *H. PAN[1], Z. CHEN[1], N. XU[1], B. WANG[1], Y. HU[1], H. ZHOU[1], A. PERRY[2], X. KONG[3], Z. GAO[1];
[1]Zhejiang Univ., Hangzhou, China; [2]Hebrew Univ. of Jerusalem, Jerusalem, Israel; [3]Dept. of Psychological and Behaviroal Sci., Zhejiang Univ., Hangzhou, China

Abstract: Social working memory (SWM)—the ability to maintain and manipulate social information in the brain—plays a crucial functional role in social interactions. Despite its complexity, research on SWM is still in its infancy and the intrinsic structure of SWM has remained elusive, hindering our comprehensive understanding of this essential ability. Our study utilized converging neural and behavioral approaches to empirically test the external-internal structure of SWM that conceptualize SWM as two relatively autonomous components: externally oriented SWM (e-SWM) and internally oriented SWM (i-SWM). To uncovered distinct patterns of brain activity and functional associations of e-SWM and i-SWM, we adopted a modified ranking working memory task with fMRI scans and an empathic accuracy task (N=35). Specifically, univariate fMRI analyses showed that e-SWM engaged regions involved in processing visual, motor, and emotional information, while i-SWM activated brain areas associated with mentalizing. Multivariate pattern analyses further highlighted the distinct

activation patterns in the dorsal medial prefrontal cortex, as well as a distinct joint pattern of 11 SWM-specific regions, that differentiated the two SWM components. Additionally, correlation analyses with the Neurosynth maps covering 123 mental processes suggest the activation maps of e-SWM and i-SWM correlate most with externally oriented processes and internally oriented processes respectively. Furthermore, partial least squares analyses demonstrated that e-SWM brain activity was primarily associated with affective empathy, while i-SWM activity was linked to cognitive empathy, underscoring the divergent functional roles of these SWM components in social abilities. Together, these findings provide novel data on distinguishable neural and behavioral correlates of e-SWM and i-SWM, supporting the external-internal dichotomy of SWM.

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Poster

PSTR089: Circuits and Neural Mechanisms of Social Cognition I

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR089.20/N8

Topic: H.06. Social Cognition

Title: Moral conviction interacts with metacognitive ability to modulate neural activity during social decision-making

Authors: *Q. CAO, M. S. COHEN, J. DECETY;
Univ. of Chicago, Chicago, IL

Abstract: The extent to which a belief is rooted in one's sense of morality has significant societal implications. While such moral convictions can inspire positive collective action, they can also prompt dogmatism, intolerance, societal divisions, and violent collective actions (Decety, 2024). These strong and radical opinions may be reinforced by a cognitive style that includes low metacognitive sensitivity (Rollwage & Fleming, 2021; Yoder & Decety, 2022). There has been extensive work in social psychology about the characteristics of moral convictions. However, their neural mechanisms, how they are incorporated into the valuation and decision-making process, and how these mechanisms interact with metacognitive sensitivity remain poorly understood. These questions were specifically examined in the current study. Prior to functional MRI scanning, participants rated their levels of moral conviction and support for 40 sociopolitical issues and then completed a perceptual confidence task to assess their metacognitive sensitivity (Fleming & Lau, 2014). During scanning, on each trial, participants (N = 44, 27 females; Age range 18 – 48 years; $M_{age} \pm SD_{age}$: 22.27 ± 5.06) chose which of two groups of political protesters they supported more. As predicted, stronger moral conviction was related to faster response times. Hemodynamic response in regions including the anterior insula (aINS), anterior cingulate cortex (ACC), lateral prefrontal cortex (lPFC) was elevated during decisions involving issues with higher moral conviction. The lPFC is hypothesized to reflect the

cognitive aspects of identifying a topic as morally convicted, while aINS and ACC are hypothesized to reflect the emotional salience of morally convicted topics. Metacognitive sensitivity negatively correlated with parametric effects of moral conviction on hemodynamic response, particularly in lPFC, providing a potential neural correlate for how metacognition influences processing of morally convicted topics. Finally, brain regions involved in valuation, specifically ventromedial prefrontal cortex (vmPFC) and amygdala, were associated with mean support rating of the protesters but not with moral conviction. At the same time, functional connectivity between the lPFC and vmPFC was elevated during decisions involving high levels of moral conviction. These findings suggest that information related to moral conviction is represented in the valuation circuit, but in a more complex manner. These findings support the role of both emotional and cognitive dimensions of moral conviction and shed light on the mechanisms through which moral conviction is incorporated into social decision-making.

Disclosures: Q. Cao: None. **M.S. Cohen:** None. **J. Decety:** None.

Poster

PSTR089: Circuits and Neural Mechanisms of Social Cognition I

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Program #/Poster #: PSTR089.21/N9

Topic: H.06. Social Cognition

Support: NSF Award #1707408
U01 NS122124
U01 NS126050

Title: Accelerated social representational drift in the nucleus accumbens in a model of autism

Authors: *P. ZHAO, A. BELLAFARD, D. AHARONI, P. GOLSHANI;
Neurol., UCLA, Los Angeles, CA

Abstract: Impaired social interaction is one of the core deficits of autism spectrum disorder (ASD) and may result from social interactions being less rewarding. How the nucleus accumbens (NAc), as a key hub of reward circuitry, encodes social interaction and whether these representations are altered in ASD remain poorly understood. We identified NAc ensembles encoding social interactions in mice by performing calcium imaging using miniaturized microscopy. NAc population activity, specifically D1 receptor-expressing medium spiny neurons (D1-MSNs) activity robustly encoded social interaction epochs. NAc-based decoders showed higher performance than decoders trained with medial prefrontal cortex (mPFC) or dorsal hippocampal CA1 (dCA1) activity. Surprisingly, non-specific optogenetic inhibition of NAc core neurons increased social interaction time. Inhibition of D1-or D2-MSNs showed reciprocal effects, with D1 inhibition decreasing social interaction and D2 inhibition increasing social interaction, indicating a causal role for NAc neurons in regulating sociability. To determine the stability of the social representation, we recorded from the same NAc neurons over 6 days.

Despite a high turnover of NAc neurons modulated by social interaction, we found a stable long-term population social code in NAc which was dramatically degraded in Cntnap2$^{-/-}$ mouse model of ASD but not in Shank3B$^{-/-}$ mouse model although both models showed social deficits including early adaptation and delayed initiation, respectively. Impaired sociability in Cntnap2$^{-/-}$ mice was significantly improved by optogenetic inhibition of NAc, suggesting NAc modulation could potentially serve a therapeutic role for social interaction deficits. Therefore, social interactions are preferentially, specifically and dynamically encoded by NAc neurons and social representations are degraded in Cntnap2 mouse model of autism. Furthermore, cell-type specific modulation of NAc may play a critical role for regulating social interactions in multiple disorders where these interactions are affected.

Disclosures: P. Zhao: None. **A. Bellafard:** None. **D. Aharoni:** None. **P. Golshani:** None.

Poster

PSTR089: Circuits and Neural Mechanisms of Social Cognition I

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR089.22/N10

Topic: H.06. Social Cognition

Title: The multi-stage plasticity in the aggression circuit underlying the winner effect

Authors: *R. YAN[1], D. WEI[1], A. VARSHNEYA[1], L. SHAN[1], H. ASENCIO III[1], D. LIN[2,1]; [1]NYU langone medical center, New York, NY; [2]New York Univ. Neurosci. & Physiol., New York, NY

Abstract: Aggression is a natural behavior found in various animal species, serving crucial purposes such as competing for food, defending territory, securing mates, and protecting families and oneself. While aggression is often instinctual and not learned, its expression can vary significantly among individuals within the same species, including those with similar genetic backgrounds like inbred mice. Individual differences in aggression can be influenced by prior experiences, with winning and losing previous encounters playing a significant role. In insects, reptiles, birds, and mammals, numerous studies have shown that winning experience leads to heightened aggression, readiness to attack and an increased probability of winning, a phenomenon referred to as the “winner effect”. Here, we reveal a transition from target-specific to generalized aggression enhancement over 10 days of winning in male mice, which is supported by three stages of plasticity in the ventrolateral part of the ventromedial hypothalamus (VMHvl), a critical node for aggression. Over 10-day winning, VMHvl cells experience monotonic potentiation of long-range excitatory inputs, a transient local connectivity strengthening, and a delayed excitability increase. These plasticity events are causally linked. Optogenetically coactivating the posterior amygdala (PA) terminals and VMHvl cells potentiates the PA-VMHvl pathway and triggers the cascade of plasticity events as those during repeated winning. Optogenetically blocking PA-VMHvl synaptic potentiation eliminates all winning-induced plasticity. These results reveal the complex Hebbian synaptic and excitability plasticity

in the aggression circuit during winning that ultimately leads to an increase in “aggressiveness” in repeated winners.

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Poster

PSTR089: Circuits and Neural Mechanisms of Social Cognition I

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Topic: H.06. Social Cognition

Support: NextGenerationEU Project Project IR0000023, CUP B53C22001810006, SEE-LIFE
Project COoperation and BRAin-Synchrony: a multiscale and translable approach CUP B53D23026560001

Title: An experimental platform to conduct hyperscanning studies in awake freely moving mice

Authors: *A. SCAGLIONE[1], J. LUCCHESI[1], G. BARBERA[2], A. ALLEGRA MASCARO[3], F. T. RESTA[4], D.-T. LIN[2], F. S. PAVONE[5];
[1]Univ. di Firenze, Firenze, Italy; [2]NIH, Natl. Inst. On Drug Abuse, Baltimore, MD; [3]Neurosci. Inst., Natl. Res. Council, Pisa, Italy; [4]LENS - European Lab. for Non-Linear Spectroscopy, CNR-INO, Florence, Italy; [5]LENS, Sesto Fiorentino, Italy

Abstract: Social interaction entails complex behavior based on the reciprocal interchange of information among interacting individuals. Identifying the neural correlates of social behavior requires monitoring the brains of socially interacting peers while observing their behavior. While such studies have almost uniquely been conducted in humans at a macroscale level, they have only recently been extended to other animal models by monitoring the neural activity of small portions of the cortex. Since many cortical processes rely on distributed brain networks encompassing a wide portion of the cortex, we designed an experimental platform that allows us to perform hyperscanning studies at the macroscale level in awake freely moving mice. By taking advantage of recent developments in optical methods, we developed a miniaturized wide-field microscope, “MiCe-µScope”, capable of monitoring neural activity over almost the entire dorsal surface of the cortex. By comparing our miniaturized scope with a conventional fluorescence microscope in GCaMP6f mice, we show that the MiCe-µScope is capable of capturing both the hemodynamic and the fluorescence signals associated with neuronal activation. We employed our platform to characterize the cortical dynamics underlying social interaction and natural exploration. Our results suggest the emergence of a shared network of cortical areas related to social behaviors. We believe that using this platform to study social interaction generates an invaluable tool to investigate the cortical processes of social behavior beyond individual brains.

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Poster

PSTR089: Circuits and Neural Mechanisms of Social Cognition I

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Topic: H.06. Social Cognition

Support: NIH Grant R01 AG076937
NIH Grant R01 MH134776

Title: The Dynamic Conflictome: Brain-wide Changes in Functional Circuitries Revealed at Different Stages of Chronic Social Conflict

Authors: *E. M. AMELCHENKO[1], D. SMAGIN[2], S. SHUVAEV[3], N. N. KUDRYAVTSEVA[2], A. KOULAKOV[3], G. N. ENIKOLOPOV[1];
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Abstract: Social conflict, and its resolution is evolutionary conserved adaptive mechanism that allows to establish social roles in a group, and at the same time ensures a degree of flexibility of group's structure. Successful acts of aggression may be rewarding, with a series of wins increasing aggressive motivation and propensity to engage in aggressive behavior. Contributing to the plasticity of the group's structure, encounters between animals of comparable status may alter the group's hierarchy and the status of the engaged animals. The interplay between stability and flexibility of social behavior is expected to be defined by stability and flexibility of the underlying neural circuitry. However, little is known about brain-wide architecture, characteristic features, and plasticity of distributed networks involved in social conflict. Here we addressed these questions through a large-throughput production, analysis, and comparison of 3D maps of activated (c-Fos expressing) neurons in a mouse model of social conflict. Male C57Bl/6 mice were trained in a chronic social conflict model. Mice were pair-housed in the cage separated by a transparent perforated partition. The partition was removed for 10 min daily to allow agonistic interactions between the animals. We generated cohorts of experienced winner and loser mice (after 3, 10, and 20 days of agonistic interactions), fight-deprived experienced mice, and mice following the inversion of social roles. Animal brains were processed using iDISCO+, imaged under the light-sheet microscope and postprocessed using ClearMap pipeline to map and analyze c-Fos expression as a proxy for neuronal activation. Mice exposed to 3, 10 or 20 days of agonistic interactions showed increased aggressive motivation. We also found an increased aggressiveness in fight-deprived winners and rapid inversion of social role in the new social environment. Next, we established a whole-brain c-Fos response matrix of the regions with increased and decreased activity in aggressive/defeated groups. Based on the data of co-varying

activity across different brain regions, we formed a global inter-region connectivity graph and identified brain regions with hub-like properties. We then established cluster-based activity "signatures" unique to the behavioral groups and described the dynamic of activity in these clusters under different behavioral conditions. We also tested *in silico,* which brain regions are critically important for the establishment of a particular behavioral phenotype. Finally, we applied *in vivo* chemogenetics to demonstrate that manipulation of a particular area is capable of altering behavior in aggressive mice.

Disclosures: E.M. Amelchenko: None. **D. Smagin:** None. **S. Shuvaev:** None. **N.N. Kudryavtseva:** None. **A. Koulakov:** None. **G.N. Enikolopov:** None.

Poster

PSTR090: Human LTM: Encoding and Retrieval I

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR090.01/N13

Topic: H.07. Long-Term Memory

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NIH (R01MH129426)

Title: Multidimensional encoding of visual attention and objects in the primate brain

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Abstract: Visual attention and object recognition are two critical cognitive functions that significantly influence our perception of the world. Although deep convolutional neural networks (DCNNs) are currently the best model for object recognition, and their similarity with the primate's intermediate and higher ventral visual stream areas in the representation of complex naturalistic stimuli has been revealed, how this representation interacts with attentional control during active vision remains largely unclear. Here, we systematically investigated the intricate interplay between visual attention and object feature coding by training macaques to perform a free-gaze visual search task categorizing natural face and object stimuli and recording more than 10,000 units from visual and frontal brain areas. We found that the activities of 18.1%, 31.76%, 11.96%, and 3.15% of units in V4, TE, TEO, and OFC respectively, were a linear readout of DCNN features of the images. We discovered that units exhibiting such visual feature coding displayed a distinct attentional response profile and functional connectivity compared to units not exhibiting feature coding. Attention directed towards search targets modulated the responses of neurons not only by affecting the average firing rates, but also by changing the geometry of the

high-dimensional neural population, which enhanced the pattern separation of stimuli across brain areas. Notably, this enhancement was more pronounced for units encoding visual features. Our findings suggest two stages of neural processing, with the early stage primarily focused on processing visual features and the late stage dedicated to processing attention. Importantly, feature coding in the early stage could predict the attentional effect in the late stage. Together, our results suggest an intricate interplay between visual feature and attention coding in the primate brain, which can be attributed to the differential functional connectivity and neural networks engaged in these processes.

Disclosures: J. Zhang: None. **R. Cao:** None. **X. Zhu:** None. **H. Zhou:** None. **S. Wang:** None.

Poster

PSTR090: Human LTM: Encoding and Retrieval I

Location: MCP Hall A

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NIH/NINDS (R21-NS128307)
NIH/NIMH (R01-MH120194)

Title: Language processing by single neurons in the human amygdala and hippocampus

Authors: *Y. WANG[1], R. CAO[1], J. T. WILLIE[2,3], P. BRUNNER[4,3], S. WANG[1]; [1]Washington Univ. in St.Louis, St. Louis, MO; [2]Neurolog. Surgery, Sch. of Med., Saint Louis, MO; [3]National Center for Adaptive Neurotechnologies, St. Louis, MO; [4]Dept. of Neurosurg., Washington Univ., St. Louis, MO

Abstract: Language processing represents a pivotal pursuit in cognitive neuroscience. Recent strides in neural recording techniques have facilitated the exploration of language-related processes at the granular level of individual neurons. However, it remains unclear whether and how neurons in the human amygdala and hippocampus, all brain areas critical for semantic analysis, are involved in linguistic processing. In this study, we recorded single-neuron activity from patients with intractable epilepsy using microelectrodes implanted in the amygdala and hippocampus while the patients performed a series of language tasks. First, using a visual language localizer task where patients were presented with 6 consecutive words and non-words

that formed sentences, we found that a subset of amygdala and hippocampal neurons was selective to words but not to non-words. Notably, the majority of these word-selective neurons also exhibited tuning to specific words. Second, using an auditory language localizer task where patients listened to the phonetics of words and non-words, we confirmed word-selectivity and tuning to specific words in the amygdala and hippocampus. Third, patients listened to short sentences from the TIMIT stimulus set, and we used the SBERT model to tokenize the embeddings of each sentence and a principal component analysis (PCA) to extract the components that explained the majority of the variance in sentence structures. We found that neurons in the amygdala and hippocampus not only represented sentence structures but also clustered the sentences based on semantics. Our findings illuminate that the linguistic embedding space adeptly encapsulates both semantic content and emotional nuances. We delve into how these brain structures, conventionally linked with emotional processing and memory consolidation, intricately contribute to language comprehension, production, and semantic analysis. Through scrutinizing the firing patterns of individual neurons during language tasks, we unveil the nuanced contributions of the amygdala and hippocampus to various linguistic functions.

Disclosures: Y. Wang: None. **R. Cao:** None. **J.T. Willie:** None. **P. Brunner:** None. **S. Wang:** None.

Poster

PSTR090: Human LTM: Encoding and Retrieval I

Location: MCP Hall A

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Program #/Poster #: PSTR090.03/N15

Topic: H.07. Long-Term Memory

Support: AFOSR (FA9550-21-1-0088)
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Title: Neuronal dynamics during free-gaze visual memory recall in the human medial temporal lobe

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Abstract: The medial temporal lobe (MTL) plays a crucial role in visual memory formation. It facilitates the encoding and consolidating of information that can be retrieved later to support

recall. What computations underlie these functions? To study this, we had 10 human neurosurgical subjects with micro depth-electrodes implanted in the MTL complete a visual memory recall task with high-resolution eye tracking. Subjects were shown a random sequence of natural scene images for 3 seconds each. Within a session, 50 images would be repeated twice. Subjects judged whether they had seen each scene before with 3 confidence levels (low, medium, and high). While they performed this task, we simultaneously monitored their gaze and recorded responses from single neurons from the bilateral amygdala and hippocampus. Using a comprehensive salience analysis, we showed that MTL neurons encode salience across the pixel, object, and semantic levels, with faces being the most preferred category for around 33% of the 788 neurons recorded across observers and sessions. Furthermore, during repeated viewing, around 40% of the neurons also signaled consistency of gaze sampling by firing at a significantly higher rate when an observer sampled a previously fixated location than a novel location. The strength of the match response depended on image memorability at the fixated locations, such that more memorable locations showed a stronger modulation of neuronal responses. The overall modulation of neuronal responses due to the match between encoded and incoming visual information predicted the observer's recall decision. Finally, we observed both flexible and invariant encoding of visual information between encoding and recall in MTL neurons. Our results demonstrate a possible mechanism by which MTL neurons support visual memory recall: by signaling a match between previously sampled information and the incoming visual information.

Disclosures: P.N. Chakravarthula: None. **R. Cao:** None. **P. Brunner:** None. **J.T. Willie:** None. **N.J. Brandmeir:** None. **S. Wang:** None.

Poster

PSTR090: Human LTM: Encoding and Retrieval I

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McDonnell Center for Systems Neuroscience
Fondazione Neurone

Title: Single-neuron Activity and Saccade-modulated Neural Oscillation during Memory Retrieval in the Human Medial Temporal Lobe

Authors: *Y. LI[1,2,3,5], G. TAN[1,2,3,5], Z. LI[1,2,3,5], J. R. SWIFT[2,3,5], K. L. WAHLSTROM[6], C. S. INMAN[6], S. WANG[4,1], J. T. WILLIE[2,1,3,5], P. BRUNNER[2,1,3,5];
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Abstract: The medial temporal lobe (MTL) plays a crucial role in declarative memory. Systems-level patterns of successful memory encoding and retrieval have been well described in the human brain. Single-neuron recordings provide unprecedented opportunities to study the neural processes underlying memory in the human brain. Microelectrodes are implanted into the brain in epileptic patients undergoing clinically indicated stereo-electroencephalography monitoring. We recorded local field potentials (LFPs) and single-unit activity (SUA) from the hippocampus and amygdala in fourteen patients while they performed a declarative memory task that contained separate encoding and retrieval phases. During the encoding session, patients memorized a sequence of images. During the retrieval session, patients were presented with the images from the encoding session as well as a set of new images and were asked to discriminate between recognized and unrecognized images. In addition to LFPs and SUA, we recorded gaze and pupillometry throughout the experiment. Eye movements reflect prior exposure to new visual stimuli and have been associated with hippocampal activity. Recent studies have shown that the spike patterns of single units predict saccades in the primate hippocampus. In our study, we determined saccade modulation of neural firing. To accomplish this, we aligned neural firing with saccade onset and applied a template-matching procedure to the activity of each neuron. In our analysis, we were interested in identifying SUA related to memory processes. For this purpose, we analyzed the neural activity during old and new images in retrieval sessions. Specifically, we determined the difference in neural responses between recognized and unrecognized images. We found four populations of neuronal cells: 1) cells tuned to the old images irrespective of subjects' awareness of the image type; 2) cells tuned to the unrecognized and new images; 3) cells tuned when subjects failed to correctly recognize old images; and 4) cells tuned to saccades irrespective of memory conditions. We found populations 1-3 to be distinct, while population 4 overlaps with populations 1-3, and the overlap among these populations indicates multiplexing processes. In summary, we identified four populations of neurons in the human hippocampus and amygdala associated with memory retrieval and gaze.

Disclosures: Y. Li: None. **G. Tan:** None. **Z. Li:** None. **J.R. Swift:** None. **K.L. Wahlstrom:** None. **C.S. Inman:** None. **S. Wang:** None. **J.T. Willie:** None. **P. Brunner:** None.

Poster

PSTR090: Human LTM: Encoding and Retrieval I

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR090.05/N17

Topic: H.07. Long-Term Memory

Title: Differential effects of slow versus fast theta-burst patterned rTMS on hippocampal-cortical network activity measured via concurrent TMS-fMRI

Authors: *T. BROWN[1], M. S. HERMILLER[2];
[1]Florida State Univ., Tallahassee, FL; [2]Psychology, Florida State Univ., Tallahassee, FL

Abstract: The hippocampus supports episodic memory via interactions with a distributed brain network. Neural activity from regions of this network synchronize at theta frequencies, providing a possible mechanism of interregional communication and coordination. Prior research using network-targeted noninvasive transcranial magnetic stimulation (TMS) has demonstrated episodic memory enhancements and modulation of activity in the hippocampal network. We previously (Hermiller et al., 2020, J Neuro) used concurrent TMS-MRI to show immediate encoding-related hippocampal activation in response to theta-burst patterned TMS volleys delivered to the left parietal cortical node of the hippocampal-cortical network. Notably, our prior experiment used 5-Hz theta-burst volleys to engage the hippocampus. Here, we build upon our previous work to also deliver slow (3-Hz) and fast (8-Hz) theta-burst volleys to test for immediate and differential effects downstream (i.e., not at the local stimulation site) in the hippocampus and surrounding medial temporal lobe. Research in rodents suggests the presence of prominent Type 2 (slower frequencies; ~3-7 Hz) versus Type 1 (faster frequencies; ~7-12 Hz) theta along the ventral versus dorsal hippocampus, respectively. Thus, we hypothesized that slow versus fast theta-burst volleys would cause a differential effect along the longitudinal axis of the human hippocampus. To accommodate the theta-burst volley's timing, we developed a novel MRI scan sequence to accommodate 2-sec volleys of 3-Hz and 8-Hz theta-burst TMS volleys. During the encoding phase of an episodic memory task, TMS was delivered immediately prior to stimulus (complex outdoor visual scenes) presentation concurrent with fMRI. Slow theta was delivered for a third of the trials, fast theta was delivered for a third of the trials, and the remaining trials had no stimulation. We found robust fMRI correlates of encoding-related activity due to theta-burst stimulation, replicating our previous results. Additionally, we demonstrate that the human hippocampus and surrounding medial temporal lobe responded differentially to slow versus fast theta-burst volleys, with slow theta-burst having more robust effects in the anterior regions, and fast causing greater effects in the posterior regions. This suggests a direct, beneficial, and differential influence of theta-patterned TMS within the hippocampus, which may be relevant to various memory processes that may rely on slower versus fast theta rhythms. Findings may motivate future treatments using noninvasive brain stimulation to address specific memory impairments due to aberrant hippocampal and network activity.

Disclosures: T. Brown: None. **M.S. Hermiller:** None.

Poster

PSTR090: Human LTM: Encoding and Retrieval I

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR090.06/N18

Topic: H.07. Long-Term Memory

Title: Characterizing the role of scene familiarity in novelty detection and memory

Authors: *E. QUATTROCKI[1], K. N. WARREN[2], M. S. HERMILLER[3];
[1]Florida State Univ., tallahassee, FL; [2]Psychology and Neurosci., Allegheny Col., Meadville, PA; [3]Psychology, Florida State Univ., Tallahassee, FL

Abstract: You might assume that the places where you spend a lot of time - like your university campus - are stored as detailed, highly precise representations, and that you would notice if a familiar landmark was missing or had been altered. Rosenbaum and colleagues (2024) found that subjects actually perform poorly at detecting such modifications to well-known scenes, and concluded that familiar scenes may be represented at a global, gist-like level rather than a precise, fine-detailed level. We extend this work by having subjects view familiar as well as unfamiliar scenes, with modifications to the photos akin to those used by Rosenbaum et al. (e.g., changes to perceptual details, scale/dimensions, transposing an aspect, or removing a component). We also added a memory test to our paradigm, to assess the relationships between scene familiarity, modification detection, and later memory performance. Participants completed a multi-phase paradigm. In the first phase, they were shown photos from two college campuses (their own campus, and one they've never visited or seen) for 7-sec, were instructed to study the details of each photo, and rated their familiarity with each scene. In the second phase, a modified version of each campus photo was shown for 7-sec before the modification was highlighted on the screen. In the third phase, participants were shown the original photos and instructed to click on the location of the modification they previously saw. Our preliminary findings indicate replication of the Rosenbaum et al., (2024) results, such that modifications to well-known campus scenes are poorly detected, and more so than modifications in unfamiliar scenes. Notably, these findings provide supporting evidence to prominent memory theories that suggest that global, gist-like versus fine-scale, detailed-level memory representations may involve distinct cognitive processes and rely on different interactions within the hippocampal-cortical network. We also hypothesized that spatial memory for the modifications would be more precise for the familiar scenes, as the well-known photos would provide a foundation for new memories (i.e., modifications) to be bound with and integrated. Indeed, we show that participants were able to recall the location of the modification more precisely on familiar versus unfamiliar scenes. Our findings inform memory theories about long-term scene representations and how our spatial memories undergo representational transformations as they become more familiar. Further research utilizing neuroimaging and causal methods (i.e., brain stimulation) is needed to identify underlying neural mechanisms that support such transformations.

Disclosures: E. Quattrocki: None. **K.N. Warren:** None. **M.S. Hermiller:** None.

Poster

PSTR090: Human LTM: Encoding and Retrieval I

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR090.07/N19

Topic: H.07. Long-Term Memory

Support: Nathan Kline Institute internal pilot funding

Title: Modulating memory strength and hippocampal-cortical network interactions to understand consolidation processes

Authors: *M. HERMILLER[1], **M. MUNROE**[1], K. LOCKWOOD[2], L. DAVACHI[3]; [1]Florida State Univ., Tallahassee, FL; [2]Columbia Univ., New York, NY; [3]Psychology, Columbia Univ., New York, NY

Abstract: Episodic memory, the ability to recall detailed events from one's life, is a core cognitive function that contributes to decision making, social cognition and emotion regulation. Much research indicates that hippocampal interactions with distinct cortical regions (i.e., hippocampal-cortical networks, HCN) are critical for episodic memory. Here, we aim to test if modulating HCN mechanisms improves behavioral and neural measures of once presented (i.e., weak memories) and repeated associations (i.e., strong memories) during encoding. Using this paradigm, we recently found that post-encoding memory reactivation in the hippocampus did not significantly differ between events seen once versus thrice, whereas reactivation in cortical regions was significantly enhanced for repeated events versus those seen once. These findings suggest that repetition accelerates cortically-involved consolidation processes. Here, we assess if delivering transcranial magnetic stimulation (TMS) to modulate the HCN would increase post-encoding reactivation as well as retrieval reinstatement, permitting the causal testing of HCN connectivity in memory consolidation and reinstatement in this within-subjects, multi-session design. Each session begins with a pre-encoding resting-state fMRI scan, followed by an associative encoding task (word-picture pairs, half presented once, the other half presented thrice), followed by a post-encoding resting-state scan. Subjects then come out of the scanner, and theta-burst TMS is delivered either to the HCN (i.e., left parietal cortex) or an out-of-network control site (left supplemental motor area, SMA). Subjects then immediately move back into the scanner for a post-stimulation resting-state scan, and a cued-recall test. Memory retrieval accuracy was greater for repeated associations relative to those presented once. HCN stimulation increased hippocampal connectivity in the medial temporal lobe and mPFC (i.e., network-specific effects) relative to SMA stimulation, which caused widespread increases (i.e., distributed, non-specific effects). HCN stimulation also increased retrieval activity in the targeted left network regions relative to SMA stimulation. Assessing relationships between changes in network connectivity during consolidation, frequency of reactivation events, and retrieval accuracy informs our understanding of the role of hippocampal-cortical connectivity in consolidation processes for weak versus strong memories. Findings may motivate future interventions using noninvasive brain stimulation to treat memory impairments, particularly for rescuing and strengthening weak memories.

Disclosures: M. Hermiller: None. **M. Munroe:** None. **K. Lockwood:** None. **L. Davachi:** None.

Poster

PSTR090: Human LTM: Encoding and Retrieval I

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR090.08/N20

Topic: H.07. Long-Term Memory

Support: NIH Grant F31AG081045

Title: Effects of aging on semantic and episodic contributions to false memory

Authors: *I. L. MOORE, N. M. LONG;
Univ. of Virginia, Charlottesville, VA

Abstract: Healthy older adults are more likely to commit false memories than young adults. Traditional false memory paradigms leverage semantic overlap -- shared meaning -- to induce false memories, but experiences can also overlap temporally meaning that they occur close together in time. Prior work has shown that older adults have impaired episodic memory -- memory for events within a spatiotemporal context -- corresponding to an overall shift toward semantic memory and away from episodic memory across the lifespan. We hypothesize that compared to young adults, older adults rely more heavily on semantic versus temporal information, which promotes false memory. To test our hypothesis, we collected behavioral and electroencephalographic (EEG) data in young and older adults performing an old/new recognition memory task in which we manipulated the degree of semantic and temporal overlap between study words. Specifically, participants studied individual words with either one related word (weak semantic overlap) or three related words (strong semantic overlap) presented in either neighboring positions on the study list (strong temporal overlap) or separated by four intervening words (weak temporal overlap). Participants were tested on study words and critical lures -- unstudied words that semantically overlap with studied words -- and made button-press responses indicating whether each word was old or new. We measured false memory rate as a function of overlap strength and age. Our preliminary results demonstrate that young adults have a greater false memory rate for critical lures associated with weak than strong temporal overlap, however, older adults' false memory rate differs as a function of semantic, but not temporal, overlap strength. These findings suggest that older adults' shift toward semantic memory and away from episodic memory may contribute to increased susceptibility to false memory.

Disclosures: I.L. Moore: None. **N.M. Long:** None.

Poster

PSTR090: Human LTM: Encoding and Retrieval I

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR090.09/N21

Topic: H.07. Long-Term Memory

Support: UVA Brain Institute and Strategic Investment Fund

Title: Executive control deficits and memory brain state engagement in healthy aging

Authors: *H. BURAS, S. HAN, N. M. LONG;
Univ. of Virginia, Charlottesville, VA

Abstract: Healthy older adults exhibit both selective impairments in episodic memory - memory for events situated within a specific time and place - and deficits in executive function, reflected by difficulty switching between different tasks and inhibiting task-irrelevant information. Given that older adults exhibit a bias toward accessing semantic knowledge and have difficulty inhibiting retrieval of prior experiences, one potential account for episodic memory deficits in healthy aging is that older adults are biased toward retrieving when they should be encoding and cannot easily switch out of this task-irrelevant retrieval state. Our aim in the present study is to determine the extent to which stimulus processing time impacts older adult memory state engagement, with the expectation that longer compared to shorter stimulus durations will enable older adults to switch out of a task-irrelevant retrieval state and into a task-relevant encoding state. We collected scalp electroencephalography data during a mnemonic state task in which we explicitly instructed younger and older adult participants to encode or retrieve object images, and in which we manipulated the stimulus duration. We find that young adults are able to selectively engage task-relevant memory states even with decreased stimulus processing time, as evidenced by better subsequent memory for objects paired with the encode (vs. retrieve) instruction even at the shortest stimulus duration. Furthermore, using multivariate decoding of mnemonic states, we find that younger adults preferentially engage encoding vs. retrieval states in response to task instructions during the shortest stimulus duration. These initial results suggest that younger adults can quickly switch between task-relevant states. We anticipate that compared to younger adults, older adults will show task-relevant state engagement only at the longest stimulus duration.

Disclosures: H. Buras: None. **S. Han:** None. **N.M. Long:** None.

Poster

PSTR090: Human LTM: Encoding and Retrieval I

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Program #/Poster #: PSTR090.10/N22

Topic: H.07. Long-Term Memory

Support: NIH Grant R01NS132872

Title: Investigating the time course of retrieval state initiation

Authors: *S. HAN[1], N. M. LONG[2];
[1]Univ. of Virginia, Charlottesville, VA, VA; [2]Univ. of Virginia, Charlottesville, VA

Abstract: Engagement of a retrieval state (or mode) is theorized to be a precursor to successful retrieval, but precisely when the retrieval state is engaged is unclear. Our aim in the present study

is to determine the time course of retrieval state initiation. We hypothesize that the retrieval state is reactionary rather than preparatory, whereby the retrieval state is engaged following - rather than preceding - a memory probe. We collected scalp electroencephalography data during a mnemonic state task in which we explicitly instructed participants to encode or retrieve object images, and in which we manipulated the stimulus onset asynchrony (SOA) between the instruction and the stimulus onsets. Our general expectation is that whereas general preparatory mechanisms non-specific to encoding or retrieval will be engaged more during longer SOAs, specific engagement of the retrieval state will only occur after stimulus presentation and thus be unaffected by the SOA. Our preliminary behavioral results show that regardless of the SOA, retrieve instructions lead to worse memory for object stimuli. We find robust engagement of the retrieval state approximately 700 ms following stimulus onset and no evidence for selective retrieval state engagement during the instruction interval. Together, these initial findings suggest that retrieval state engagement is reactionary.

Disclosures: S. Han: None. **N.M. Long:** None.

Poster

PSTR090: Human LTM: Encoding and Retrieval I

Location: MCP Hall A

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Program #/Poster #: PSTR090.11/N23

Topic: H.07. Long-Term Memory

Support: NIH Grant F32-AG-054116
NIH Grant R01-AG-034570
Tau Consortium

Title: Sex differences in associations between sleep, memory, and Alzheimer's disease biomarkers via PET and fMRI

Authors: *H. K. BALLARD[1], L. FERGUSON[1], S. L. LEAL[2,1];
[1]Psychological Sci., William Marsh Rice Univ., Houston, TX; [2]Integrative Biol. & Physiology, Psychology, Univ. of California, Los Angeles, CA

Abstract: Given well-documented sex differences in the prevalence and severity of Alzheimer's disease, as well as normative aging outcomes, it is important to elucidate potential biological variables that may contribute to sex-specific aging trajectories in order to combat cognitive impairment and disease progression in the aging population. To this effect, we tested for sex differences among a range of associations incorporating relevant variables in these contexts, including sleep quantity (number of hours slept) and quality (subjective rating), general and detailed memory measures with emotional and 24-hour delay components, amyloid/tau pathology using PET imaging, and functional activation via fMRI during memory task performance. This study was carried out in a sample of cognitively-normal adult females and males; thus, those with active dementia or mild cognitive impairment were screened out prior to

enrollment. Through a series of stepwise linear regressions, we observed 1) sex differences in PET-derived pathology, where females presented higher amyloid and tau levels than males, 2) interactions between sleep habits and sex when predicting various domains of memory performance, though 3) null interactions between PET-derived pathology, sex, sleep habits, and memory performance when considered collectively. Upcoming comparisons with fMRI results may reveal underlying neurological contributions to the associations observed thus far. This work provides insight on the biological mechanisms that may subserve sex differences in aging outcomes, in terms of biomarkers for both normative aging and Alzheimer's disease. We suggest that the interplay between sex and sleep, in particular, may partially explain disproportionate impacts of memory impairment with older age and age-related disease in females, relative to males, though follow-up research investigating these principles with objective sleep measures may offer a more detailed perspective.

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Poster

PSTR090: Human LTM: Encoding and Retrieval I

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Topic: H.07. Long-Term Memory

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Title: Cross-cultural differences in emotional perception and memory specificity

Authors: *F. MORALES-CALVA[1], I. AHUJA[1], B. POLANCO[1], A. VELGEKAR[1], S. L. LEAL[2,1];
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Abstract: Most studies examining perception and memory include stimuli that are highly familiar to WEIRD populations. However, it is unclear if stimuli are processed similarly in different populations. To this end, we created a culturally inclusive and ecologically valid novel image set and emotional mnemonic discrimination task. We collected subjective ratings of emotional valence, emotional arousal, and lure similarity of all stimuli in a sample of Latinos and non-Latinos. The mnemonic discrimination task examines two memory measures: *target recognition*, a general memory measure for repeated items, and *lure discrimination*, a measure of how well participants discriminate similar stimuli and depends on hippocampal pattern separation. We tested this task in an independent sample of Latinos and non-Latinos. First, we

found that Latinos were more likely to focus on emotional valence, interpreting negative images as more negative and positive stimuli as more positive compared to non-Latinos. These results suggest that cultural identity may play an important role in the perception of information that may then impact subsequent memory performance. Second, we found that Latinos were significantly more likely to rate paired stimuli with overlapping features are as more similar than non-Latinos. This has important implications on memory specificity, which can be more finely captured through lure discrimination measures. Through the development of a culturally inclusive, mnemonic discrimination task, we have shown that cultural identity can impact perception and memory. Moreover, mnemonic discrimination paradigms provide a sensitive, low-cost behavioral framework to identify and examine memory within this context. Our results have important implications for cognitive and neuropsychological research, as more emphasis should be placed on considering the impact that ethnicity and culture may have on task performance.

Disclosures: F. Morales-Calva: None. **I. Ahuja:** None. **B. Polanco:** None. **A. Velgekar:** None. **S.L. Leal:** None.

Poster

PSTR090: Human LTM: Encoding and Retrieval I

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR090.13/N25

Topic: H.07. Long-Term Memory

Title: Subclinical depressive symptoms and job stress differentially impact emotional memory in working and retired older adults

Authors: *L. FERGUSON[1], A. HARIKUMAR[2], S. L. LEAL[3];
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[3]Psychological Sci., UCLA, Los Angeles, CA

Abstract: Retirement has been associated with cognitive decline beyond normal age-related decline. However, there are many individual differences in retirement that can influence cognition. Subclinical depression is common in late life after retirement and is associated with general memory decline and a bias towards remembering negative events, in opposition to a reported positivity bias in aging more broadly. Furthermore, job stress is often a major contributor in the decision to retire, which may also impact subsequent cognition post-retirement. Retirement may offer a reprieve from job stress and mitigate the detrimental impacts of work-related stressors. Alternatively, high stress jobs may require more cognitive demand, thus may serve to confer benefits toward cognition, a benefit which may be lost after retirement. Thus, the current study aimed to examine how subclinical depressive symptoms, retrospective job stress in retired, and current job stress in working older adults impacted emotional memory. We utilized an emotional mnemonic discrimination task given its sensitivity to age-related memory impairment and its inclusion of emotional and neutral stimuli, which allows for the examination

of emotional biases that may exist with increased depressive symptoms and job stress. We found that retired, but not working, older adults with higher levels of depressive symptoms showed enhanced negative and impaired positive memory. Second, we found opposing effects of job stress on memory, such that working older adults with high levels of current job stress showed better memory overall and a weaker positivity bias compared to those with low levels of current job stress, while retired older adults with high levels of retrospective job stress showed worse memory overall and a stronger positivity bias. These findings suggest that retirement status interacts with subclinical depressive symptoms and job stress and is a major driver of memory impairment in aging.

Disclosures: L. Ferguson: None. **A. Harikumar:** None. **S.L. Leal:** None.

Poster

PSTR090: Human LTM: Encoding and Retrieval I

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR090.14/N26

Topic: H.07. Long-Term Memory

Title: Post-encoding music differentially impacts general and detailed memory

Authors: *K. CLARK[1], J. BUERGLER[2], S. L. LEAL[3];
[1]Rice Univ., Houston, TX; [2]Psychological Sci., Rice Univ., Houston, TX; [3]Psychological Sci., UCLA, Los Angeles, CA

Abstract: Music often plays a role in everyday life and has the ability to elicit an emotional response across most listeners. The emotional arousal hypothesis suggests that emotional arousal leads to a release of stress hormones, which then exert their effects on the amygdala and hippocampus, brain regions involved in emotion and memory processing. As such, music may be used as a tool for modulating memory. There is a critical window of time closely following learning where emotional arousal is most effective in modulating memory consolidation, providing a framework for when music administration may be most impactful on memory. Our memory for everyday events is known as episodic memory and is processed by the hippocampus. Hippocampal pattern separation is a neural computation that supports episodic memory by reducing interference across memories with overlapping content and allows for the storage of unique events. Mnemonic discrimination tasks provide a behavioral correlate of hippocampal pattern separation and is more sensitive to changes in memory compared to standard memory tasks. Here, we aimed to examine how post-encoding music-induced emotional arousal impacts mnemonic discrimination performance. Using an individual differences approach and isolating the effects of music-induced emotional arousal on memory performance, we utilized post-encoding music administration during consolidation of a mnemonic discrimination task. We found that more drastic changes in arousal (either increased or decreased changes from baseline) in post-encoding music-induced arousal resulted in gist versus detail trade-offs in memory, with improved general memory but impaired detail memory. However, moderate arousal changes

corresponded with improved detailed memory but impaired general memory, suggesting that differential levels of optimal change in arousal target specific facets of episodic memory. These findings have important implications in developing more personalized music-related interventions for those with memory and mood impairments.

Disclosures: K. Clark: None. **J. Buergler:** None. **S.L. Leal:** None.

Poster

PSTR090: Human LTM: Encoding and Retrieval I

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR090.15/N27

Topic: H.07. Long-Term Memory

Title: Examination of antidepressant effects on emotional mnemonic discrimination and medial temporal lobe function

Authors: *M. CASTRO[1], L. FERGUSON[1], H. BALLARD[1], S. L. LEAL[2];
[1]Rice Univ., Houston, TX; [2]Psychological Sci., UCLA, Los Angeles, CA

Abstract: Antidepressants (AD) are the first-line pharmacological treatment for depression. Prior research has found that AD treatment has an impact on hippocampal function, primarily through direct neuromodulation of serotonin, dopamine, and norepinephrine receptors as well as increasing hippocampal neurogenesis. However, research on AD treatment has primarily focused on changes in mood-related symptomology even though ADs impact brain regions important for memory processing. The medial temporal lobe (MTL), which includes the hippocampus, amygdala, and surrounding cortical regions, is involved in episodic memory, or memory for events. The hippocampus can perform two key computations in support of episodic memory: pattern separation, or the ability to discriminate between representations with similar features, and pattern completion, or the ability to generalize across representations with similar features. Depression is associated with changes in mood and cognition, and prior work has found deficits in hippocampal pattern separation, amygdala hyperactivity, and corresponding changes in memory across species, in which depressed individuals tend to show a negativity bias in memory. We have developed an emotional mnemonic discrimination task that taxes the emotional modulation of hippocampal pattern separation and is particularly sensitive to depression-related cognitive dysfunction. Here, we aimed to explore whether AD treatment could rescue memory dysfunction in depression, and whether there are differential effects of AD type on emotional memory given they target different neurotransmitters. Participants underwent high-resolution fMRI during task performance of an emotional mnemonic discrimination task in individuals with diagnosed depression or currently experiencing depressive symptoms taking ADs. Behaviorally, individuals who perceived their ADs to be effective at reducing their depressive symptoms showed a reduction in the negativity bias in mnemonic discrimination as well as enhanced neutral mnemonic discrimination. Furthermore, those taking selective-serotonin reuptake inhibitors versus other types of ADs showed a selective reduction of the

negativity bias in memory, while those taking other types of ADs showed a selective enhancement in neutral mnemonic discrimination. We also examined how ADs modulate underlying medial temporal lobe function using high-resolution fMRI, with a focus on activity and connectivity between hippocampal subregions and amygdala subnuclei. These results provide important context for how ADs can provide effective treatment in those with depressive symptoms.

Disclosures: M. Castro: None. **L. Ferguson:** None. **H. Ballard:** None. **S.L. Leal:** None.

Poster

PSTR090: Human LTM: Encoding and Retrieval I

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR090.16/N28

Topic: H.07. Long-Term Memory

Title: Effects of hormonal contraceptives on emotional memory and emotion regulation

Authors: B. M. BRANDAO[1], M. CASTRO[1], J. BUERGLER[1], B. T. DENNY[1], *S. L. LEAL[2,3]; [1]Rice Univ., Houston, TX; [2]UCLA, Los Angeles, CA; [3]Rice University, Houston, TX

Abstract: Around 65% of women use contraceptives, with oral hormonal pills being the most popular. Yet, their impact on cognitive and affective processes is understudied. Previous work has shown that women using hormonal contraceptives show increased emotional valence ratings of images and memory performance for visual emotional information. These findings suggest that hormonal contraception use may affect the ability to perceive and process emotional information in women, potentially contributing to the development of mood-related disorders. The current study investigates the effects of hormonal contraceptives on emotional memory and emotion regulation. We recruited healthy female participants (ages 18-35) and who were either naturally cycling or taking hormonal contraceptives. Participants underwent an emotional mnemonic discrimination task to assess memory performance for emotional content. We also evaluated the effectiveness of emotion regulation training applied during memory encoding, focusing on cognitive reappraisal strategies such as psychological distancing (i.e., taking the perspective of an impartial observer) and reinterpretation (i.e., imagining a better outcome than what was initially apparent) in addition to control trials where participants were asked to respond naturally. Preliminary findings indicate that distancing was more effective than reinterpretation and no regulation trials in reducing negative affect. Additionally, women on hormonal contraceptives exhibited greater reactivity to negative images compared to naturally cycling women, suggesting a differential impact of contraceptive use on emotional processing. We also examined subsequent memory across groups and emotional memory conditions, taking into account menstrual cycle phase. Preliminary results show that menstrual cycle phase was associated with mnemonic discrimination but not target recognition. These results highlight the potential cognitive and emotional implications of hormonal contraceptive use. Understanding these effects is crucial for improving reproductive health choices and managing mood-related

side effects, potentially informing clinical practices and interventions aimed at improving women's health outcomes.

Disclosures: B.M. Brandao: None. **M. Castro:** None. **J. Buergler:** None. **B.T. Denny:** None. **S.L. Leal:** None.

Poster

PSTR090: Human LTM: Encoding and Retrieval I

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR090.17/N29

Topic: H.07. Long-Term Memory

Support: NIH R21AG073973-01
NIH F32AG071263-01A1
AARFD-21-852597

Title: Age-related and disease-related differences in object location memory using immersive virtual reality

Authors: *T. TRAN[1], D. F. TADEO[4,5], L. DACORRO[6,5], O. CHATZIFOTI[6], E. JOHNSON[6,5], K. NGUYEN[7,5], J. BAILENSON[6,2], A. D. WAGNER[1], H. HOSSEINI[3];
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Abstract: Object misplacement is a commonly reported clinical symptom that scales with disease severity in Alzheimer's disease. In both aging and Alzheimer's disease, patients report losing common household items, suggesting a potential role of object misplacement as a possible early indicator of Alzheimer's disease clinical symptoms. However, tracking object misplacement clinically has proven to be challenging, with typical assays involving self-report and questionnaire-based approaches or 2D screen-based learning where participants recall the location of an object on a screen. While offering some insights, these approaches do not encompass the complexity of real-world naturalistic behaviors; immersive virtual reality promises to fill this gap. In the current study, we used immersive virtual reality to investigate object misplacement in a naturalistic interactive environment with young adults, older adults, and patients with mild cognitive impairment, a transitional stage between healthy aging and Alzheimer's disease dementia. Participants encoded and retrieved the locations of objects within the environment, including a test of the precision of their object location memory. In a second task, participants' allocentric object location memory and mnemonic object discrimination tests examined object location binding and object memory specificity. Initial findings reveal age-related differences in allocentric and egocentric object location memory. Older adults also demonstrate decreased precision for object location memory compared to young adults, as well as decreased mnemonic object discrimination. Together, these findings indicate that examining

real-world behaviors in an immersive virtual reality can reveal clear age-related differences in memory performance. Ongoing work is examining the links between these cognitive changes to structural and functional magnetic resonance imaging along with plasma biofluid biomarkers of Alzheimer's disease (Aβ42:40 and pTau181) to examine the potential of immersive virtual reality to detect and track age-related and clinical symptoms of memory decline.

Disclosures: T. Tran: None. **D.F. Tadeo:** None. **O. Chatzifoti:** None. **K. Nguyen:** None. **A.D. Wagner:** None. **H. Hosseini:** None.

Poster

PSTR090: Human LTM: Encoding and Retrieval I

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR090.18/N30

Topic: H.07. Long-Term Memory

Support: NIH R01MH112357
F99 NS120644-01
T32MH065214
ONR MURI 90105642

Title: How strong is your memory palace? Reliable room representations predict subsequent memory for placed objects

Authors: *R. MASIS OBANDO[1,2], K. NORMAN[3], C. BALDASSANO[4];
[1]Johns Hopkins Univ., Baltimore, MD; [2]Princeton University, Princeton, NJ; [3]Princeton Univ., Princeton, NJ; [4]Psychology, Columbia Univ., Pelham, NY

Abstract: Real-world experiences happen at physical spatial locations. When we encode these experiences into memory, we can use our spatial map of the world to help organize these memories and later retrieve their episodic details. However, it is still not well understood what psychological and neural factors make spatial contexts an effective scaffold for storing and accessing memories. We hypothesized that a critical requirement for spatial contexts is that they must be both stable over time (to provide a consistent cue for retrieval) and distinct from other spatial context memories (to be free from interference). To test how the neural properties of a spatial context memory supports new memories, we developed a novel paradigm that allowed us to quantify the within-subject stability and distinctiveness of a spatial context ("room reliability"), which could then be used to predict later memory for episodic information occurring at this spatial location. To do this, we constructed a virtual reality (VR) "memory palace", a custom-built environment made up of 23 distinct rooms that participants (11 females and 14 males between ages 21-32) explored using a head-mounted VR display. The day after learning the layout of the environment, participants underwent whole-brain fMRI while being presented with videos of the rooms in the memory palace, allowing us to measure the reliability of the neural activity pattern associated with each room. They were taken back to VR and asked

to memorize the locations of 23 distinct objects randomly placed within each of the 23 rooms, and then returned to the scanner as they recalled the objects and the rooms in which they appeared. We found that our room reliability measure was predictive of object reinstatement across cortex, and further showed that this was driven not only by the group-level reliability of a room across participants but also the idiosyncratic reliability of rooms within each participant. Together, these results showcase how the quality of a spatial context memory can be quantified and used to 'audit' its utility as a memory scaffold for future experiences.

Disclosures: R. Masis Obando: None. **K. Norman:** None. **C. Baldassano:** None.

Poster

PSTR091: Long-Term Memory: Episodic and Episodic-Like Memory

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR091.01/N31

Topic: H.07. Long-Term Memory

Title: Dissociating episode specific and concept specific population codes in hippocampal subfields using ultra-high resolution 7T fMRI

Authors: *S. HANSLMAYR[1], E. MARCANTONI[2], J. MCDIARMID[3], F. CRABBE[1], L. HAKAJOVA[4], Y. LAZAROVA[1], A. PATON[1], M. WIMBER[5], D. BERRON[6], L. MUCKLI[7], A. FRACASSO[8];
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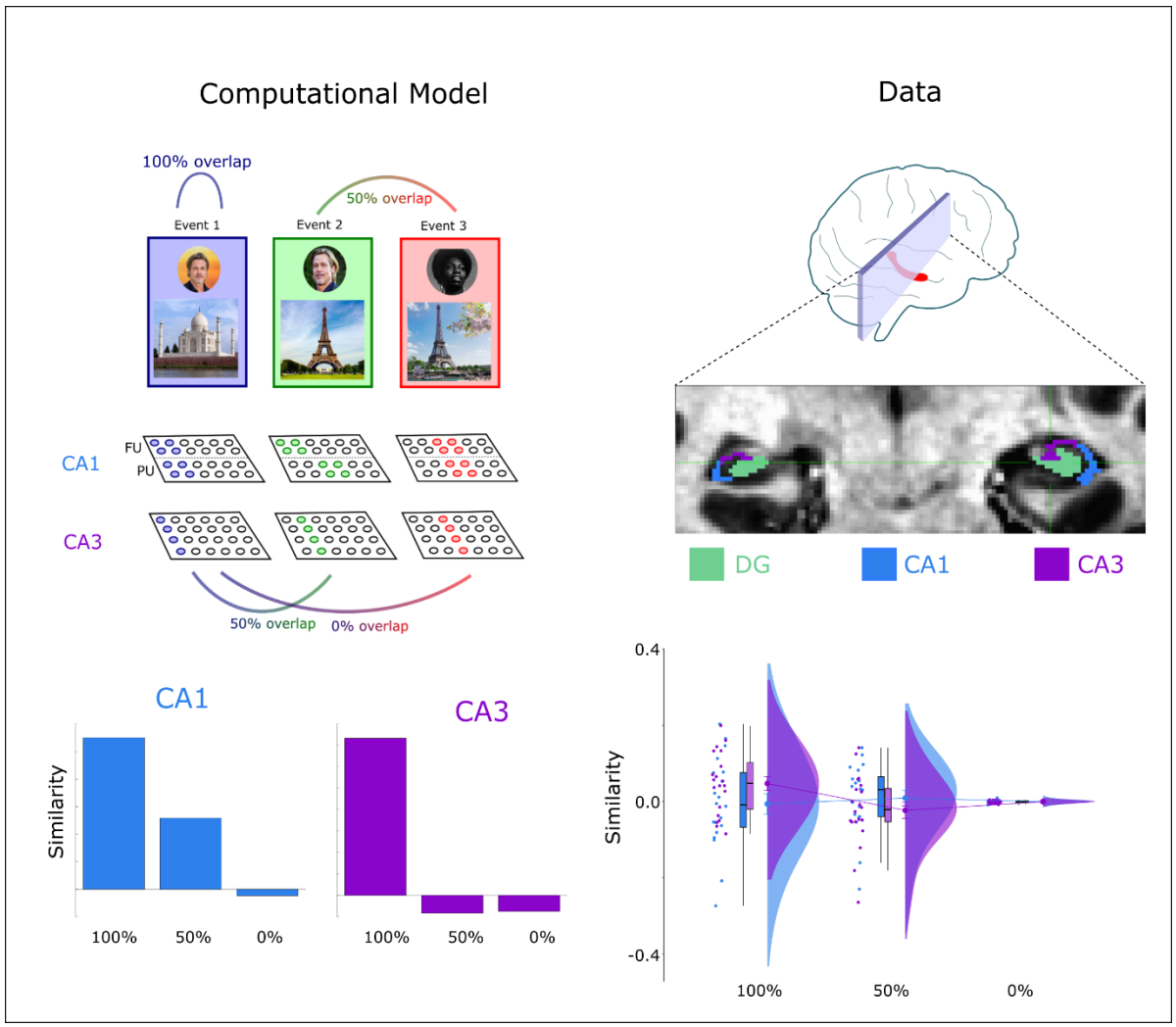
Abstract: To turn unique experiences into memory episodes the human hippocampus can rely on at least two types of neurons. Concept neurons, which store general semantic concepts, and, Episode Specific Neurons, which hold together all the elements that belong to an episode. Computational modelling suggests that these two codes map onto different subfields, with concept neurons in CA1, and episode specific neurons in CA3. We tested this prediction using high-resolution fMRI at 7 Tesla. Participants performed a memory task which required them to form single-shot associations between well-known places and faces. For each person/place two different images were used, which allowed us to compare neural similarity between identical episodes (100% overlap), different episodes but sharing the same person/place (50% overlap), and different episodes with different images (0% overlap). An episode-specific code predicts increased similarity only for identical episodes (100%) with no difference between 50% and 0% overlapping episodes. In contrast, a concept-specific code predicts a linear decrease in similarity

with decreasing overlap. We scanned 20 human neurotypical participants (mean age 25.9; range: 20-39 years; 14 female; all right-handed) and acquired high-resolution structural as well as functional images. GLM-Beta weights were extracted for hippocampal subfields to quantify neural similarity between encoding and retrieval via voxel-wise Pearson correlations. Only voxels which showed a signal variation above the 95th percentile were used for analysis. Results show a significant interaction between Overlap and Region (F2,38=5.574; p=0.0126) which was driven by a main effect of Overlap for CA3 (F2,38=4,399; p=0.032) but not CA1 (F2,38=0.14; P=0.802). In CA3, significantly higher neural similarity was found for identical (100%), compared to 50% and 0% overlapping events (p=0.0031, and 0.0402, respectively). These results are in line with episode-specific populations residing in CA3, but not in CA1.



Disclosures: S. Hanslmayr: E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Clarity Technologies. **E. Marcantoni:** None. **J. McDiarmid:** None. **F. Crabbe:** None. **L. Hakajova:** None. **Y. Lazarova:** None. **A. Paton:** None. **M. Wimber:** None. **D. Berron:** None. **L. Muckli:** None. **A. Fracasso:** None.

Poster

PSTR091: Long-Term Memory: Episodic and Episodic-Like Memory

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR091.02/N32

Topic: H.07. Long-Term Memory

Support: 1R21AG058161-01A1

Title: Understanding the mechanisms of lateral parietal memory modulation

Authors: *M. SLAYTON[1], R. E. CABEZA[1], S. W. DAVIS[2];
[1]Duke Univ., Durham, NC; [2]Duke Univ. Med. Ctr., Durham, NC

Abstract: Alzheimer's Disease (AD) is characterized by progressive impairment of cognition and memory, including the loss of episodic memory. The use of non-invasive brain stimulation therapies to modulate memory processes is a promising avenue for potential treatment. Previous studies have shown that the use of Theta-Burst Stimulation (TBS) applied to lateral parietal cortex can improve memory in older adults who have received a diagnosis of Mild Cognitive Impairment. These studies have largely relied on a systems-level explanation of efficacy, arguing that connectivity from the cortex to the hippocampus explains the TBS-related benefit. However, such explanations fail to address the underlying cortical information supporting such memory benefits. The current project seeks to address how the underlying visual and semantic information coded in the brain changes as a function of a parietal TBS over the course of three repeated TBS and subsequent neuroimaging sessions. MCI patients received six minutes of intermittent TBS immediately before a deep semantic encoding task for everyday objects while in the scanner, with post-scan conceptual and perceptual recognition memory tests. We used Representational Similarity Analysis (RSA) to evaluate whether behavioral improvements in perceptual or conceptual memory are driven by the modulation of visual or semantic information in the brain. Consistent with the role of lateral parietal cortex as a hub for the processing of abstract knowledge, we show that semantic (but not visual) representations show greater TMS-related changes and are more directly associated with improvements in conceptual memory success. We found no TMS-related benefits in visual representations or visual memory. This result clarifies the underlying mechanisms by which neuromodulation may improve episodic memory in MCI, which may lead to more reliable clinical applications of noninvasive brain stimulation in AD.

Disclosures: M. Slayton: None. **R.E. Cabeza:** None. **S.W. Davis:** None.

Poster

PSTR091: Long-Term Memory: Episodic and Episodic-Like Memory

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR091.03/N33

Topic: H.07. Long-Term Memory

Support: NIH R01MH132223

Title: Investigating memory strength and precision at recent and remote timepoints

Authors: *A. R. HOLM[1], R. T. LALUMIERE[2];
[1]Univ. of Iowa, Iowa City, IA; [2]Dept. of Psychological and Brain Sci., Univ. of Iowa, Iowa City, IA

Abstract: Associative aversive learning paradigms such as inhibitory avoidance (IA) have been frequently been used to examine episodic-like memories in rodents. Such memories exist along at least two axes: strength, or the degree of retention, and precision, or generalization vs. discrimination. In IA tasks, these dimensions can be assessed by testing the animal in the original training context and in a similar yet distinct neutral context. Evidence suggests that, at early retention tests, memories show high levels of discrimination, but at later time points, generalization occurs. The present work used male and female rats to examine how different parameters influence memory strength vs. precision at both recent (2 d) and remote (28 d) timepoints after training. The IA apparatus was a trough-shaped chamber containing a lit compartment and a darkened compartment with a retractable door between the two. During training, rats were placed into the lit compartment and permitted to cross into the dark compartment, wherein they received a single inescapable footshock (0.6 mA for 1 s). Rats then underwent 2-d and 28-d retention tests by being placed back into the original shock chamber, and latencies to cross over into the dark compartment were measured. Rats also underwent tests on those days in which they were placed in the neutral IA chamber. Longer latencies in the original chamber indicated better memory strength and differences in latencies between the two chambers reflected memory precision. Initially, we examined how keeping rats in the lit chamber during training for 10 s vs. 60 s altered subsequent tests. We also used both males and females to determine how both sexes performed in these tasks. To measure any strain-specific effects, we used both Sprague-Dawley rats (n = 47) and Long-Evans rats (n = 37). We found that both strains of rats showed significant differences in latency between the shock chamber and the neutral chamber at Day 2 retention tests, indicating discrimination at recent timepoints. By Day 28, however, there were no significant latency differences between the shock chamber and the neutral chamber for either strain, indicating generalization at remote timepoints. Additionally, the 60 s habituation condition was found to increase memory strength for the Long-Evans rats at both timepoints for both sexes. In a final experiment, we examined whether a pre-exposure to the neutral context the day before training would alter subsequent tests and found that such pre-exposure promoted generalization at both timepoints. These data provide a behavioral foundation for our ongoing studies on the neurobiological mechanisms underlying memory strength and precision in IA.

Disclosures: A.R. Holm: None. **R.T. LaLumiere:** None.

Poster

PSTR091: Long-Term Memory: Episodic and Episodic-Like Memory

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR091.04/Web Only

Topic: H.07. Long-Term Memory

Support: UNAM DGAPA PAPIIT IG300121, IG300124

Title: Effects of physical, mental, social, cultural, and passive leisure activities on episodic memory across adulthood

Authors: *S. CANSINO[1], F. TORRES-TREJO[1], C. ESTRADA MANILLA[1], S. RUIZ VELASCO ACOSTA[2];
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Abstract: The impact of leisure activities on cognition has been mainly investigated in older adults by means of composite measures of leisure activities and general measures of cognition. The majority of these studies have reported that leisure activities improve cognitive functions and even prevent cognitive impairment. However, the independent influences of each leisure activity on episodic memory across adulthood, and specifically in young, middle-aged, and older adults, have not been investigated. Therefore, the aim of the present study was to estimate the separate influence of physical, mental, social, cultural, and passive leisure activities on episodic memory in an adult lifespan sample and in the main stages of adulthood. A sample of 1,557 healthy adults between 21 and 80 years of age participated in the study. Leisure activities were assessed through a lifestyle questionnaire created for the study. Episodic memory performance was measured through a computerized task that allowed us to reliably measure recollection and recognition, the main processes within episodic memory. Physical and mental (computer use) leisure activities predicted higher recollection and recognition across adulthood. Young adults' recollection and recognition benefited from physical, mental (computer use), and social leisure activities. Middle-aged adults' recollection benefited from physical and mental (computer use) leisure activities. Only the mental leisure activity of engaging in hobbies predicted higher recollection in older adults. Although we observed that physical, mental and social leisure activities improved episodic memory processes, with advancing age, individuals tend to cease these activities.

Disclosures: S. Cansino: None. **F. Torres-Trejo:** None. **C. Estrada Manilla:** None. **S. ruiz velasco acosta:** None.

Poster

PSTR091: Long-Term Memory: Episodic and Episodic-Like Memory

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR091.05/N34

Topic: H.07. Long-Term Memory

Support: PID2021-122338NA-I00
CIDEGENT/2021/027
UJI-B2022-45)

Title: Flexible hippocampal representation of abstract boundaries supports memory-guided choice.

Authors: M. ESPOSITO, L. ABDUL PARVEEN, A. GHOUSE, M. RODRÍGUEZ ARAMENDÍA, ***R. KAPLAN**;
Univ. Jaume I, Castelló de la Plana, Spain

Abstract: Cognitive maps in the hippocampus encode the relative locations of spatial cues in an environment and dynamically adapt their representation when boundaries geometrically change. In parallel, hippocampal cognitive maps can represent abstract knowledge, yet it's unclear whether the hippocampus is sensitive to geometric changes to the borders, extreme coordinates, of abstract knowledge spaces. Here, we use a memory-guided decision making task to test whether the human hippocampus and medial prefrontal cortex(mPFC) flexibly learn abstract boundary representations in distinct two-dimensional(2D) knowledge spaces. Despite being unnecessary to accurately make decisions, participants conserve a 2D map-like representation of abstract boundaries after the task, where the precision of their representation relates to prior choice accuracy. Finding that the hippocampus and mPFC represent the Euclidean distance of a decision cue to the most proximal boundary during decision making, we then test whether there are brain regions sensitive to boundary-defined contextual changes in abstract spaces. We observe flexible hippocampal representation of abstract boundaries, where the fidelity of this representation relates to task performance. Taken together, our results highlight the importance of hippocampal boundary representations in facilitating flexible knowledge retrieval in dynamically changing abstract contexts.

Disclosures: M. Esposito: None. **L. Abdul Parveen:** None. **A. Ghouse:** None. **M. Rodríguez Aramendía:** None. **R. Kaplan:** None.

Poster

PSTR091: Long-Term Memory: Episodic and Episodic-Like Memory

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR091.06/N35

Topic: H.07. Long-Term Memory

Title: Does Recent vs. Remote Memory Differ in Post-Reactivation Malleability?

Authors: *C. M. YANG[1], K. JARDINE[2], Q. H. NGUYEN[1], S. JI[1], L. T. JIANG[1], T. AFGHANIAN[1], B. D. WINTERS[2], K. D. DUNCAN[1], M. D. BARENSE[1,3];

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Abstract: Memory reactivation can temporarily return a previously stabilized memory to a labile state in which it can be updated. However, not all memories are equally susceptible to updating upon reactivation. The literature has identified several important factors that influence the selectivity of post-reactivation memory malleability, but two factors remain theoretically controversial: the age of the memory (delay between acquisition and reactivation) and the strength of the memory at reactivation. Memory age and strength are often confounded, which potentially contributes to the inconsistent findings surrounding them. Additionally, these two factors were identified in rodent models, and how they might influence human memory remains to be elucidated. In our study, we aimed to disentangle how the age of a memory and its strength of reactivation influence its malleability in human episodic memory. We leverage prediction error (PE), or the surprising mismatch between expectation and reality, to reliably trigger memory updating in a previously established multi-day movie (Sinclair & Barense, 2018). Additionally, given that PE is mainly required to update highly stabilized memories, we infer a memory's malleability based on whether it requires PE to update. In Session 1, we showed participants a set of videos featuring salient action-outcome events. In Session 2, participants saw the videos again when they returned after one of three delays (1 hr, 24 hr, 2 weeks). Here, we elicited PE in half of the videos by abruptly interrupting the action-outcome contingency. After each video had been reactivated, participants rated the strength with which they remembered the original presentation. Immediately following this, we introduced new interfering videos. In Session 3, we conducted a structured memory interview for Session 1 videos. We operationalize memory updating as the number of details from the new interfering videos incorporated into memories for the original video. Preliminary data (n=57 of 114) suggest recent and remote memories did not differ in their post-reactivation malleability and that the strength of the memory at reactivation, rather than memory age, was the critical factor in influencing the amount of memory updating. Our study integrates theories of memory storage and updating dynamics, and we expect our final results to elucidate how these dynamics might converge or differ when translating across rodent and human memory.

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Poster

PSTR091: Long-Term Memory: Episodic and Episodic-Like Memory

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR091.07/N36

Topic: H.07. Long-Term Memory

Support: NSF Grant 1633873

Title: Dissociating content-selective and generic retrieval-related fMRI BOLD effects

Authors: *S. MONIER[1], S. SROKOVA[2], P. F. HILL[3], M. D. RUGG[4];
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Abstract: Episodic memory retrieval engages both content-selective and 'core' neural regions, the latter including the hippocampus, angular gyrus, medial prefrontal cortex, and parahippocampal gyrus. Few studies have directly assessed regional dissociations between category-selective and generic retrieval activity. Here, we investigated the extent to which content-selective and core regions are segregated during successful recollection. Young adults (N = 24) underwent fMRI while completing two phases of an associative memory task. At encoding, participants viewed words paired with either faces or scenes. At retrieval, they judged whether test words were old, and if so, whether they had been paired with a face or a scene. We report only the retrieval phase results. We first identified brain regions demonstrating significant recollection effects (greater activity for correct vs. incorrect source retrieval). To identify regions common to both face and scene recollection, we conducted a conjunction analysis, where we inclusively masked face and scene recollection effects (main contrast: $p = .005$, mask: $p < .05$). To identify category-selective recollection effects, we conducted two exclusive masking analyses (main contrast: $p = .001$, mask: $p < .05$). We exclusively masked the face recollection contrast with the scene recollection contrast to identify regions demonstrating face-selective effects. We also performed the analogous contrast to identify scene-selective effects. Content-independent and content-dependent recollection effects were spatially segregated. Regions exhibiting content-independent effects included bilateral hippocampus, left dorsal and ventral parietal cortex, left medial parahippocampal cortex and left ventral striatum. Scene-selective effects were identified in lateral parahippocampal cortex bilaterally, medial anterior occipital cortex, and left dorsolateral frontal cortex. Conversely, face recollection effects were observed in the precuneus and bilateral medial prefrontal cortex. Our findings reveal a clear dissociation between content-selective and generic recollection effects in medial temporal and parietal cortices. The dissociation between closely adjacent non-selective and selective effects in the parahippocampal cortex and medial parietal region highlights the complex role these regions play in episodic retrieval. These findings advance our understanding of the neural basis of episodic memory retrieval, emphasizing the importance of considering the interplay between content-selective and general retrieval processes.

Disclosures: S. Monier: None. **S. Srokova:** None. **P.F. Hill:** None. **M.D. Rugg:** None.

Poster

PSTR091: Long-Term Memory: Episodic and Episodic-Like Memory

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR091.08/N37

Topic: H.07. Long-Term Memory

Support: NIH Grant R21AG071231

Title: Age invariant dissociation of fMRI correlates of task effects during episodic memory retrieval

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Abstract: In the present study, 24 younger and 23 cognitively healthy older adults encoded a series of concrete words denoting objects that, on different trials, were superimposed on images of scenes, objects, or pixelated backgrounds. The word-image pairs were presented at one of two locations (either the left or the right side of the screen). In a scanned test task that employed words as the retrieval cues, the participants performed two different retrieval tests, which were organized into 8 blocks (4 blocks for each test). Participants were informed at the onset of each block which task they would be completing. In the background task, the requirement was to first judge whether each test item was studied or unstudied, and if studied, whether it had been paired with a scene, an object, or a pixelated image. In the location task, the old/new judgment was followed by the requirement to signal the location (left/right) of the word when it was studied. Both item and source memory performance was higher in the background task.fMRI BOLD activity elicited by recognized test items was contrasted according to task block (background vs. location). The two contrasts were height thresholded at $p < 0.0001$ (uncorrected) with a 50-voxel extent threshold. Extremely robust age invariant task effects were observed. Elevated activity was identified in left dorsolateral prefrontal cortex (DLPFC) for test items presented in the background task. Conversely, for retrieval of items presented in the location task, enhanced activity was observed in right supramarginal gyrus (SMG). The effects remained when the contrasts were broken down by background type (i.e. scene, object or pixelated).These findings represent a double dissociation in the effects of task on test items subjected to identical study conditions. A possible explanation for the enhanced left DLPFC activity in the background task is that the task imposed stronger demands on retrieval monitoring than did the location task. The right SMG task effect evident in the location task may reflect the spatial nature of the task and the consequent adoption of a spatially oriented retrieval orientation, which biased the processing of the retrieval cues accordingly. Further research is needed to elucidate the mechanisms and cognitive processes underlying these contrasting findings.

Disclosures: A. Kidwai: None. **S. Srokova:** None. **M.D. Rugg:** None.

Poster

PSTR091: Long-Term Memory: Episodic and Episodic-Like Memory

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR091.09/N38

Topic: H.07. Long-Term Memory

Support: Swebilius Foundation

Title: Differentiation of similar memories in the human hippocampus manipulated and measured via RNS

Authors: *I. ZHOU[1], K. N. GRAVES[1], E. A. MCDEVITT[4], G. L. STEMERMAN[1], G. GRANDEL[1], T. BUI[2], K. A. NORMAN[4,5], N. B. TURK-BROWNE[1,3], I. H. QURAISHI[2]; [1]Psychology, [2]Neurol., [3]Wu Tsai Inst., Yale Univ., New Haven, CT; [4]Princeton Neurosci. Inst., [5]Psychology, Princeton Univ., Princeton, NJ

Abstract: The hippocampus is critically involved in distinguishing similar experiences in memory via pattern separation, a process that orthogonalizes representations of similar experiences to reduce interference during retrieval. However, when experiences are highly similar, pattern separation may leave considerable overlap between their representations and impair future discrimination. The nonmonotonic plasticity hypothesis (NMPH) posits the existence of an additional differentiation process in the hippocampus that can discriminate highly similar experiences by reducing overlap beyond the point of orthogonality (to anti-correlation). We explore this phenomenon by recording and stimulating the hippocampus bilaterally in adults with epilepsy who are chronically implanted with responsive neurostimulation (RNS) devices. RNS offers localized, reversible manipulation of hippocampal circuits through direct electrical stimulation (DES), while local field potential (LFP) recordings from the same contacts enable time-resolved investigation of hippocampal computations. Participants first encoded a series of unique object images. This was followed by two blocks of a memory test in which they viewed old items from encoding (targets), objects highly similar to encoded items (lures), and novel objects (foils), and labeled each as "old", "similar", or "new". During one test block (order counterbalanced), 1s of DES was applied at each stimulus onset to disrupt hippocampal function; during the other test block, no stimulation was applied. In a final post-test, participants viewed lures from the test blocks and their similar counterparts from encoding. Hippocampal stimulation during the test phase selectively impaired lure discrimination, providing causal evidence that the hippocampus is necessary for this function. LFP recordings from the hippocampus during the non-stimulated test block showed significantly elevated high-frequency activity (HFA; 45-100Hz) for correctly identified lure items, peaking 1.5-2s after stimulus onset. This may reflect a mismatch effect or active competition between overlapping representations. In the post-test, HFA patterns for correctly identified lures became significantly anti-correlated from their similar encoding items 1.5-2s after stimulus onset. These findings outline a critical role for the hippocampus in supporting representations that allow for the differentiation of highly similar memories.

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Poster

PSTR091: Long-Term Memory: Episodic and Episodic-Like Memory

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR091.10/N39

Topic: H.07. Long-Term Memory

Support: NIH Grant R21AG071231

Title: Goal-dependent attenuation of retrieval-related scene reinstatement in young and older adults

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Abstract: Findings from a recent study employing fMRI measures of cortical reinstatment indicated that young, but not older, adults employ 'retrieval gating' to attenuate aspects of an episodic memory that are not relevant to the retrieval goal. Given that source memory accuracy in that study was markedly lower for older than for young adults, one possibility is that the findings reflected weak memories in the older adults for the study events, rendering the memories insufficiently intrusive to motivate the employment of retrieval gating. Here, we examined this possibility by strengthening memory for a critical feature of the study events. Young and older adults (Ns = 24, mean ages 23 yrs. and 69 yrs., respectively) studied a series of concrete nouns superimposed on rural scenes, urban scenes, or a pixelated background. To bolster memory for the background information, each word-image pair was presented twice, the first time centrally, and the second time on the left, the center or the right side of the viewing monitor. In the subsequent scanned test phase, two memory tests were completed using studied and unstudied words as retrieval cues. One test probed memory for the word's studied background and the other tested memory for its studied location. Of importance, across age groups, source memory performance was significantly better than in the previous study. To quantify retrieval-related scene reinstatement, a reinstatement index was computed using voxel-wise single-trial parameter estimates elicited by correctly recognized test words paired with either scenes or pixelated backgrounds. Two scene-selective regions of interest were examined - the parahippocampal place area (PPA) and the medial place area (MPA). The reinstatement index was computed for each ROI as the difference between the across-trial mean BOLD response (averaged over voxels) elicited by correctly recognized test items paired at study with scenes as opposed to pixelated images, scaled by the pooled inter-trial variance. In the background task, robust retrieval-related scene reinstatement effects were identified in these regions in both age groups. Crucially, these effects were reliably attenuated in the location task regardless of age group, indicating retrieval gating of scene information when location information was the retrieval goal. The findings are consistent with the proposal that older adults are capable of gating goal-irrelevant memory information when incentivized to do so.

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Poster

PSTR091: Long-Term Memory: Episodic and Episodic-Like Memory

Location: MCP Hall A

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Program #/Poster #: PSTR091.11/N40

Topic: H.07. Long-Term Memory

Support: Ministry of Trade, Industry and Energy (No. 1415181023), and the name of the project is Alchemist Brain to X (B2X) (No.20012355).

Title: Enhancing Associative Memory through Hippocampal Theta-based Alarm: Human intracranial EEG Study

Authors: *S. LEE[1], C. CHUNG[2];
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Abstract: Introduction
The hippocampus plays a crucial role in memory formation, particularly in associative memory encoding, with hippocampal theta oscillation being a key factor. Increased hippocampal theta power during encoding has been linked to successful associative memory performance. However, there is limited research on real-time modulation of hippocampal theta power and its impact on memory. This study utilized iEEG to monitor hippocampal activity in epilepsy patients undergoing iEEG electrode implantation. The algorithm was developed to track hippocampal theta power in real-time. The hypothesis posited that a decrease in hippocampal theta power during encoding would impair memory performance, and preventing this decrease would enhance memory performance.
Experimental design
The experimental session included practice encoding and retrieval, encoding with three conditions (no alarm, random alarm, theta-based alarm), distraction with math problems, and retrieval with word-pairs. Two sessions were conducted with varied condition orders, ensuring no word-pair repetition.
Results
Band power analysis during encoding revealed significant differences in theta, alpha, beta, and gamma bands between successful and failed trials. Theta power notably increased after alarms, indicating its role in successful encoding. Theta-based alarms effectively increased hippocampal theta power compared to random alarms, leading to improved memory accuracy and discrimination between correct and incorrect answers. This suggests that real-time modulation of theta power enhances memory encoding and performance.
Discussion
This study investigated the impact of a theta-based alarm on hippocampal theta power during memory encoding and its effect on memory performance. Results showed that the theta-based alarm significantly increased hippocampal theta power post-alarm, leading to improved memory accuracy and better discrimination between correct and incorrect answers compared to other conditions. The findings suggest that real-time modulation of hippocampal theta power can

enhance memory encoding and may have implications for memory enhancement strategies and neurological disorder prevention.

Disclosures: S. Lee: None. **C. Chung:** None.

Poster

PSTR091: Long-Term Memory: Episodic and Episodic-Like Memory

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Topic: H.07. Long-Term Memory

Support: PNRR project (T.H.E.) ECS_00000017
CNR grant NutrAge (nr. DSB.AD005.225)

Title: Brain-wide mapping of neuronal activation during the retrieval of object-place-context memory

Authors: S. GUGLIELMO[1], A. CATTANEO[2], *N. ORIGLIA[3];
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Abstract: Episodic memory is defined as the ability to recollect events with their specific spatiotemporal details. This form of memory is critically dependent on the coordinated activity of the hippocampus and entorhinal cortex. Using the object-place-context recognition task (OPCRT), memory engrams have been identified not only in the hippocampus but also in the lateral entorhinal cortex of the mouse. However, it has been hypothesized that a specific memory is encoded by a distributed network of engram cells, suggesting the involvement of other brain regions in episodic memory. Consequently, we conducted a brain-wide mapping of neurons activated during the retrieval of OPCR memory. After the execution of the OPCRT or exposure to the context, we collected whole-brain coronal slices and performed immunostaining for the product of the immediate early gene c-Fos, as a marker of neuronal activity. We then acquired fluorescence images that were registered to the Allen Institute CCFv3 reference atlas. Finally, we measured changes in c-Fos expression for over 600 regions of the mouse brain. We also computed the inter-regional correlation matrices and generated functional connectivity networks. Brain-wide analysis suggested that OPCR memory recall specifically increases the activity of neuronal populations in isocortical areas. A significant activation was found in associative regions involved in memory processing, navigation, and decision-making, such as the retrosplenial cortex, the orbitofrontal cortex, and the medial prefrontal cortex. Based on the brain-wide analysis, we validated our approach by focusing on the medial prefrontal cortex (mPFC), which showed significant activation. In order to investigate its specific role in memory recall, we used an inducible dual-virus system based on TRAP to express inhibitory or excitatory DREADDs only in the neurons activated during the learning of the OPCRT. We confirmed that mPFC learning-tagged neurons are active and necessary but not sufficient for the retrieval of

OPCR memory. Our brain-wide approach coupled with chemogenetic manipulation will allow to better characterize the OPCR memory network

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Poster

PSTR091: Long-Term Memory: Episodic and Episodic-Like Memory

Location: MCP Hall A

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Program #/Poster #: PSTR091.13/O2

Topic: H.07. Long-Term Memory

Support: DFG SA-2146/6-1
DFG 425899996-SFB 1436

Title: Recalling gist memory depends on CA1 hippocampal neurons for lifetime retention and CA3 neurons for memory precision

Authors: *M. SAUVAGE[1,2,3], S.-P. KU[4], M. LIPPERT[5], E. ATUCHA[4];
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Abstract: Why some of us remember events more clearly than others and why memory loses precision over time is a major focus in memory research. Here, we show that the recruitment of specific neuroanatomical pathways within the medial temporal lobe (MTL) of the brain defines the precision of the memory recalled over the lifespan. Using optogenetics, neuronal activity mapping, and studying recent to very remote memories, we report that the hippocampal subfield CA1 is necessary for retrieving the gist of events and receives maximal support from MTL cortical areas (MEC, LEC, PER, and POR) for recalling the most remote memories. In contrast, reduction of CA3's activity alone coincides with the loss of memory precision over time. We propose that a shift between specific MTL subnetworks over time might be a fundamental mechanism of memory consolidation.

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Poster

PSTR091: Long-Term Memory: Episodic and Episodic-Like Memory

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NIH MH055687
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Title: Open source intracranial EEG data from human memory experiments

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Abstract: In human cognitive electrophysiology, many studies are completed with modest numbers of participants, largely due to the financial and logistical difficulties involved in collecting EEG. Particularly uncommon are intracranial recordings of the brain, given the small subset of the population who require invasive neural implants for medical treatment. However, over the past decade, the University of Pennsylvania's Computational Memory Lab has compiled some of the largest intracranial EEG datasets in the world through collaborations with multiple institutions, yielding dozens of peer-reviewed publications. Currently, we are working to standardize these data to comply with the Brain Imaging Data Structure (BIDS) specifications, for upload to the open-source neuroscience data sharing platform OpenNeuro. To date, more than 1,000 hours of continuous intracranial EEG recordings, from over 450 unique participants and over 1,400 experimental sessions are publicly available on OpenNeuro. The participant pool ranges from young adults (age 18) to older adults (age 65) and includes hundreds of participants with hippocampal and medial temporal lobe electrode placements, among other regions of interest. These data are recorded while participants complete a variety of memory experiments, which are often variants of the canonical recall task. Specific modulations feature semantically categorized word lists, cuing of paired associates, and targeted electrical stimulation of the brain. In turn, the behavioral data contain over 300,000 encoding events and more than 120,000 annotated recall events. We hope to publicize the release of these rich datasets to empower researchers to make novel discoveries that advance the field of human cognitive neuroscience.

Disclosures: H.G. Herrema: None. **M.J. Kahana:** None.

Poster

PSTR091: Long-Term Memory: Episodic and Episodic-Like Memory

Location: MCP Hall A

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Program #/Poster #: PSTR091.15/O4

Topic: H.07. Long-Term Memory

Support: R01 AG055500
R25NS130966

Title: Volume of the anterior and posterior hippocampus is associated with verbal and nonverbal episodic memory in aging

Authors: *M. B. BLEVINS[1], B. MADERO[2], K. BALLER[3], V. MAGNOTTA[1], C. OEHLER[1], E. HAZELTINE[4], M. VOSS[5];
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Abstract: Background Episodic memory is the ability to recall and relive a past event from your life. As people age, they begin to struggle recalling episodic memories. The hippocampus integrates sensory information from experience to create new episodic memories. Evidence shows that posterior hippocampal volume is correlated to better episodic memory performance in young adults, however the hippocampal subregions most associated with memory in older adults are unknown. In both mice and humans, anterior and posterior volume atrophy at different points as we age. Therefore, this study looks to understand if the relationship between hippocampal volume and episodic memory is stronger for the posterior compared to the anterior hippocampus in older adults. **Method**This study looked at MRI (Magnetic Resonance Imaging) images from 122 cognitively healthy older adults ages 55-80 and 65.6% female. Memory was measured with the Rey Auditory Verbal Learning Task (RAVLT) and a non-verbal faces paired associates learning task. Linear regression was utilized to test whether greater volume in the posterior hippocampus would be related to better episodic memory scores compared to the anterior. **Results:** As expected, age was negatively related to hippocampal volume for both posterior and anterior sub-regions, and age was negatively associated with paired associate memory performance. However, contrary to our prediction, results showed a negative relationship between hippocampal volume and performance on the associative learning task. In late learning, the left posterior hippocampus had the strongest relationship. Results suggest that smaller hippocampal volume is associated with higher non-verbal episodic memory performance in older adults. **Conclusion/Implications** Results do not support a positive association between hippocampal volume and memory in our sample of cognitively healthy older adults. This may be due to memory in our task being processed in other parts of the brain. We plan to examine associations between volume and paired associates learning with other cortical structures such as the fusiform gyrus to give reasoning to our results and analyze the RAVLT (verbal memory task).

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Poster

PSTR091: Long-Term Memory: Episodic and Episodic-Like Memory

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Program #/Poster #: PSTR091.16/O5

Topic: H.07. Long-Term Memory

Support: ONR N00014-17-1-2961
5 T32 MH 112507-7

Title: Post-learning reactivation of memories for naturalistic events

Authors: *N. WOLF[1], J. W. ANTONY[2], A. I. DELARAZAN[3], Z. M. REAGH[4], C. RANGANATH[1], X. LIU[5];
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Abstract: People often think of memory as a record that stores everything we learn, but in reality, we forget most of the large amount of information we are exposed to every day. According to theories of memory consolidation, memories can be reactivated during offline states post-learning, acting as a mechanism to save memories that might otherwise be forgotten. Transient reactivation of sequences of place cells have been shown in rodents during waking rest and sleep, but it is unclear how this translates to human memories for natural events that unfold across longer timescales. Here, we investigated whether neural representations of discrete naturalistic events are reactivated in the human brain during post-learning rest, and if so, whether reactivation influences what we remember. Participants (N=34) underwent functional magnetic resonance imaging (fMRI) while watching a film between two resting state scans. Participants then freely recalled the episode both that same day and one week later. We averaged neural activity patterns during discrete events based on event boundaries identified by a separate group of participants, and tested for reactivation of these patterns during post-learning rest in networks known to be involved in episodic memory. Preliminary analyses revealed evidence for post-encoding reactivation of event information in the posterior medial (PM) and anterior temporal (AT) networks. Further analyses will test for relationships between reactivation and event memory within these networks, and whether reactivation emphasizes neural representations at event boundaries. These findings will help bridge the gap between our knowledge of offline reactivation in rodents and humans, extending our understanding of consolidation for continuous narrative experience.

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Poster

PSTR092: Learning and Memory in Invertebrates

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Program #/Poster #: PSTR092.01/O6

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Title: Evidence of Active-Forgetting Mechanisms? Blocking Arachidonic Acid Release May Slow Forgetting of Sensitization in Aplysia

Authors: *R. CALIN-JAGEMAN[1], B. GONZALEZ DELGADILLO[2], E. GAMINO[3], Z. JUAREZ[5], A. KURKOWSKI[2], **N. MUSAJEVA**[2], L. VALDEZ[2], D. WITTROCK[2], T. WILSTERMAN[4], J. ZARATE TORRES[2], I. CALIN-JAGEMAN[2];
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Abstract: Long-term sensitization in *Aplysia* is accompanied by a persistent up-regulation of mRNA encoding the peptide neurotransmitter Phe-Met-Arg-Phe-amide (FMRFa), a neuromodulator that opposes the expression of sensitization through activation of the arachidonic acid second-messenger pathway. We completed a preregistered test of the hypothesis that FMRFa plays a critical role in the forgetting of sensitization. *Aplysia* received long-term sensitization training and were then given whole-body injections of vehicle (N = 27), FMRFa (N = 26), or 4-bromophenacylbromide (4-BPB; N = 31), a phospholipase inhibitor that prevents the release of arachidonic acid. FMRFa produced no changes in forgetting. 4-BPB decreased forgetting measured 6 days after training [d_s = 0.55 95% CI(0.01, 1.09)], though the estimated effect size is uncertain. Our results provide preliminary evidence that forgetting of sensitization may be a regulated, active process in Aplysia, but could also indicate a role for arachidonic acid in stabilizing the induction of sensitization.

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Poster

PSTR092: Learning and Memory in Invertebrates

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Topic: H.08. Learning and Memory

Support: NINDS Grant 15NS118408

Title: Interaction between serotonin and nitric oxide in the formation of a neural correlate of long-term sensitization in Aplysia

Authors: L. RICHARDS, M. L. WAINWRIGHT, *R. MOZZACHIODI;
Life Sci., Texas A&M University-Corpus Christi, Corpus Christi, TX

Abstract: Long-term memory is linked to plasticity of intrinsic neuronal excitability (e.g., Mozzachiodi and Byrne, 2017). Long-term sensitization (LTS) in *Aplysia* is an extensively studied example of learned fear in which memory is associated with intrinsic plasticity (Cleary et al. 1998). LTS in *Aplysia* manifests as an enhancement of defensive responses, such as the tail-siphon withdrawal reflex (TSWR), triggered by repeated exposure to noxious stimuli. A neural correlate of LTS in *Aplysia* is long-term (i.e., 24 h) increased excitability (LTIE) in tail sensory neurons (TSNs; Cleary et al. 1998). LTIE can be induced *in vitro* by repeated nerve stimulation of afferent nerves in a reduced preparation of *Aplysia* nervous system (e.g., Weisz et al., 2017). The neurotransmitter serotonin (5-HT) is a key neurotransmitter necessary and sufficient for mediating LTS *in vivo*, and for inducing TSN LTIE *in vitro* (Byrne and Hawkins 2015). Recent studies have shown that the gaseous neurotransmitter nitric oxide (NO) is also required for LTS *in vivo* but not for trained-induced LTIE *in vitro* (Farruggella et al. 2019). This study examined whether NO was necessary for 5-HT-induced LTIE, which is produced by five *in vitro* 5-HT applications (bath concentration: 50 μM dissolved in L-15 culture medium; Liu et al. 2011). L-NAME (bath concentration: 0.37 mM dissolved in L-15) was utilized as NO synthase inhibitor (Farruggella et al. 2019). After pre-test TSN excitability was measured, preparations were subjected to five consecutive 5-min 150-μL bath applications of either L-15, 5-HT, L-NAME, or 5-HT with L-NAME. Each bath application was followed by 15-min, 7.5-mL washout using either L-15 or L-15 with L-NAME. Post-test TSN excitability was measured 24 h after treatment, with post/pre percent changes compared among the four groups using the Kruskal-Wallis H test followed by the Student-Newman-Keuls *post-hoc* comparison (Farruggella et al. 2019). Results showed that LTIE equally occurred in the 5-HT and 5-HT with L-NAME groups, without significant difference between the two groups, thus demonstrating that L-NAME did not block 5-HT-induced LTIE in TSNs. Overall, this finding indicates that NO is not required for either trained-induced LTIE or 5-HT-induced LTIE. The other known neural correlate of LTS, long-term facilitation (LTF) of the synaptic connections between TSNs and motor neurons in the TSWR circuit (Byrne and Hawkins 2015), has been recently found to depend on NO signaling (Chen et al. 2023). Combined with previous results, the current findings strengthen the view that, because LTS and LTF are NO dependent, whereas LTIE is not, LTF may have a larger contribution than LTIE to LTS expression.

Disclosures: L. Richards: None. **M.L. Wainwright:** None. **R. Mozzachiodi:** None.

Poster

PSTR092: Learning and Memory in Invertebrates

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR092.03/O8

Topic: H.08. Learning and Memory

Support: SNSF grant 31003A_178937

Title: M6a dna methylation controls forgetting and long-term memory in c. elegans

Authors: L. KASPAR[1], A. PAPASSOTIROPOULOS[2], ***A. STETAK**[2];
[1]Max Planck Inst. of Psychiatry, Munich, Germany; [2]Univ. of Basel, Basel, Switzerland

Abstract: Understanding neural circuits and molecular mechanisms underlying changes of synapse strength during learning and memory are the major challenges of neuroscience. While the mechanisms of learning and memory are widely studied, the decay of memories (forgetting), a poorly investigated but apparently highly complex mechanism, is also essential for proper functioning of the brain.Recently, we identified a core set of genes differentially regulated during long-term memory, out of them *nmad-1* represents the *C. elegans* homolog of DNA m6A demethylase enzyme (Freytag et al., 2017). Using an aversive olfactory associative long-term memory test, we confirmed that *nmad-1* gene is indeed transcriptionally upregulated; levels peaking 4h post-training. Furthermore, *nmad-1* loss-of-function mutants surprisingly have an increased long-term but normal short-term memory performance compared to wild-type worms. We generated a knock-out mutant of the DNA adenosine methyltransferase gene, *damt-1*, likely acting opposing to the *nmad-1* function. As expected, deletion of the *damt-1* impaired long- but not short-term memory suggesting that dynamic modification of the DNA m6A modification plays and important role in long-term memory maintenance and elimination. Using tissue specific rescue experiments we demonstrated that *damt-1* function is required in AVA neuron. Additionally, immunostaining with m6A-specific antibody showed reduced DNA 6-adenosine methylation specifically in AVA neuron upon long-term memory training, while global or AVA-specific RNA methylation levels were not affected. Finally, we compared gene expression differences in wild-type, *nmad-1* and *damt-1* mutant worms and compared global gene expression profiles and also filtered with the previously defined core memory regulated gene-set in order to identify the methylation regulated memory genes.Altogether, we show that DNA m6-adenosine methylation plays a role in associative long-term memory in worms. Since *nmad-1* expression level increases during memory and deletion of the gene results in enhanced memory performance, this may represent a controlled forgetting mechanism in the AVA neuron in *C. elegans*. As DNA m6A methylation was recently described in humans as well, our findings likely represent an evolutionary conserved forgetting mechanism also present in vertebrates.

Disclosures: L. Kaspar: None. **A. Papassotiropoulos:** None. **A. Stetak:** None.

Poster

PSTR092: Learning and Memory in Invertebrates

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR092.04/O9

Topic: H.08. Learning and Memory

Support: Flinders University Research Scholarship
NHMRC GNT1173448
Flinders University Early Career Research Impact Grant 2022
Rebecca L Cooper Project Grant 2020-22

Title: Investigating the role of dopamine in the process of forgetting in C. elegans

Authors: *A. L. MCMILLEN, R. ANSAAR, Y. CHEW;
Flinders Univ., Bedford Park, Australia

Abstract: Dopamine plays an important role in the processes of learning and memory, conserved across species. Studies using *Drosophila melanogaster* implicate dopamine in forgetting, a process mechanistically distinct from learning and memory formation. This project aims to determine the precise neural circuits and molecular pathways involved in forgetting, using the model organism *Caenorhabditis elegans* (1). Dopaminergic neural circuits in flies and mammalian models consist of hundreds of neurons while the compact *C. elegans* brain has only 300 neurons including 8 dopaminergic neurons, facilitating the study of behavioural plasticity at a single neuron resolution. In this study, we used an appetitive associative learning assay that pairs the odorant butanone with the presence of abundant food (2). Naïve *C. elegans* show a mild attraction to butanone; following a conditioning period they change their behaviour to show increased attraction to butanone. Data consisted of 4 biological replicates per genotype, each consisting of 4 technical replicates of 50 to 250 worms. We found that worms lacking the CAT-2 enzyme required for dopamine synthesis showed a significantly higher magnitude of this learnt behavioural change compared with wild-type controls. *cat-2* mutant worms retained the learned behaviour up to 2 hours post-conditioning, while wild-type worms 'forgot' within 30 minutes. Re-expression of CAT-2 in dopaminergic neurons rescued this behaviour to wild-type levels, showing that the regulation of forgetting in this behavioural paradigm is dopamine-dependent. We next investigated the neural circuit through which dopamine regulates forgetting: interestingly, single *dop-1*, *dop-2*, and *dop-3* mutants did not show a phenotype that differed from wild-type worms. We are now testing double and triple dopamine receptor mutants to further investigate potential mechanisms. In future work, we will test a longer version (up to 40 hours post-conditioning) of the butanone associative learning assay to determine if the same signalling pathway is also involved in long-term memory. Investigating the role of dopamine in forgetting using *C. elegans* not only expands our understanding of neural networks but may lead to new ways to address memory-related challenges in broader contexts. 1. McMillen A, Chew YL. Neural mechanisms of dopamine function in learning and memory in Caenorhabditis elegans. Neuronal Signaling. 2023;8(1):NS20230057. 2. Kauffman A, Parsons L, Stein G, Wills A, Kaletsky R, Murphy C. C. elegans positive butanone learning, short-term, and long-term associative memory assays. JoVE (Journal of Visualized Experiments). 2011(49):e2490.doi:10.3791/2490.

Disclosures: A.L. McMillen: None. **R. Ansaar:** None. **Y. Chew:** None.

Poster

PSTR092: Learning and Memory in Invertebrates

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR092.05/O10

Topic: H.08. Learning and Memory

Support: UNAM-DGAPA-PAPIIT IN228523

Title: Memory recognition and social dynamics: investigating tritocerebral electrical activity in crayfish agonistic encounters

Authors: I. OLIVER-DOMÍNGUEZ, A. GARCÍA-KROEPFLY, M. OSORIO PALACIOS, J. HERNANDEZ-FALCON, *K. MENDOZA-ANGELES;
Univ. Nacional Autonoma de Mexico, México, Mexico

Abstract: Crayfish, a decapod crustacean, display agonistic behavior when a triad of animals interacts under laboratory conditions and establishes a hierarchical order, with a dominant animal and two submissives. During agonistic encounters, heart and respiratory rates increase, and this changes also occur without a physical interaction when animals are in the same aquarium. These changes are autonomic-like responses despite the lack of a described autonomic nervous system. During rest conditions, crayfish's brain electrical activity was recorded from protocerebrum, deutocerebrum and tritocerebrum and a possible relation between tritocerebrum and cardiorespiratory electrical activity was shown.
In order to study the tritocerebral activity during the first and final days of a 5-day protocol of memory recognition, we used triads of adult crayfish that were implanted with Pt-Ir electrodes in tritocerebrum. We recorded the tritocerebral electrical activity of each crayfish at rest, in their individual aquaria, for 15 minutes (condition 1), then we placed each triad in the same aquarium and recorded behavior and electrophysiological activity for one hour. In the first 15 minutes, the arena was divided by a plastic separator that allowed chemical but not physical contact (condition 2). For the next 45 minutes, we removed the separator and animals fought with each other (condition 3).
We reconstructed the state space of the tritocerebral electrical activity for every crayfish in all the conditions in both days with delay coordinate embedding.
We found that the number and type of possible brain states changes depending on the protocol's stage. During the control condition the trajectories form a wide figure indicating multiple possible brain states. In day 1 the trajectories flatten in condition 2, indicating a reduction of the possible brain states, and in condition 3 the trajectories form a wide figure again.
In the condition 2 of day 5, the trajectories show the appearance of an attractor, the location of the attractor varies depending on the crayfish's hierarchy status, and in condition 3 the trajectories flatten, and the attractor is no longer in the state space.
These results suggest that there is a shift in the dynamics of tritocerebral activity from day 1 to day 5 in the memory protocol. This change may indicate that the tritocerebrum is involved in the cardiorespiratory adjustments necessary for an individual to respond to a) unfamiliar, b) dominant and c) submissive conspecifics.

Disclosures: I. Oliver-Domínguez: None. **A. García-Kroepfly:** None. **M. Osorio Palacios:** None. **J. Hernandez-Falcon:** None. **K. Mendoza-Angeles:** None.

Poster

PSTR092: Learning and Memory in Invertebrates

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR092.06/O11

Topic: H.08. Learning and Memory

Support: DFG Project 376818398

Title: How to improve motor learning in Drosophila

Authors: *R. LYUTOVA-HRISTOVA, A. EHWEINER, B. BREMBS;
Univ. of Regensburg, Regensburg, Germany

Abstract: Motor learning, skill-learning or habit formation share conceptual similarities, but it is debated how much biology these processes have in common. There is genetic evidence linking motor learning and habit formation in flies, song-learning in birds and language acquisition in humans to an evolutionary conserved operant self-learning process. We show different biological manipulations of *Drosophila* that all enhance motor learning. We suggest a world-learning mechanism inhibiting premature habit formation and interfering with self-learning. We identified a neural circuit which actively controls the process of motor learning depending on the animal's environment. Our results show that mutations in genes involved in classical conditioning, such as rutabaga or radish, enhance motor learning. Overexpression of an operant learning gene, atypical PKC (aPKC) enhances motor learning as well as habit formation. Inhibition of an aPKC interaction partner, bazooka, also enhances motor learning. We will also show data comparing the motor learning efficacy of rover and sitter flies, which carry different variants of the protein kinase G (PKG) gene. We further investigated the effects of PKG RNAi knockdown on motor learning. Further, inhibition of a prominent insect neuropil, the mushroom bodies (MBs), leads to formation of premature habits. We show that this function is mediated via MB output neuron 2 (MBON-02). The anatomy of this neuron indicates that non-olfactory MB Kenyon cells (KCs) of the β2 and β'2-lobes are involved in this enhancement by receiving input within the little-studied lateral (lACA) and dorsal (dACA) accessory calyx regions of the MB. However, our data shows that both the visual (via dACA) and the thermosensory (via lACA) input are separately sufficient but not necessary for premature habit formation. We propose a network within the MB circuitry controlling the transition from goal-directed behavior (world-learning) to habits (self-learning). We hypothesize that MBON-02 might be a site of coincident input of sensory stimuli in combination with signal amplification via KC-to-KC feed-forward loops. Given the conserved nature of these learning processes in all bilaterian animals including humans and the role of motor learning in language acquisition, habit formation/addiction and rehabilitation after stroke or spinal cord injury, the diversity of these learning enhancements promises a rich field for the development of medical applications.

Disclosures: R. Lyutova-Hristova: None. **A. Ehweiner:** None. **B. Brembs:** None.

Poster

PSTR092: Learning and Memory in Invertebrates

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR092.07/O12

Topic: H.08. Learning and Memory

Support: MEXT KAKENHI, JP25115006
JSPS KAKENHI, JP19H02013
SPS KAKENHI, JP17K07070
MEXT KAKENHI, JP21H05642

Title: Aberrant dopaminergic activity causes memory generalization and age-dependent memory loss in Drosophila

Authors: M. MATSUNO, N. UEMURA, T. MIYASHITA, M. SAITOE, ***J. HORIUCHI**; Tokyo Metropolitan Inst. of Med. Sci., Setagaya, Japan

Abstract: Memory decreases upon aging in humans and other animals. However, the molecular and cellular mechanisms causing these impairments are still unclear. Here we determined that aberrant dopaminergic activity during memory consolidation is responsible for age-related impairments in long-term memory in *Drosophila*.
Drosophila can be taught to associate an odor with aversive electrical shocks, and they form long-term memories of this association when exposed to multiple odor/shock trainings with interspersed rest intervals. Similar to other organisms, flies demonstrate impaired long-term memory upon aging. Long-term memory formation requires the formation of memory engram cells, which can be identified by increased expression of the immediate early gene, c-fos. We found that old flies form engram cells similarly to young flies. However, while engram cells are activated by the shock-paired odor and not other odors in young flies, they are activated by both shock-paired and unpaired odors in old flies. Consistent with this result, young flies show increased avoidance to the shock-paired odor, but not other odors after training, while old flies show an increased avoidance to both paired and unpaired odors, a phenomenon known as memory generalization.
We previously reported that reduced long-term memory in old flies is caused by the inability of old flies to inhibit glutamate signaling during memory consolidation. Here we demonstrate that pharmacological inhibition of NMDA-type glutamate receptors after training rescues prevents activation of engram cells by inappropriate odors and rescues memory generalization in old flies. Aberrant glutamate activity increases activity of a subset of dopaminergic neurons in old flies. Suppressing dopaminergic activity after training prevents memory generalization in old flies, while increasing dopaminergic activity in young flies induces generalization in young flies. Overall, our data indicate that aberrant glutamate signaling during memory consolidation increases dopaminergic activity which induces plasticity of engram cells, leading to memory generalization and impairment.

Disclosures: M. Matsuno: None. **N. Uemura:** None. **T. Miyashita:** None. **M. Saitoe:** None. **J. Horiuchi:** None.

Poster

PSTR092: Learning and Memory in Invertebrates

Location: MCP Hall A

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Program #/Poster #: PSTR092.08/O13

Topic: H.08. Learning and Memory

Support: Wellcome Trust Early Career Award - 226333/Z/22/Z
Oxford University Press John Fell - AVD00790

Title: Subcellular localization of proteins in dopaminergic neurons in Drosophila melanogaster

Authors: *Y. ZHANG, A. PARK, S. WADDELL;
Univ. of Oxford, Oxford, United Kingdom

Abstract: Depending on where proteins are localized within a neuron can influence the computations that neuron can perform. Dopaminergic neurons are critical for forming associative reward memories, but not much is known about how subcellular localization of proteins affects their neuronal physiology. We are therefore examining how the subcellular expression pattern of specific molecules can influence the physiology of dopaminergic neurons. We are investigating these questions in *Drosophila melanogaster*, as they have a simpler nervous system despite being able to form associative reward memories. Dopaminergic neurons in Drosophila exhibit remarkable anatomical and molecular heterogeneity anatomically across distinct subtypes. Using our single-cell sequencing results we have begun to determine the subcellular localization of specific molecules of interest within subtypes of dopaminergic neurons involved in encoding food and mating-related reward. We find that knocking down individual molecules (e.g. channels, receptors or signalling molecules) does not significantly change their anatomical features, despite exerting changes in physiology. Using the EM-resolution connectome we have also begun to investigate how inputs into dopaminergic neurons can be used to predict the subcellular localization of key proteins of interest. We are currently validating their role in food and mating reward memories.

Disclosures: Y. Zhang: None. **A. Park:** None. **S. Waddell:** None.

Poster

PSTR092: Learning and Memory in Invertebrates

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR092.09/O14

Topic: H.08. Learning and Memory

Support: NIHR24MH11478
Johns Hopkins University Applied Physics Laboratory’s Independent Research & Development (IR&D) Program

Title: Using DotMotif to compare the distribution of synaptic convergent motifs across Mushroom Body lobes in the Drosophila Hemibrain connectome

Authors: *P. K. RIVLIN, J. K. MATELSKY, M. ROBINETTE, B. A. WESTER;
Johns Hopkins Applied Physics Lab., Laurel, MD

Abstract: The Mushroom Body (MB) is the center of associative learning and memory in the insect brain. In Drosophila, sensory stimuli are represented by the sparse activity of ~ 2000 Kenyon cells (KCs) whose parallel axons divide the MB into α, β, α', β' and γ lobes, and form synaptic connections with 23 types of MB output neurons (MBONs) whose dendrites further divide the lobes into compartments. Three connectomes have been generated with electron microscopy to study MB neural circuitry: MB-6, centered on the α-lobe (Takemura et al. 2017); Hemibrain, a partial brain volume containing the MB of the right hemisphere (Scheffer et al. 2020; Li et al. 2020); and FlyWire, a whole brain volume (Dorkenwald et al. 2023). As first reported in MB-6, the majority of KC-to-MBON synapses occur in a convergent motif, defined as a tight grouping of two KC axons whose active zones are ≤ 300 nm apart and presynaptic to the same target. The potential importance of convergent motifs is underscored by their appearance across species (e.g. Drosophila, locust, octopus) in the learning center as well as the central complex or navigation center of the brain (Homberg et al. 2016; Hulse et al. 2021). The functional role of convergent motifs in the MB lobes is not known. However, as points of heavy convergence, this motif may allow the effects of synapses from different KCs onto the same dendritic location to act synergistically (Takemura et al. 2017). To better understand their role, we are using big-data graph tools including DotMotif (Matelsky et al. 2021) to detect and map the distribution of convergent motifs across MB lobes in the hemibrain. Given differences in KC and MBON development across lobes (Truman et al. 2022), it is unclear if convergent motifs occur at a similar rate across lobes. Here we report our progress to analyze the distribution of convergent motifs across MB lobes and individuals. Although the α-lobe contains more KCs in MB-6 versus hemibrain (949 and 889, Schlegel et al. 2023), we detected slightly more KC-to-MBON synapses in the α-lobe of the hemibrain versus that reported in MB-6 (64,861 and 61,301, respectively). In agreement with Takemura et al. (2017), we found that the majority of KC-to-MBON synapses in the α-lobe, 87-94% depending on the MBON type, form convergent motifs in MB-6. In contrast, we found that 60-70% of KC-to-MBON synapses in the α-lobe of the hemibrain form convergent motifs. It is unclear if this difference is due to variation in synapse detection (semi-automated versus fully-automated), neuron reconstruction, or represent sex-specific differences (male MB-6 versus female hemibrain). Further insights may be gained as we extend our analysis to other MB lobes in the hemibrain.

Disclosures: P.K. Rivlin: None. **J.K. Matelsky:** None. **M. Robinette:** None. **B.A. Wester:** None.

Poster

PSTR092: Learning and Memory in Invertebrates

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR092.10/O15

Topic: H.08. Learning and Memory

Title: Risk assessment behavior and learning related to negative phototaxis in Madagascar hissing cockroaches

Authors: V. VAZQUEZ[1], B. BARLOW[1], E. REESE[1], **E. M. EVANS**[2], A. WILSON[2], S. C. JOHNSON[2], *J. O. TAYLOR[2];
[1]Utah Valley Univ., Orem, UT; [2]Behavioral Sci., Utah Valley Univ., Orem, UT

Abstract: There is extensive literature on observations of memory and learning in many insects. Research on insects can be used to inform our understanding of behavior and cognitive processes and add to our existing knowledge about the studied species. Cockroaches are frequently selected as a model organism for this type of research due to their adaptability, resilience, and availability. Despite being widely used as a model organism in life science courses, little research exists on Madagascar hissing cockroaches (*Gromphadorhina portentosa*, MHC) specifically, especially in regard to memory and learning. The first study was designed to observe habituation of negative phototaxis in the MHC using a truncated Y-maze. One arm of the maze was transparent and brightly lit, the other dark and enclosed. Subjects were allowed to freely explore the apparatus for six trials per day for three consecutive days. Comparisons of time spent in each arm and number of entries into each arm between the first and third day were used to assess learning. Results demonstrated non-significant differences in time within the dark arm, increased time in the light arm, and a decrease in the number of movements between the arms. In conjunction with a lack of spontaneous recovery to initial preference one week later, these results suggest that subjects reduced risk-assessment like behaviors across time, but may not have habituated to the context. Additional pilot testing explores learning with escape/avoidance and appetitive preference testing using the perspective of risk assessment in the MHC

Disclosures: V. Vazquez: None. **B. Barlow:** None. **E. Reese:** None. **E.M. Evans:** None. **A. Wilson:** None. **S.C. Johnson:** None. **J.O. Taylor:** None.

Poster

PSTR092: Learning and Memory in Invertebrates

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Program #/Poster #: PSTR092.11/O16

Topic: H.08. Learning and Memory

Support: NIH R01 NS121220

Title: Competing non-associative memory traces use distinct network-level strategies when overlapping in Tritonia'sescape swim network space

Authors: V. K. MISTRY, E. S. HILL, ***W. N. FROST**;
Ctr. for Brain Function and Repair, Rosalind Franklin Univ. of Med. and Sci., North Chicago, IL

Abstract: The marine mollusk Tritonia diomedea's ventral/dorsal flexion escape swim is a rhythmic motor program that undergoes two forms of non-associative learning: sensitization, a rapid increase in response to an initial stimulus, and habituation, a gradual decrease in response with repeated stimuli. This learning can be observed in both intact animals and in the isolated CNS, and learning induced changes in the swim network can be observed using voltage imaging. Through this, we have previously identified neural correlates of three behavioral parameters of this swim: the swim onset latency, the number of cycles, and the jump height achieved on the first ventral flexion. We have also previously identified circumstances where specific behavioral parameters remain sensitized when others have habituated, showing the two memories can co-exist within the escape network. These characteristics make Tritonia's escape swim an excellent model for investigating how two competing non-associative memories, sensitization and habituation, are encoded into the same network space. Here we report that the sensitization and habituation memory traces employ distinct network strategies consisting of different alterations to encode learning into Tritonia's escape swim network. Sensitization learning makes two network level modifications: it increases the network size by making inactive neurons active, and it selectively increases the burst intensity of the ventral bursters during the first swim cycle. Preliminary work is also revealing that this selective burst intensity increase is driven by an increase in intrinsic excitability in ventral burster neurons. Habituation learning, however, was not simply the inverse of this. The habituated network shows a decrease in burst intensity on both the ventral and dorsal phases, but shows no decrease in the size of the network compared to naive. Meanwhile, preliminary work suggests that the intrinsic excitability of both ventral and dorsal bursters does not decrease below naive with habituation. Thus, these two competing forms of learning are utilizing distinct network-level strategies to encode different memories into the same network space: one memory, sensitization, modifies both network size and phase-selective burst intensity, and the other memory, habituation, only modifies global burst intensity. These different strategies suggest a fundamental principle of how competing memory networks can overlap in the same network space is the utilization of different alterations for different memories within the same population of neurons.

Disclosures: V.K. Mistry: None. **E.S. Hill:** None. **W.N. Frost:** None.

Poster

PSTR092: Learning and Memory in Invertebrates

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Topic: H.08. Learning and Memory

Support: NIH Grant NS113903
HHMI

Title: Distinct roles of Aplysia neurotrophin isoforms in neuronal morphogenesis, synaptogenesis and long term facilitation at sensory-motor synapses of the gill withdrawal reflex

Authors: *S. KASSABOV[1], C. UPRETI[2], Y.-B. CHOI[3], I. JIN[2], E. R. KANDEL[2], R. D. HAWKINS[2];
[1]Psychiatry, Columbia University/NYSPI, New York, NY; [2]Columbia Univ., New York, NY; [3]Rutgers Univ., East Orange, NJ

Abstract: Key aspects of neurotrophin biology remain ill understood due to the extraordinary complexity of the mammalian neurotrophin signaling system, which consists of three distinct Trk receptors, a common p75 NTR receptor and four neurotrophin ligands, BDNF, NT3,4 and NGF, each of which is processed into mature and pro forms with different receptor affinities. We previously identified in *Aplysia californica* a simpler, functionally conserved neurotrophin signaling system consisting of a single neurotrophin ApNT and a single receptor ApTrk (Kassabov et al 2013). ApNT is spliced into two isoforms ApNT(+) and ApNT(-), that are differentially trafficked, processed, and secreted as mature and pro forms respectively, suggesting they fulfill distinct functions. Here, we interrogate these functions in dissociated *Aplysia* neuronal culture. We found that ApNT(+) mature was expressed in sensory neurons (SNs) in the circuit for the gill withdrawal reflex, whereas ApNT (-) pro and ApTrk were expressed in motor neurons (MNs). Blocking ApNT(-) pro but not ApNT (+) mature or ApTrk led to a dramatic reduction in branching of motor neurons indicating branching is mediated by ApNT (-) pro, likely interacting with a homolog of p75 NTR. In contrast, our earlier findings showed that overexpression of ApNT(+) mature, but not ApNT (-) pro in SNs was sufficient for induction of baseline synaptic growth and increased synaptic strength. Combining a single pulse of serotonin with overexpression of either ApNT(+) or ApNT (-) produced robust long-term synaptic facilitation (LTF) and blocking each of the isoforms significantly reduced LTF induced by five pulses of serotonin. The MAPK kinase inhibitor UO126 was able to suppress the facilitation produced by 1 pulse of serotonin combined with overexpression of ApNT(+) but not ApNT (-), consistent with ApNT (+) mature signaling through the ApTrk - MAPK pathway and ApNT (-) pro signaling through a different receptor, likely p75NTR. Moreover, overexpressed ApNT (+) was highly enriched in newly growing synaptic varicosities, whereas ApNT (-) was preferentially localized in stable varicosities, indicating potential differential roles of the isoforms in induction and stabilization/maintenance of synaptic growth. Our current and earlier findings indicate that ApNT splice isoforms are expressed in cell type specific manner in the Aplysia CNS and employ distinct receptor signaling systems to effect distinct structural and functional aspects of neuronal and synaptic growth and facilitation. Consistent with these findings we demonstrate distinct roles of the ApNT isoforms in several types of learning in an accompanying abstract (Yang et al, 2024).

Disclosures: S. Kassabov: None. **C. Upreti:** None. **Y. Choi:** None. **I. Jin:** None. **E.R. Kandel:** None. **R.D. Hawkins:** None.

Poster

PSTR092: Learning and Memory in Invertebrates

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Topic: H.08. Learning and Memory

Support: NIH Grant R01 NS019895
NIH Grant R01 NS102490

Title: Complex interactions of kinase and growth factor cascades contribute to 5-HT-induced dynamics of RSK activation in Aplysia sensory neurons

Authors: *Y. ZHANG, R.-Y. LIU, P. D. SMOLEN, J. H. BYRNE;
McGovern Med. Sch. of UTHSC At Houston, Houston, TX

Abstract: The p90 ribosomal S6 kinase (RSK) is required for 5-HT-induced long-term synaptic facilitation (LTF) of the *Aplysia* sensorimotor synapse and long-term enhancement of intrinsic excitability of sensory neurons (SNs) (Liu et al. 2020). To better understand the regulation of RSK by 5-HT, we used immunofluorescence analyses to compare the dynamics of RSK activation and the dynamics of two upstream kinases of RSK, protein kinase A (PKA) and extracellular signal-regulated kinase (ERK) (Liu et al. 2020; Zhang et al., 2021), for up to 24 h after treatment with five pulses of 5-HT (interstimulus intervals of 20 min). Compared to individual vehicle controls examined at the same time points, all three kinases showed complex dynamics of activation. Two waves of increase in activation were observed for all three kinases. The first wave occurred shortly after treatment and ended within 5 h. The second wave was observed at 18 h. However, the initiation of waves of RSK activation did not exactly follow the dynamics of its upstream kinases PKA and ERK. The first wave of PKA and ERK activation occurred immediately after treatment (PKA: 32.7 ± 10.8%, n = 6, p = 0.04; ERK: 57.4 ± 9.9%, n = 10, p = 0.01), whereas the first wave of RSK activation was delayed until 1 h after treatment (0h: 4.2 ± 7.6%, n = 11, p > 0.5; 1h: 24.4 ± 7.7%, n = 15, p = 0.04). However, RSK activation was significantly increased immediately after treatment if the inhibitor of RSK downstream effects, BI-D1870, was applied before and during the treatment (0h: 28.1 ± 8.4%, n = 12, p<0.01). RSK activation was also increased immediately after 5-HT treatment by an inhibitor of p38 MAP kinase, SB 203580 (0h: 16.7 ± 2.8%, n = 8, p<0.05). Because p38 MAPK is downstream of RSK, these results suggest that a self-inhibitory feedback loop was responsible for the delay in the increase of RSK activation. The second wave of increase in RSK and PKA activation started at 5 h after 5-HT treatment (PKA: 16.3 ± 3.4%, n = 8, p = 0.03; RSK: 33.1 ± 7.6%, n = 8, p < 0.01), whereas ERK activity remained around the basal level at 5 h (12.6 ± 5.6%, n = 10, p > 0.5). The increase of RSK at 5 h was suppressed by an inhibitor of PKA (KT5720) (11.6 ± 11.8%, n = 8, p= 0.03) or antagonist of growth factor transforming growth factor-β (TGF-β Fc chimera) (3.7 ± 5.5%, n = 8, p< 0.05), suggesting that the initiation of this second wave was regulated by multiple pathways, likely independent of ERK. These results suggest that complex interactions among the kinase pathways and growth factor cascades contribute to the dynamics of RSK activation. Further study is needed to investigate how they contribute to the dynamics of transcription factors that regulate LTF.

Disclosures: Y. Zhang: None. **R. Liu:** None. **P.D. Smolen:** None. **J.H. Byrne:** None.

Poster

PSTR092: Learning and Memory in Invertebrates

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR092.14/O19

Topic: H.08. Learning and Memory

Support: HHMI
NIH grant NS113903

Title: Differential roles of Aplysia neurotrophin isoforms and receptors in several simple forms of learning

Authors: Q. YANG, S. R. KASSABOV, E. R. KANDEL, ***R. D. HAWKINS**;
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Abstract: The precise roles of BDNF and other neurotrophins are not well understood because the mammalian brain is very complex and has multiple neurotrophins, which are each processed into pro and mature isoforms that act on multiple receptors. Why are there so many possible combinations? The Aplysia siphon withdrawal reflex is advantageous for addressing this question because it has a simple neural circuit and a single neurotrophin (ApNT) with an ApNT(+) mature isoform that acts through a single Trk receptor (ApTrk) and an ApNT(-) pro isoform that acts through a putative p75NTR receptor. ApNT(-) pro is enriched in motor neurons whereas ApNT(+) mature is enriched in sensory neurons, and overexpression of ApNT(+) mature but not ApNT(-) pro in sensory neurons increased both synaptic growth and long-term facilitation in culture (Kassabov et al., 2013). In addition, knockdown of ApNT total or ApNT(-) pro but not ApNT(+) mature led to a severe loss of branching in motor neurons (Kassabov et al., 2024), and blocking ApNT signaling with Trk-Fc reduced behavioral sensitization in a semi-intact preparation (Yang et al., 2018). We have now used LNA modified gapmers that inhibit selectively each of the two ApNT isoforms and ApTrk to examine their respective roles in several simple forms of learning in the semi-intact preparation. Repeated testing produced a gradual decrease or habituation (HAB) of siphon withdrawal that was blocked by knockdown with oligos targeting both isoforms (ApNT total), ApNT(+) mature or ApTrk but not ApNT(-) pro. Tail shock produced a gradual increase or sensitization (SEN) compared to test alone control that may also be in part dishabituation. The SEN was reduced by knockdown of ApNT total, ApNT(-) pro, or ApTrk but not ApNT(+) mature. These results suggest that whereas HAB preferentially involves ApNT(+) mature, like synaptic growth and facilitation, SEN preferentially involves ApNT(-) pro, like motor neuron morphogenesis. Knockdown of ApNT total (only) also revealed a transient inhibition after the tail shock similar to inhibiting PKA (Antonov et al., 2021), which acts both up and downstream of ApNT (Jin et al., 2018a,b). Paired training produced an increase in responding or classical conditioning (COND) compared to unpaired control, which was blocked by knockdown of ApNT total or ApNT(+) mature but not ApTrk. However, in preliminary experiments COND was blocked by a p75NTR blocking antibody, suggesting that is the functional receptor in that case. Collectively these results suggest that different combinations of neurotrophin isoforms and receptors may contribute preferentially to different aspects of synaptogenesis, morphogenesis, and types of learning.

Disclosures: Q. Yang: None. **S.R. Kassabov:** None. **E.R. Kandel:** None. **R.D. Hawkins:** None.

Poster

PSTR092: Learning and Memory in Invertebrates

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Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR092.15/O20

Topic: H.08. Learning and Memory

Support: NIH grant NS019895

Title: Optimal intervals for multi-block training protocol to induce persistent LTF

Authors: *R.-Y. LIU[1], Y. ZHANG[2], P. D. SMOLEN[3], J. H. BYRNE[4];
[1]McGovern Med. Sch. at UTHealth, Dept. of Neurobio. and Anat., Houston, TX; [2]Neurobio. & Anat., McGovern Med. Sch. of UTHSC At Houston, Houston, TX; [3]Dept. of Neurobio. and Anat., McGovern Med. Sch. of UTHSC At Houston, Houston, TX; [4]Dept. of Neurobio. and Anat., McGovern Med. Sch. at UTHealth Houston, Houston, TX

Abstract: Long-term facilitation (LTF) of the *Aplysia* sensorimotor synapse is an established model system that has provided insights into mechanisms of learning and memory. LTF induced by a single block of a Standard protocol, consisting of five, 5-min pulses of 5-HT with regular interstimulus intervals (ISIs) of 20 min, persists for at least 24 h but decays to baseline by 48 h after treatment. Multiple blocks of 5-HT treatment, or of training, produce much longer lasting (i.e., 168 h) LTF and long-term sensitization (Frost et al. 1985; Hu et al. 2015; Wainwright et al. 2002) than single blocks, implying that some "trace" left behind after the first block of trials facilitates the effects of a second block. We predicted that, in the presence of the presumed trace, one pulse of 5-HT, a protocol that normally only produces short-term facilitation, would induce LTF, but only when applied at the "right" time (Smolen et al. 2016). Prior studies indicate that 24 h after LTF induction, the phosphorylated form of the transcription activator CREB1 is elevated, whereas the expression of the transcription repressor CREB2 is at basal level (Liu et al., 2008; 2011). In contrast, immunoflurosescence assays indicated that phosphorylation of p38 MAPK, a kinase that suppresses LTF (Guan et al. 2003) was significantly elevated at 18 h (34.6 ± 6.7% of vehicle control, paired t-test, $t_7 = -4.831$, $p = 0.013$) but not at 24 h (3.6 ± 6.4%, paired t-test, $t_8 = -0.622$, $p > 0.5$) after a single block of the Standard protocol. Therefore, we predicted that a second, single pulse of 5-HT at 24 h after induction of LTF may induce persistent LTF, but a second, single pulse of 5-HT at 18 h would not. To test this hypothesis, a single pulse of 5-HT was applied 18 h, or 24 h, after the first block of 5-HT treatment, and the EPSP amplitude was measured 24 h after the 2nd block. One 5-HT pulse given at 24 h induced a 44 ± 9% ($n = 7$) increases in EPSP amplitude measured at 48 h post first block treatment, whereas in the one pulse of vehicle control and one pulse of 5-HT at 18 h groups, the changes in EPSP amplitude were 1 ± 10% ($n = 6$) and 7 ± 10% ($n = 6$), respectively. One-way ANOVA revealed a significant difference among these three groups ($F_{2,16} = 7.15$, $p = 0.006$). Subsequent pair-wise comparisons (SNK) indicated one pulse of 5-HT at 24 h induced significant facilitation compared to vehicle ($q = 4.9$, $p = 0.009$), or to one pulse at 18 h ($n = 7$, $q = 4.2$, $p = 0.01$), suggesting that as predicted, the single pulse at 24 h, but not 18 h, induced 48 h LTF. These

results suggest the dynamics of key kinases such as p38 MAPK, and transcription factors CREB1 and CREB2, can be used to predict successful training protocols to prolong LTF.

Disclosures: R. Liu: None. **Y. Zhang:** None. **P.D. Smolen:** None. **J.H. Byrne:** None.

Poster

PSTR092: Learning and Memory in Invertebrates

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR092.16/O21

Topic: H.08. Learning and Memory

Support: NSF Grant 2322317

Title: Exploring the Effects of Ferulic Acid onLearning and Expression of Glutamate receptors in a C. elegans Alzheimer model

Authors: *J. ROSE[1], **C. CROPPI**[2], E. WESTGARD[2], G. HEINER[2], J. GAUVIN[3]; [1]Western Washington Univ. Behavioral Neurosci. Program, Bellingham, WA; [2]Western Washington Univ., Bellingham, WA; [3]Psychology, Western Washington Univ., Bellingham, WA

Abstract: Currently, 6.9 million Americans are living with Alzheimer's Disease (AD), a neurodegenerative disease associated with memory loss, cognitive decline, and disordered mood. The lead hypothesis on the cause of AD is a combination of amyloid beta plaques and tau tangles, cellular proteins that occur naturally in the brain. This study aims to evaluate if ferulic acid (FA), a dietary antioxidant, aids learning deficits and learning-associated receptor expression in a *Caenorhabditis elegans* (*C. elegans*) AD model. Our AD model (CL2355) expresses amyloid beta plaques panneuronally after cultivation in 23-degree Celsius environments. CL2355 has also shown learning deficits, movement challenges, and sterility issues in previous research. Learning was evaluated by conducting an associative chemotaxis assay pairing benzaldehyde with starvation. This learning test found little effect of FA, but interestingly the vehicle, dimethyl sulfoxide (DMSO) did seem to show some recovery in learning. To examine specific glutamate receptors (GLR-1) and the effect of FA on expression in this AD model, we created a new transgenic line that expressed the AB protein and GLR-1-mRFP. There was an increase in GLR-1::mRFP intensity in worms exposed to FA, but this change in GLR-1 expression was not seen with the AD model. To assess the gene expression of GLR-1 in the AD model after FA treatment we also performed RT-qPCR. By diving deeper into behavior, receptor localization, and genetic expression we can assess FA’s ability to rescue learning deficits associated with AD.

Disclosures: J. Rose: None. **C. Croppi:** None. **E. Westgard:** None. **G. Heiner:** None. **J. Gauvin:** None.

Poster

PSTR092: Learning and Memory in Invertebrates

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Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR092.17/O22

Topic: H.08. Learning and Memory

Support: NSF Grant 2322317

Title: Investigating CaMKIIγ (UNC-43) in Neuronal Mechanisms of Learning and Memory in C. elegans

Authors: *K. NELSON[1], A. AHMED[1], J. KING[1], A. HUYNH[2], T. JURGENS[1], J. K. ROSE[3]; [1]Western Washington Univ., Bellingham, WA; [2]Western Washington Univ. Behavioral Neurosci. Program, Bellingham, WA; [3]Psychology, Western Washington Univ. Behavioral Neurosci. Program, Bellingham, WA

Abstract: Calcium/calmodulin-kinase II (CaMKII) plays a role in neuronal mechanisms of learning and memory. In *C. elegans*, the unc-43 gene is an ortholog of CaMKII with *C. elegans* isoform sequences aligning to mammalian CaMKIIδ or CaMKIIγ. A mutation that affects expression of all UNC-43 isoforms (i.e., *unc-43*(n498)) modulates glutamate receptor expression (specifically GLR-1) in neurons; however, behavioral studies of learning with this strain are limited due to the uncoordinated motor phenotype. The *unc-43*(gk452) mutant strain is unique to other *unc-43* mutants as it is superficially wild-type; thus, allowing for behavioral studies of learning and memory. Interestingly, the *unc-43*(gk452) mutation affects the coding region of UNC-43, isoform t, for which the protein sequence is more than 40% identical to CaMKIIγ. Previous studies report that expression of *unc-43*(gk452) regulates learning pathways by activating cAMP-response element binding (CREB) protein. The current study examines the *unc-43*(gk452) strain using a relatively novel learning protocol where conditioning is restricted to a brief, discrete time period. Based on signaling competition, this learning assay described previously by our lab employs pairing two stimuli that drive opposing motor responses: blue light ~480 nm elicits forward locomotion while a mild mechanosensory vibration results in backward locomotion. Learning and memory in *unc-43*(gk452) mutant worms is tested at 1-, 10-, or 60 minutes after one block of 5 stimulus pairings. Initial data with this protocol indicates a deficit in learning after one block of training measured at 10 minutes. To examine the effect of *unc-43*(gk452) on GLR-1 glutamate receptor expression, confocal imaging of an *unc-43*(gk452); GLR-1::GFP cross was performed. Additionally, an mCherry tagged UNC-43, isoform t, construct will be expressed to assess localization in the ventral nerve cord and colocalization with GLR-1::GFP. Observing learning and memory, as well as receptor expression in intact animals, we will be able to further describe the role of CaMKIIγ in associative learning and memory.

Disclosures: K. Nelson: None. **A. Ahmed:** None. **J. King:** None. **A. Huynh:** None. **T. Jurgens:** None. **J.K. Rose:** None.

Poster

PSTR092: Learning and Memory in Invertebrates

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Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR092.18/O23

Topic: H.08. Learning and Memory

Support: NS118606

Title: Neural substrate of repetition priming of egestive motor patterns in Aplysia.

Authors: *C. NEVEU[1], E. C. CROPPER[2], J. H. BYRNE[3];
[1]UTHealth, Houston, TX; [2]Neurosci., Icahn Schl Med/Mt Sinai, New York, NY; [3]Dept. of Neurobio. and Anat., McGovern Med. Sch. at UTHealth Houston, Houston, TX

Abstract: Repeated expression of a behavior increases the performance of that behavior by a form of learning called repetition priming. Although ubiquitous, the mechanism underlying repetition priming is poorly understood. To better understand repetition priming, an egestive repetition priming protocol was implemented for the feeding behavior of *Aplysia* (Siniscalchi et al., 2016). *Aplysia* feeding consists of motor activity patterns that include closure of a tongue-like structure during either the protraction (egestive motor pattern) or the retraction phase (ingestive motor pattern) and is mediated by the buccal ganglia that continue to express fictive motor programs and egestive priming even when isolated from the animal. Previous research indicates that monotonic stimulation (2 Hz) of the esophageal nerve (EN) increases the activity of B8, a neuron that sends an axonal projection through the radular nerve (RN) to mediate radula closure (Siniscalchi et al., 2016). We predict that additional neurons are essential for the expression of egestive priming. Therefore, we monitored the activity of 10-100s of neurons by staining the buccal ganglia with voltage-sensitive dye, Di-4-ANNEPS, and imaging before and during egestive priming of isolated buccal ganglia (N = 12). Consistent with previous findings, egestive priming increased the RN activity during protraction. By examining the VSD imaging data, we identified neuron B8 in 6 preparations. Egestive priming significantly increased B8 activity during the protraction phase. We then investigated whether additional neurons were modified by egestive priming. Egestive priming significantly increased the activity of two previously uncharacterized neurons projecting through RN and active during the retraction phase. These results indicate that egestive priming modifies the network to a greater extent than previously anticipated and that VSD imaging can be used to locate and identify these plasticity loci.

Disclosures: C. Neveu: None. **E.C. Cropper:** None. **J.H. Byrne:** None.

Poster

PSTR092: Learning and Memory in Invertebrates

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR092.19/O24

Topic: H.08. Learning and Memory

Support: NIH Grant NS101356

Title: Operant conditioning induces parallel and combinatorial synaptic and nonsynaptic plasticity.

Authors: *Y. MOMOHARA[1], C. L. NEVEU[2], J. H. BYRNE[2];
[1]Univ. of Texas Hlth. Sci. Ctr., Houston, Houston, TX; [2]Neurobio. and Anat., McGovern Med. Sch. at The Univ. of Texas Hlth. Sci. Ctr. at Houston, Houston, TX

Abstract: Operant conditioning (OC) is a form of associative learning in which reward increases the expression of a behavior. Despite the prevalence of OC, there is a lack of understanding of how rewards modulate complex neural networks to reinforce the expression of behavior. To address this issue, we exploited the technical advantages of feeding behavior of *Aplysia*. The neural circuit underlying feeding is well characterized and is modified by OC. Feeding consists of two types of buccal motor patterns (BMPs); ingestion-like BMPs (iBMP) and rejection-like BMPs (rBMP). These can be distinguished by the timing of radula closure relative to the two phases of the BMPs, protraction and retraction. Patterns with>50% of total duration of closure activity occurring during retraction are defined as iBMP. In a recent study, Costa et. al. (2022) showed that OC resulted in the earlier recruitment of neurons active during the retraction phase. Here, we used intracellular recording techniques to examine the extent to which changes in their intrinsic and synaptic properties could explain the shift in neural activities in retraction. We focused on the retraction generator neuron B64 and retraction terminator neuron B52. The expression of iBMPs was increased in the reinforced group compared to a control group ($p<0.001$, n=12). In the reinforced group, the burst threshold of B64 was significantly reduced ($p=0.023$, n=11) and the number of spikes in B52 elicited by a suprathreshold current injection was decreased ($p<0.001$, n=12). In B52, the sag potential and input resistance were also reduced (sag potential, $p=0.004$; Input resistance, $p=0.02$, n=10). These data suggest that OC accelerates initiation of retraction and prolongs its duration, by increasing the excitability of retraction generators and decreasing the excitability of retraction terminating neurons. In addition, we examine whether OC modulates protraction neurons. B20 protraction neuron, which has an excitatory synaptic connection to radula closer neuron B8 and thereby contributes to its activity during protraction. The excitatory synaptic connection from B20 to B8 was significantly reduced by OC (p=0.016, n=7). Given that robust B8 firing is observed in the retraction phase rather than protraction in iBMP, reduction of B20-B8 synapse during protraction could contribute to the generation of iBMPs. Therefore, OC modulates in parallel the pathways that play temporally and functionally different roles in neural circuit.

Disclosures: Y. Momohara: None. **C.L. Neveu:** None. **J.H. Byrne:** None.

Poster

PSTR092: Learning and Memory in Invertebrates

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Program #/Poster #: PSTR092.20/O25

Topic: H.08. Learning and Memory

Support: NIH grant NS101356

Title: Comparing the low dimensional signature of short- and long-term effects of operant conditioning

Authors: *N. GONZALEZ[1], C. NEVEU[2], Y. MOMOHARA[3], S. VANAKI[4,5], J. H. BYRNE[6]; [1]UTHealth Houston, Houston, TX; [2]Neurobio. and Anat., UTHealth, Houston, TX; [3]Neurobio. and Anat., McGovern Med. Sch. at The Univ. of Texas Hlth. Sci. Ctr. at Houston, Houston, TX; [4]Neurobio. and Anat., UT Hlth. Houston, Houston, TX; [5]Electrical and Computat. Engin., Rice Univ., Houston, TX; [6]Dept. of Neurobio. and Anat., McGovern Med. Sch. at UTHealth Houston, Houston, TX

Abstract: Operant conditioning (OC) is a form of learning in which a specific behavior is reinforced by a reward and has multiple temporal domains, such as short-term OC (STOC) lasting a few minutes, to long-term OC (LTOC) persisting at least 24 h. Analyzing the neural mechanisms of OC has proven challenging due to the complexity of neural circuits in the CNS of vertebrates. Thus, the present study investigated OC using feeding behavior of *Aplysia*. The buccal ganglia control feeding behavior and continue to generate fictive buccal motor programs (BMPs), consisting of a protraction and retraction phase, when isolated from the animal. An in vitro analog of OC in which an ingestive BMP (iBMP) is paired with a reward increases BMP expression immediately (Brembs et al., 2002) and for at least 24 h after training (Mozzachiodi et al., 2008). A number of neuronal correlates of STOC have been identified (Brembs et al., 2002; Momohara et al., 2021), but other than changes in one neuron, B51 (Mozzachiodi et al., 2008), little is known about correlates of LTOC. To begin to examine the extent to which ST and LT OC share common neuronal correlates, we used voltage-sensitive dye (VSD) imaging. Previously, we used VSD to record the activity of 100s of individual neurons simultaneously on the caudal surface of buccal ganglia immediately after training (STOC) (Costa et al., 2022). During training, monotonic stimulation of the Bn. 2,3 nerve elicited BMPs. The En.2 nerve was stimulated as reinforcement immediately following every iBMP in the contingent group, while the yoked group En.2 was stimulated with the same timing as the contingent group but without regard to BMP activity. Similar to previous studies, we found that conditioned ganglia produced a greater number of iBMPs than control ganglia 24 h after training (Contingent iBMP % = 74.2; Yoked iBMP % = 24.4; $p<0.001$, n=11). Importantly, the VSD recordings revealed activation patterns in phase with the BMPs, which can help identify neurons most likely to be modified by OC. The next step will be to use VSD imaging to compare the recruited neural ensembles in LTOC with those previously observed following STOC. We will use non-negative matrix factorization (NMF) (Costa et al., 2022), a dimensionality reduction technique, to identify neurons involved in protraction and retraction in LTOC between contingent and yoked ganglia. These results will be compared to previous studies that found the primary signature of STOC to be an advance in recruitment of the BMP retraction neuronal module (Costa et al., 2022) to elucidate whether LTOC has a unique signature, which neurons are specifically involved in OC and how they synergistically interact to mediate long-term memory.

Disclosures: N. Gonzalez: None. **C. Neveu:** None. **Y. Momohara:** None. **S. Vanaki:** None. **J.H. Byrne:** None.

Poster

PSTR092: Learning and Memory in Invertebrates

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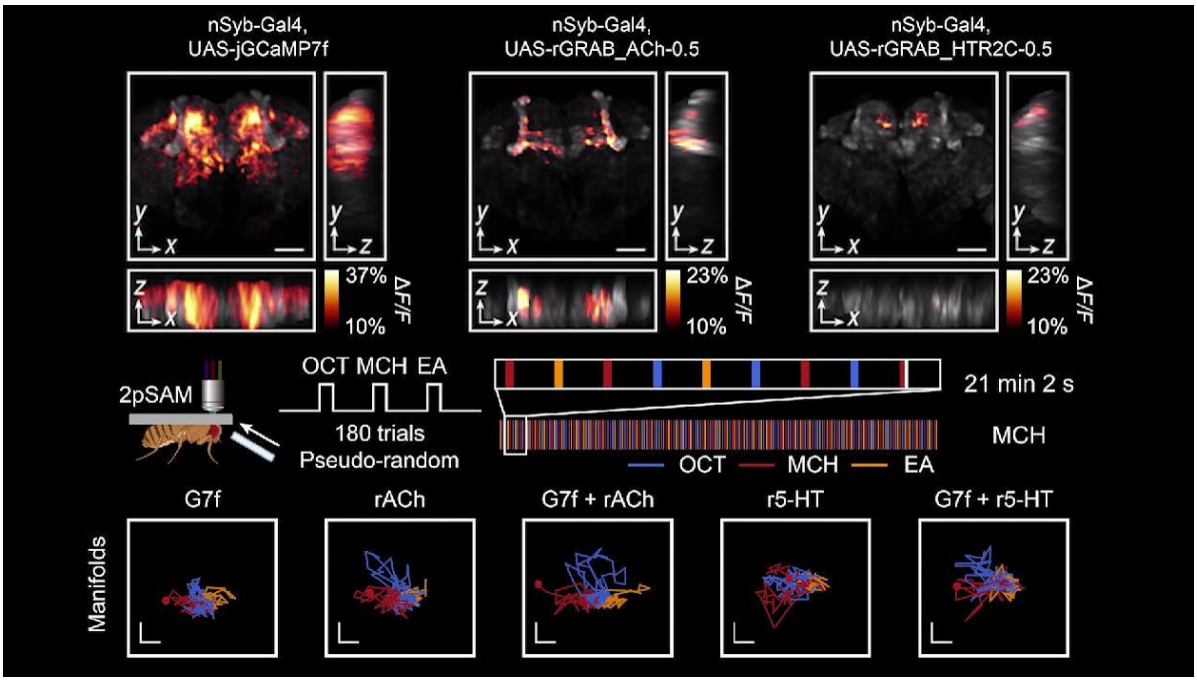
Program #/Poster #: PSTR092.21/O26

Topic: H.08. Learning and Memory

Title: Whole-brain long-term multi-modal imaging of Drosophila reveals network dynamics and information representation during olfaction, learning and memory

Authors: *J. FAN, J. WU, L. FANG, Q. DAI;
Tsinghua Univ., Beijing, China

Abstract: The rapid advancement of high-throughput microscopy techniques has catalyzed a transformative shift in neuroscience research. *In vivo* recordings of neuronal activities across brain regions provide unprecedented insights into neural functional networks and their spatiotemporal encoding mechanisms. However, the scope of brain regions and temporal extent remain constrained by throughput limitations and phototoxic effects. Moreover, despite extensive studies on neuronal dynamics, significant gaps exist in accessing other critical signals such as neuromodulators, neurotransmitters, and glia-related signals, limiting our understanding of brain function. To address these challenges, we employed two-photon synthetic aperture microscopy (2pSAM) with novel fluorescent neuromodulator indicators for high-speed, long-term imaging of neuronal and neuromodulatory activities throughout the *Drosophila* brain. This technique utilizes the three-dimensional imaging capacities and low phototoxicity of 2pSAM. Our findings revealed distinct patterns of information encoding and network dynamics between neuronal and neuromodulatory activities during repeated olfactory stimulations. We discovered a compensatory relationship between neuronal activity and cholinergic dynamics in brain-wide odor identity representation and the functional connectivity network structures of specific brain regions. Furthermore, low-dimensional manifold and functional connectivity network analyses showed that cholinergic dynamics offer a more consistent representation than neuronal dynamics over extended periods. This method also holds the potential to uncover new insights into other areas such as learning and memory, which have widespread effects across the brain. Instead of the detailed inquiry into localized learning and memory circuits, our approach provides a comprehensive perspective on network alterations across the entire brain and aids in identifying information representations in previously uncharted regions, contributing to a whole-brain functional atlas.



Disclosures: J. Fan: None. **J. Wu:** None. **L. Fang:** None. **Q. Dai:** None.

Poster

PSTR092: Learning and Memory in Invertebrates

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Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR092.22/O27

Topic: H.08. Learning and Memory

Support: NSF Grant 2322317

Title: Molecular and behavioral multigenerational outcomes of mild in-utero stress in Molecular and behavioral multigenerational outcomes of mild in-utero stress C. elegans

Authors: *A. TOKAR FALATAH[1], M. BUTLER[2], C. GOULD[2], J. K. ROSE[3];
[1]Western Washington Univ. Behavioral Neurosci. Program, Bellingham, WA; [2]Western Washington Univ., Bellingham, WA; [3]Psychology, Western Washington Univ. Behavioral Neurosci. Program, Bellingham, WA

Abstract: Past research has shown that maternal stress, also known as in-utero stress, results in anxiety-, depression-, and schizophrenia-like behaviors in rodent models. Changes in glutamate receptor expression, namely NMDA and AMPA receptors, have also been observed. Past studies in our lab demonstrated that In-utero stress in *Caenorhabditis elegans* (*C. elegans*) produces significant intergenerational differences in spontaneous locomotor behavior. Extending from this result, the current study investigates the multigenerational effects of chronic mild stress on

learning in *C. elegans*. The parental generation is subjected to stress using a chronic, unpredictable stress protocol adapted from rodent chronic stress models. Age-synchronized Wild-Type (N2) worms were subjected to three conditions: Control, suspension in liquid buffer (Sham), and suspension in liquid buffer coupled with motion (Stress) for 4 hours, the time period of egg formation in this hermaphroditic animal. Learning was quantified using an associative conditioning assay that paired two stimuli that drive opposing locomotor responses: blue light ~480 nm, which usually elicits forward locomotion, and a vibration (300 Hz) that typically evokes a backward locomotor response. After five pairings of stimuli, a vibration tone alone is presented to test learning behavior. We examined learning behavior for four generations (P0 - F3). Intergenerational effects are observed by examining the P0 - F2 generations while transgenerational effects were examined in the F3 generation. In addition to learning, glutamate receptor expression (GLR-1::GFP) was also assessed across all treatments to decipher a possible neural correlate for this learning. Together, this work examining learned behavior and receptor localization and expression will begin to elucidate the multigenerational effects of stress.

Disclosures: A. Tokar Falatah: None. **M. Butler:** None. **C. Gould:** None. **J.K. Rose:** None.

Poster

PSTR092: Learning and Memory in Invertebrates

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR092.23/O28

Topic: E.04. Voluntary Movements

Support: Deutsche Forschungsgemeinschaft, grant number BR 1892/17-1.

Title: Evidence for motor neuron plasticity as a major contributor to motor learning in Drosophila

Authors: A. EHWEINER[1], C. DUCH[2], ***B. BREMBS**[1];
[1]Univ. Regensburg, Regensburg, Germany; [2]Johannes Gutenberg Univ. of Mainz, Mainz, Germany

Abstract: Motor learning is central to human existence, such as learning to speak or walk, sports moves, or rehabilitation after injury. Evidence suggests that all forms of motor learning share an evolutionarily conserved molecular plasticity pathway. Here, we present novel insights into the neural processes underlying operant self-learning, a form of motor learning in the fruit fly *Drosophila.* We operantly trained wild type and transgenic *Drosophila* fruit flies, tethered at the torque meter, in a motor learning task that required them to initiate and maintain turning maneuvers around their vertical body axis (yaw torque). We combined this behavioral experiment with transgenic peptide expression, CRISPR/Cas9-mediated, spatio-temporally controlled gene knock-out and confocal microscopy. We discovered that expression of atypical protein kinase C (aPKC) in direct wing steering motoneurons co-expressing the transcription factor *FoxP* is necessary for this type of motor learning and that aPKC likely acts via non-

canonical pathways. Eliciting optomotor responses in yaw torque provided evidence of motoneuron plasticity as operant training altered optomotor responses in a training-specific fashion. We also found that it takes two weeks for CRISPR/Cas9-mediated knockout of *FoxP* in adult animals to impair motor learning, suggesting that adult *FoxP* expression is required for operant self-learning. Our experiments suggest that, for operant self-learning, a type of motor learning in *Drosophila*, co-expression of atypical protein kinase C (aPKC) and the transcription factor *FoxP* is necessary in direct wing steering motoneurons. Some of these neurons control the wing beat amplitude when generating optomotor responses, and we have discovered modulation of optomotor behavior after operant self-learning. We also discovered that aPKC likely acts via non-canonical pathways and that FoxP expression is also required in adult flies.

Disclosures: A. Ehweiner: None. **C. Duch:** None. **B. Brembs:** None.

Poster

PSTR093: Timing and Temporal Processing

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR093.01/O29

Topic: H.08. Learning and Memory

Title: Energy constraints force the emergence of predictive behaviors in simulated evolution

Authors: W. KANG, C. ANAND, ***Y. CHOE**;
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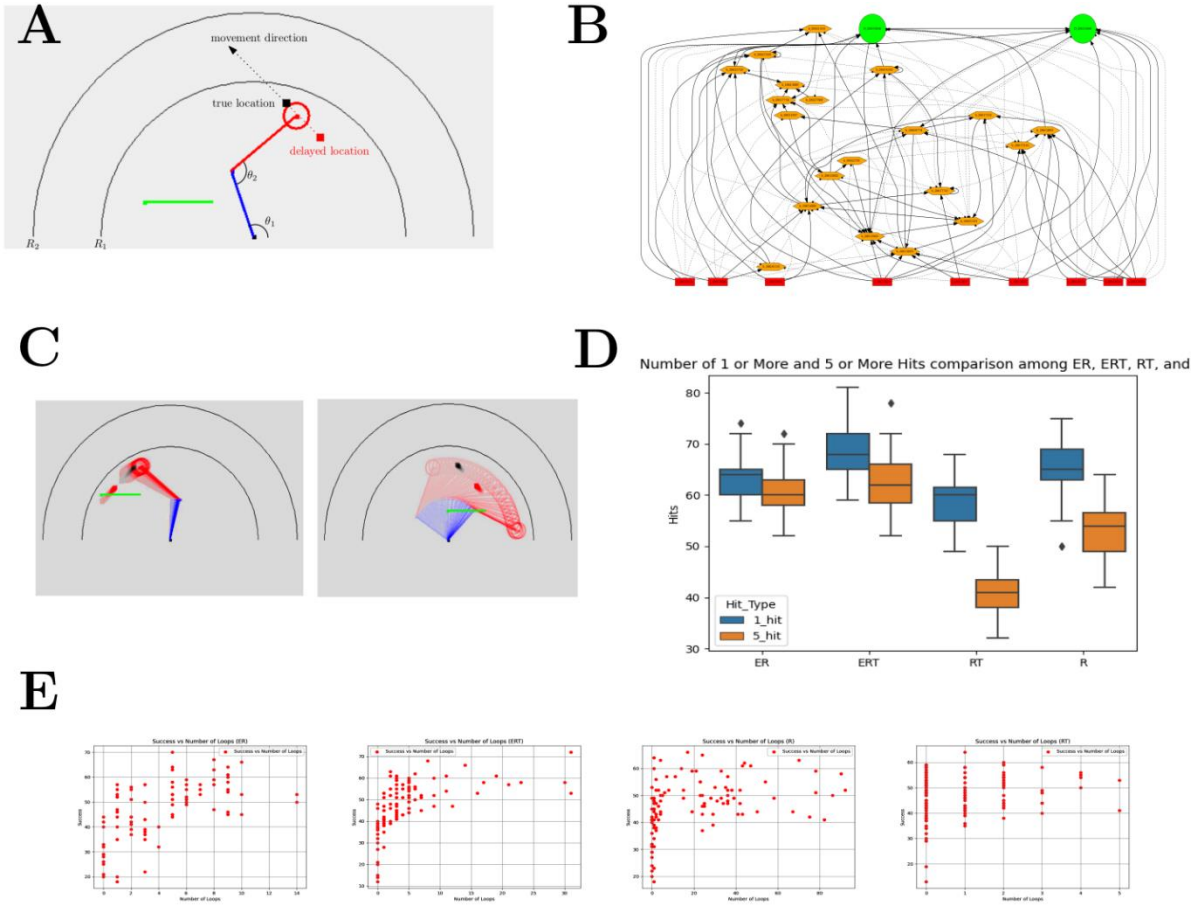
Abstract: Prediction is an important foundation of cognitive and intelligent behavior. However, how such predictive capabilities emerged through evolution from simple organisms has not been investigated fully. Prior works have shown that input delay and environmental change can lead to predictive properties. In this paper, we investigate additional factors that may contribute to the emergence of predictive behavior in evolving artificial neural networks. We set up a delayed reaching task with a two-segment articulated arm. The arm is controlled to reach a moving target, where the target's coordinate information is received with a delay (Fig A). To extend the reach, a tool (a stick) could be picked up. In this task, without predicting the trajectory of the moving target, the controller cannot reach the target. For the controller, we used the NeuroEvolution of Augmenting Topologies (NEAT) algorithm (Fig B: typical evolved neural network: red=input, orange=hidden, green=output; fitness=ERT). Our results indicate that an important fitness criterion for the emergence of predictive behavior is that of reduced energy usage. We measured predictive capability by counting the number of 5 consecutive hits (5_hit). For comparison, non-predictive touch gives the 1_hit measure. Fitness criteria that included energy (E) as a factor (other factors: R=5_hit, T=tool pickup) showed higher predictive behavior (Fig D, "5_hit"[orange]): ER>R (n=31, p=9.71e-07); ERT>RT (n=31,p=1.36e-11). These differences vanished when the criteria did not measure prediction (Fig D, "1_hit"[blue]). Typical predictive behavior (left: consecutive hits) vs. non-predictive behaviors (right: non-consecutive hits) are shown in Fig C as a time-lapse. Further analysis shows that the number of recurrent

loops correlates with target reaching performance (5_hit success rate), but more strongly so with the energy constraint (Fig E: correlation coeffcient): ER=0.59, ERT=0.51, R=0.17, RT=0.38. We expect our findings to shed new light on energy constraints on the evolution of predictive behavior.



Disclosures: W. Kang: None. **C. Anand:** None. **Y. Choe:** None.

Poster

PSTR093: Timing and Temporal Processing

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR093.02/O30

Topic: H.08. Learning and Memory

Support: Postdoc.Mobility-Stipendium Nr.P500PB_206885

Title: Brain-distributed neural representation of timing behaviour

Authors: *M. SERRANO[1], M. CASTELLI[1], Y. PENG[1], A. SHAROTT[2], D. DUPRET[3];
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Abstract: The ability to sense elapsed time is central to complex cognitive functions, informing every day the decisions we take and the actions we make. Yet, how neural populations distributed across the brain keep track of time remains unclear. Here, we set out to investigate large-scale neural population activity associated with timing behaviour. We developed a self-paced behavioural paradigm in which head-fixed mice learn to initiate reaching movements towards a spout dispensing drops of water reward. Mice start each trial themselves by holding onto a bar; the reward is then only dispensed if a certain amount of waiting time (target delay) has elapsed before they initiate the reach. We observed that mice can learn the target delay through trial-and-error, successfully adjusting their behaviour to optimize performance. We used multiple neuropixel probes to simultaneously record neural activity from several brain regions, including the striatum, nucleus accumbens, hippocampus, thalamus, parietal, and prefrontal cortices, while mice learned and performed this task. Our preliminary analyses indicate that population activity preceding self-paced reaches contains information that allows elapsed trial time to be decoded, with neurons across all recorded regions contributing to this time representation. By analysing cells with significant decoding contribution, we further observed that time keeping relates to a limited set of temporal firing patterns. Embedding population firing into a low-dimensional space allowed unsupervised retrieval of these distinct neuronal tuning curves. This ongoing work suggests a principle of organisation for time tracking by neuronal populations in goal-directed self-paced behaviour.

Disclosures: M. Serrano: None. **M. Castelli:** None. **Y. Peng:** None. **A. Sharott:** None. **D. Dupret:** None.

Poster

PSTR093: Timing and Temporal Processing

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR093.03/O31

Topic: H.08. Learning and Memory

Support: R01MH132171532

Title: Laplace neural manifolds support timed behaviors via logarithmically compressed timelines of past and expected future events

Authors: *R. CAO, A. SARKAR, M. W. HOWARD;
Dept. of Psychological and Brain Sci., Boston Univ., Boston, MA

Abstract: The ability to form an expected future timeline and plan for timed actions accordingly is crucial to our survival. Recent data suggest that the brain maintains Laplace transformed neural timelines of the past and the planned future. We apply a cognitive model that uses this

representation to explain various timing behaviors in interval timing and associative learning tasks. The model comprises of three components: 1. a population of exponentially decaying neurons that encode the Laplace transform of past events at various rates across neurons; 2. a weight matrix that stores Hebbian associations of past events with the present; 3. a population of exponentially ramping neurons at various rates that encode the Laplace transform of the expected future given the present. This model allows an agent to continuously update its memory and the predicted future in relation to the present moment as events unfold. Unlike typical recurrent neural networks (RNNs) for timing behaviors, each component in our model maps to concrete cognitive functions, which enables the agent to adjust and manipulate a logarithmically compressed timeline to meet various task demands.

Disclosures: R. Cao: None. **A. Sarkar:** None. **M.W. Howard:** None.

Poster

PSTR093: Timing and Temporal Processing

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR093.04/O32

Topic: H.08. Learning and Memory

Support: NTNU Internal grant
The Kristian Gerhard Jebsen Foundation
University Hospital Trondheim
The Central Norway Regional Health Authority

Title: Neural dynamics in the human entorhinal cortex are linked to event segmentation and processing of episodic time

Authors: *M. JÄCKELS[1,2,3,4,5], C. F. DOELLER[6,7,3], T. BONNEVIE[8,7,3,4,5];
[1]Kavli Inst. for Systems Neurosci., Norwegian Univ. of Sci. and Technol., Trondheim, Norway; [2]Department of Neuromedicine and Movement Science, Norwegian University of Science and Technology, Trondheim, Norway; [3]K.G. Jebsen Center for Alzheimer's Disease, Norwegian University of Science and Technology, Trondheim, Norway; [4]Neuroclinic, University Hospital Trondheim, Trondheim, Norway; [5]Max Planck Institute for Human Cognitive and Brain Sciences, Leipzig, Germany; [6]Max Planck Inst. for Human Cognitive and Brain Sci., Leipzig, Germany; [7]Kavli Institute for Systems Neuroscience, Norwegian University of Science and Technology, Trondheim, Norway; [8]Dept. of Neuromedicine and Movement Sci., Norwegian Univ. of Sci. and Technol., Trondheim, Norway

Abstract: Episodic memory, the recollection of past experiences, is thought to be structured by event boundaries - salient shifts in our ongoing stream of experiences. The medial temporal lobe (MTL), known for its pivotal role in episodic memory, has been associated with event boundary processing in numerous studies. However, while much of the research has concentrated on the hippocampus, the entorhinal cortex (EC) has received less attention. Our study specifically

focuses on the lateral EC (LEC), which has been implicated in the temporal organization of episodic memories in both rodents and humans. Despite this suggested role, direct evidence for a role of LEC in processing event boundaries and event structure is sparse. We aim to bridge this gap and elucidate the role of LEC in event boundary processing and its impact on episodic temporal memory. So far, we have collected fMRI brain scans from participants while they listened to an auditory story. Subsequently, participants were asked to rate the position, order, and distance of presented clip pairs. A separate group of participants listened to the same story and rated event boundaries. Our preliminary data shows a scaling between neural pattern dissimilarity and subjective distance estimates for equally spaced (120s) clip pairs from the story, for multiple MTL areas including LEC, medial entorhinal cortex (MEC), and hippocampus, but not control areas V1 and M1. Furthermore, we show a robust relationship between the variance of neural activity within voxels and the amount of event boundaries between the same clip pairs for LEC, and MEC but not the hippocampus, V1, or M1. Together these results could contribute to advance our understanding of the role of the entorhinal cortex during event segmentation and episodic temporal memory.

Disclosures: M. Jäckels: None. **C.F. Doeller:** None. **T. Bonnevie:** None.

Poster

PSTR093: Timing and Temporal Processing

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR093.05/O33

Topic: H.08. Learning and Memory

Support: NIH UF1NS116241 DC000566
NSF BCS-1926676
NSF ECCS-2319405

Title: Employing holographic stimulation to probe the cellular basis of decision-predicting time cells.

Authors: *K. STEINKE[1], C. M. MCCULLOUGH[2], G. FUTIA[3], E. GIBSON[4], D. RESTREPO[5];
[1]Univ. of Colorado Anschutz Med. Campus Grad. Sch., Aurora, CO; [2]Bioengineering, Univ. of Colorado Anschutz Med. Campus, Aurora, CO; [3]Univ. of Colorado Anschutz Med. Campus, Aurora, CO; [4]Bioengineering, Univ. of Colorado Denver Anschutz Med. Campus, Aurora, CO; [5]Cell and Developmental Biol., Univ. of Colorado, Aurora, CO

Abstract: In the United States approximately 2.55 million people were affected by a memory related disease (such as Alzheimer's) in 2017, making it the second biggest neurological burden for the country, with trends suggesting these numbers are increasing. Importantly, a hallmark of Alzheimer's is the early loss of the sense of smell, highlighting important connections between memory and olfaction. Thus, it is increasingly relevant to study the biological processes

underlying memory formation and recall in olfactory settings. Previous research demonstrates a prominent role for the hippocampus, particularly dorsal CA1 (dCA1), in learning and memory, strongly suggesting a fantastic target for studying the binding of associative, episodic, and contextual information to experiences which can be retrieved. However, how these memories are stored, processed, and recalled is currently unknown. dCA1 contains both glutaminergic excitatory pyramidal cells and GABAergic inhibitory interneurons. It has been demonstrated that following olfactory discrimination learning, pyramidal cells develop selective responses to odorants as the animal becomes proficient at the go no-go task. Post hoc neural decoding of spiking patterns results in prediction of which odor was presented to the animal during a particular trial. Our recent work demonstrates that select populations of pyramidal neurons display divergent stimulus responses taking place at discrete times, thereby exhibiting 'time tiling', which can be thought of as temporally discrete divergence in activity related to stimulus valence during the go no-go associative learning task. Time tiling of these "decision-predicting time cells" (DPTCs) is reminiscent of time tiling of dCA1 "stimulus time cells" that respond to odors at discrete times between odorant application in delayed non-match to sample tasks. This work aims to probe the cellular basis of DPTCs, testing if they are a Calbindin 2 subpopulation of pyramidal cells, and test if DPTCs are necessary for correct behavioral responses in the go-no go task. Additionally, I investigate the role of parvalbumin (PV) interneurons play in the time tiling of DPTCs.

Disclosures: K. Steinke: None. **C.M. McCullough:** None. **G. Futia:** None. **E. Gibson:** None. **D. Restrepo:** None.

Poster

PSTR093: Timing and Temporal Processing

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR093.06/O34

Topic: H.08. Learning and Memory

Title: Time and rhythm representations in the primate hippocampus during a visual metronome task

Authors: *M. SALGADO-MENEZ[1], V. DE LAFUENTE[2];
[1]Inst. de Neurobiología, Juriquilla, Mexico; [2]Neurobio. Inst., Queretaro, Mexico

Abstract: Elapsed time, in murines, is represented by time cells that fire at specific times withinam interval. Here, we asked about time and rhythm representations by hippocampal neurons in monkeys in a visual metronome task. In addition to a low proportion of time cells, we found a vast majority of oscillatory neurons that adjusted their firing rate dynamics to encode fast, medium, and slow tempi. Remarkably, these oscillatory responses were strongly modulated by task parameters such as the spatial location of the visual stimulus and whether this stimulus was visible or imagined. Thus, our results indicate that hippocampal neurons encode

behaviorally relevant and time-changing states of the world, and they do this for external and internally simulated events.

Disclosures: M. Salgado-Menez: None. **V. de Lafuente:** None.

Poster

PSTR093: Timing and Temporal Processing

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR093.07/O35

Topic: H.08. Learning and Memory

Support: National Science Foundation BCS-2043740 (M.D.R.)

Title: A brain network model of surprise generalizes to predict psychological expectation violations

Authors: *Z. ZHANG[1,2], M. D. ROSENBERG[3,4,5];
[1]The Univ. of Chicago, Chicago, IL; [2]Dept. of Psychology, University of Chicago, Chicago, IL; [3]Dept. of Psychology, Univ. of Chicago, Chicago, IL; [4]Neuroscience Institute, University of Chicago, Chicago, IL; [5]Institute for Mind and Biology, University of Chicago, Chicago, IL

Abstract: Surprise is a fundamental human experience. We can be surprised by a plot twist in a movie or an underdog's victory in a sports match. Despite being in completely different situations, does our brain process unexpected changes in those moments similarly? To address this question, we previously identified a brain network model, the surprise edge-fluctuation-based predictive model (EFPM), from interaction dynamics (i.e., co-fluctuations) between pairs of brain regions calculated as the element-wise product of their functional magnetic resonance imaging (fMRI) time series (Faskowitz et al., 2020). We demonstrated that this model predicted surprise in an adaptive learning task and generalized to predict surprise as a separate group of individuals watched suspenseful basketball games (Zhang et al., 2023). Here we ask whether the surprise EFPM generalizes to predict a different kind of surprise: expectation violations that include impossible situations (e.g., agents passing through a solid wall) and psychological interactions. We analyzed an openly available fMRI dataset collected while 29 participants watched short video clips showing expected events (expected videos) or violations of expectations (unexpected videos) in the domains of psychology and physics (Liu et al. 2024; doi:10.18112/openneuro.ds004934.v1.0.0). Violations of physics expectations included solid objects blipping in and out of existence. Violations of psychology expectations included agents changing their goals or acting inefficiently. We calculated the strength of the surprise EFPM during the expected vs. unexpected videos and conducted a t-test to compare them. Demonstrating model generalizability, surprise network strength was higher during the unexpected vs. expected psychology videos. This difference, however, was not significant during videos that violated expectations about physics. To test model specificity, we compared the surprise network strength during (a) expected psychology videos vs. periods of fixation and (b)

expected psychology vs. expected physics videos. Demonstrating specificity, surprise network strength did not differ between expected psychology videos and fixation or between expected psychology and physics videos. These results suggest that the surprise EFPM is a generalizable neural predictor of surprise across distinct contexts.

Disclosures: Z. Zhang: None. **M.D. Rosenberg:** None.

Poster

PSTR093: Timing and Temporal Processing

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR093.08/O36

Topic: H.08. Learning and Memory

Support: Fonds de la Recherche Scientifique - FNRS CDR/OL J0132.21

Title: Encoding of objective and subjective temporal uncertainties in the CNV

Authors: *D. A. DRAZYK, M. MISSAL;
Inst. of Neurosci., Univ. Catholique de Louvain, Bruxelles, Belgium

Abstract: Temporal information can be learned implicitly e.g. by repeated observation. This process probably involves an estimation of timing variability or uncertainty. In an experimental context, temporal uncertainty can be varied by presenting experimental subjects with differing delay periods (or foreperiod, 'FP') between a warning and an imperative visual stimuli. The aim of the present study was to investigate how the brain anticipates future stimuli whose timing is distributed according to a Gaussian distribution and implicitly learned. It was hypothesized that objective and/or subjective uncertainty will alter the slope of the contingent negative variation ('CNV') recorded during the FP. The current oculomotor and EEG study was conducted on 39 human subjects (21 women; average ± sd, 26.64 ± 4.40 years). The behavioural task was to execute a visually-guided saccade between a central warning stimulus and an eccentric imperative stimulus appearing at the end of a delay or foreperiod ('FP'). FP duration in each experimental block was drawn from a different distribution. Firstly, the impact of increasing objective uncertainty was tested by increasing the variability of FP duration from 'low' to 'high'. Secondly, the mean of the FP distribution was either short (1600 ms) or long (2400 ms), increasing subjective uncertainty. This design created four different uncertainty contexts: 'short-low', 'short-high', 'long-low' and 'long-high'. We found that the centrally localised CNV had significantly lower amplitude during the short FP length. This could imply that anticipation of a promptly appearing imperative stimulus could cause an increase of CNV slope. Further, the centro-parietal CNV amplitude was lower for the low variability blocks of trials but only in the long FP condition. In conclusion, both objective and subjective temporal uncertainties influenced the time course of the CNV signal even in conditions when temporal information was implicit.

Disclosures: D.A. Drazyk: None. **M. Missal:** None.

Poster

PSTR093: Timing and Temporal Processing

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR093.09/O37

Topic: H.08. Learning and Memory

Support: JSPS KAKENHI (22K18263)

Title: Effects of a tactile flicker on the cutaneous rabbit illusion

Authors: *M. HAKAMATA[1], K. TAKAMA[1], N. KAWAGUCHI[3], M. MIYAZAKI[1,2];
[1]Fac. of Informatics, [2]Grad. Sch. of Integrated Sci. and Technol., Shizuoka Univ., Hamamatsu, Japan; [3]Epileptology, Natl. Epilepsy Center, NHO Shizuoka Inst. of Epilepsy and Neurolog. Disorders, Shizuoka-city, Japan

Abstract: The cutaneous rabbit illusion refers to illusory displacements of perceived positions of two rapid, consecutive taps, such that the first tap attracts the perceived position of the second tap and vice versa (Geldard, 1975). This illusion occurs stably when the interstimulus interval (ISI) of the two taps is smaller than 100 ms, and the illusionary distance becomes shorter when the ISI was shorter. Although this illusory effect occurs within a short time window, it indicates that the perceptual experience of an event can be modified by past and future events. Especially, the effect by future events has been called “postdiction” (Eagleman & Sejnowski, 2000), suggesting that sensory inputs are not sequentially processed but are reconstructed before reaching our consciousness. To calculate the processes for postdiction, we focused on the flicker (or click train) effects. Prior repetitive stimuli with high frequencies (e.g., 20-25 Hz) shorten (Johnston et al. 2006, vision) or elongate (Jones et al. 2011, audition) the perceived duration of subsequent stimuli. We tested the flicker effects on the cutaneous rabbit illusion. In the present experiments, we used a tactile flicker composed of repetitive taps with a frequency of 25 Hz and duration of 5 s. Additionally, we used two taps with a blank of 5 s as control prior stimuli. While the tactile flicker shortened the perceived intervals of the subsequent two taps with ISIs of 30-100 ms compared to the control stimuli, it had no effect on the perceived position of the subsequent tap. In the main experiment, after the tactile flicker or control stimuli, participants were presented with two sequential taps (P1 and P2). P1 and P2 were separated by 100 mm in distance and 60 ms in time, which induced the cutaneous rabbit illusion. Consequently, the perceived distance between P1 and P2 was significantly shorter when the tactile flicker was presented than when the control stimuli were presented. Thus, the tactile flicker shortened the perceived time interval between the taps and enhanced the cutaneous rabbit illusion. These results suggest that the cutaneous rabbit illusion is affected by the perceived time intervals of the two taps rather than by the actual time intervals. Moreover, this finding suggests that the tactile postdiction was processed after the flicker modulated the perceived time intervals of tactile inputs.

Disclosures: M. hakamata: None. **K. Takama:** None. **N. Kawaguchi:** None. **M. Miyazaki:** None.

Poster

PSTR093: Timing and Temporal Processing

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Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR093.10/P1

Topic: H.08. Learning and Memory

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NSF CAREER Award: IOS-2145814
Whitehall Foundation
Brain and Behavior Research Foundation
Basic Science Research Program through the National Research Foundation of Korea (NRF) RS-2023-00242639

Title: Neural network underlying time cells of medial entorhinal cortex in temporal delayed non-match to sample task

Authors: *H.-W. LEE, J. C. BOWLER, J. G. HEYS;
Neurobio., Univ. of Utah, Salt Lake City, UT

Abstract: Increasing evidence indicates that the medial entorhinal cortex (MEC) plays a role in interval timing behavior (Dombeck and Heys, 2018; Heys et al., 2020; Vo et al., 2021; Dias et al., 2021). Recently, we have shown that inactivation of the MEC disrupts the ability to learn timing behavior, and MEC 'time cells' exhibit firing at distinct moments during interval timing behavior (Bigus et al., 2024). However, the neural circuit mechanisms underlying the generation of time cell activity in the MEC remain elusive. We hypothesize that MEC time cells might emerge from a common circuit mechanism that could also generate the spatial firing of grid cells in the MEC. It has been proposed that grid cells can be generated from a continuous attractor network (CAN), which requires a particular pattern of structured recurrent connectivity (Burak and Fiete, 2009). We note that the same CAN model could be utilized for integrating a constant input, instead of running speed and direction, to estimate elapsed time (Issa et al., 2020). To test this, we developed a temporal version of the delayed non-match to sample (tDNMS) task. In the task, mice are trained to report whether pairs of odor stimuli do not match in duration. Chemogenetic inactivation of the MEC disrupts the learning of the tDNMS task (n=15 DREADD; n=16 control), and two-photon calcium imaging of the MEC during the task reveals time cells (34% of the total cell n=2056, 6 mice) that remap according to the duration of the odors. Importantly, we found evidence that MEC time cells could be generated from the CAN model. The pairwise correlation of MEC time cells in the tDNMS task remains similar during non-task-relevant inter-trial intervals. This coherence in pairwise activity supports our hypothesis as it suggests that the relative phases of MEC time cells would be coherent across different contexts, akin to the coherence in relative phases observed in grid cells recorded across task and

non-task epochs (Fyhn et al., 2007; Yoon et al., 2013). In our ongoing experiments, we are collecting single-unit activity from the MEC using Neuropixels while animals sequentially perform in both tDNMS and virtual reality navigation tasks. This experimental design allows us to investigate the extent of overlap between the MEC grid cell and time cell populations. Through this experiment, we aim to reveal the circuit mechanism underlying the MEC time cells and determine whether distance and duration might be computed through the same local circuitry within the MEC.

Disclosures: H. Lee: None. **J.C. Bowler:** None. **J.G. Heys:** None.

Poster

PSTR093: Timing and Temporal Processing

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR093.11/P2

Topic: H.08. Learning and Memory

Support: Whitehall Foundation
Brain and Behavior Research Foundation
NIH/NIMH 1 DP2 MH129958-01
NSF CAREER Award: IOS-2145814
University of Utah

Title: Hippocampal time cells display differential activity across temporal contexts

Authors: *E. BIGUS[1], J. G. HEYS[2];
[1]Univ. of Utah, Salt Lake City, UT; [2]Neurobio. and Anat., Univ. of Utah, Salt Lake City, UT

Abstract: Experiences unfold over time, meaning the brain must encode the durations of and between events to form an accurate memory. Previous work identified “time cells” within the hippocampus (HPC), which fire at regular moments within a temporally structured experience, with the population of time cells forming a trajectory spanning the experience. It has been proposed that HPC time cells might track the temporal structure of experiences. However, HPC time cells have typically been studied in behavioral paradigms without an explicit timing demand, making it unclear whether these cells truly contribute to learning durations and encoding temporal information into memory. To address the hypothesis that HPC time cells contribute to learning temporal relationships, we formed several testable predictions. First, HPC time cells should fire in sequence to span the duration of each trial in an explicit timing task that requires attending to duration. Second, as animals learn to distinguish the temporal structures of distinct trials, time cell trajectories should diverge, so that distinct patterns of time cell activity reflect distinct temporally structured experiences. To test these predictions, we are performing cellular-resolution Ca2+ imaging in area CA1 of the HPC as mice learn the temporal delayed non-match to sample (tDNMS) paradigm we previously developed. In each trial of the tDNMS task, mice must track a series of two stimulus durations, then make a go/no-go decision based

upon the combination of stimulus durations, or the temporal structure of each trial (i.e. temporal context). By imaging before and after task learning, we aim to identify changes in time cell activity that could support learning of temporal context. Our preliminary results confirm our first prediction, demonstrating that CA1 contains time cells that fire reliably at a specific timepoint within a trial, with the sequence of time cells spanning the trial duration. Additionally, consistent with our second prediction, we find that a subset of CA1 time cells display context-dependent dynamics, whereby cells are preferentially active in specific trial types at moments when mice can behaviorally distinguish temporal context. These findings suggest that HPC time cells do encode temporal information, with context-dependent time cells putatively permitting the encoding of distinct temporally structured experiences. Given our previous finding that the medial entorhinal cortex also contains context-dependent time cells, our work further demonstrates this coding motif may be widely used to encode temporal information into memory.

Disclosures: E. Bigus: None. **J.G. Heys:** None.

Poster

PSTR094: Place Cells

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR094.01/P3

Topic: H.09. Spatial Navigation

Support: Wellcome Trust (223144)

Title: Measuring the dimensionality of neural activity in CA1

Authors: *A. LANDAU, K. D. HARRIS, M. CARANDINI;
Univ. Col. London, London, United Kingdom

Abstract: Introduction. The CA1 region of the hippocampus represents spatial coordinates through place cells, which display elevated firing rates when animals enter specific locations in the world. Does the hippocampus carry a high-dimensional representation of space?
Methods. We trained mice on a simple, head-fixed navigation track using a linear track and multiple environments presented to the mouse in virtual reality, then measured activity of excitatory cells in CA1 using virally-expressed GCaMP6f and an imaging cannula. To explore the structure of the spatial code, we measured the eigenspectrum of population activity in CA1 using cross-validated principal component analysis (cvPCA), a method introduced by Stringer et al. (2019) which yields an unbiased estimate of the signal variance.
Results. We found that the spatial code has a low-dimensional, exponentially distributed eigenspectrum. In addition, we observed an increase in the total variance of the spatial code for each virtual environment as mice grew more familiar with that environment, suggesting that the signal-to-noise of spatial representations increases with familiarity. Finally, using shared variance component analysis, another method that measures cross-validated variance, but does so

independent of stimuli, we found that CA1 activity is extremely high-dimensional and obeys a power-law, similar to that of V1.
Conclusions. We hypothesize that CA1 carries a low-dimensional representation of spatial location in addition to a high-dimensional representation of non-spatial information.

Disclosures: A. Landau: None. **K.D. Harris:** None. **M. Carandini:** None.

Poster

PSTR094: Place Cells

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR094.02/P4

Topic: H.08. Learning and Memory

Support: HHMI

Title: Learning produces a hippocampal cognitive map in the form of an orthogonalized state machine

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Abstract: Cognitive maps confer animals with flexible intelligence by representing spatial, temporal, and abstract relationships that can be used to shape thought, planning, and behavior. Cognitive maps have been observed in the hippocampus, but their algorithmic form and the processes by which they are learned remain obscure. Here, we employed large-scale, longitudinal two-photon calcium imaging to record activity from thousands of neurons in the CA1 region of the hippocampus while mice learned to efficiently collect rewards in two subtly different versions of linear tracks in virtual reality. The results provide a detailed view of the formation of a cognitive map in the hippocampus. Throughout learning, both the animal behavior and hippocampal neural activity progressed through multiple intermediate stages, gradually revealing improved task representation that mirrored improved behavioral efficiency. The learning process caused the majority of cells to emerge as splitter-like cells with varying properties, resulting in increasingly decorrelated population activity and ultimately orthogonalized representations resembling a state machine capturing the inherent structure of the task. We further demonstrate that mice exhibited adaptive behavior in novel task settings, with neural activity reflecting flexible deployment of the state machine. Computational modeling offered insights into the principles governing the generation of orthogonalized representations and the observed learning dynamics. We discovered that Hidden Markov Models (HMMs) and biologically plausible recurrent neural networks with Hebbian learning could capture the

evolving neural representations, while Long Short-Term Memory networks (LSTMs) and Transformers did not naturally produce such orthogonalized representations. Furthermore, we explored the properties of models that reproduced the dynamics of the decorrelation properties observed in mice and compared them to models that yielded different learning dynamics.These findings shed light on the mathematical form of cognitive maps, the learning rules that sculpt them, and the algorithms that promote adaptive behavior in animals. The work thus charts a course toward a deeper understanding of biological intelligence and offers insights toward developing more robust learning algorithms in artificial intelligence.

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Poster

PSTR094: Place Cells

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR094.03/P5

Topic: H.09. Spatial Navigation

Support: Howard Hughes Medical Institute
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Title: A cascade model of BTSP probability explains stable neural representations in the Hippocampus

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Abstract: How learned information is preserved in biological networks in the face of repeated learning is poorly understood. To examine this, we tracked the same population of hippocampal CA1 place cells (PC) as mice learned a task for 7 days. We found that the representation's overall stability increased with experience as both the number of PCs maintaining a stable place field and the stability of individual PCs increased across the week. The stable PCs excessively represented task-related learned information, were retrieved earlier within the session, and showed a strong correlation with behavioral performance. Both the initial formation of PCs and their retrieval on subsequent days was accompanied by prominent signs of behavioral timescale synaptic plasticity (BTSP), suggesting that even stable PCs were re-formed by new synaptic plasticity each session. The data further suggest that PCs' stability is a function of their prior activity as PCs that were previously active not only have a higher probability of forming PCs on subsequent days, but had their stability increase with the number of days they are active. This was also reflected in a higher occurrence of Ca-plateau potentials in more stable cells. In this study, we model the increase in BTSP propensity with each day of PF activity using a cascade

model of stability. Briefly, following activity PFs either transition to a reliable state with consistent activity and location on the following day or to a less reliable state with probabilistic recruitment. The likelihood of a PF transitioning to the reliable state, or being recruited from the unreliable state, rose with the number of active days. This leads to a gradient of probability of PF formation based on prior PF history which is similar to that of observed plateau potential rates in the experiments. The probabilistic reconstitution of PFs in the cascade model replicated the observed slow decay of PCs maintaining the same location of PF over days as well as the gradual buildup of sustained place cells over time. We further explore the possible circuit mechanisms behind the higher propensity for BTSP through a two-compartment model of CA1 pyramidal neuron with BTSP across sessions, allowing us to investigate the contribution of the Schaffer collateral and perforant path synapses. Our results suggest that CA1 memory is implemented by an increase in likelihood of new neuron-specific synaptic plasticity, as opposed to extensive long-term synaptic weight stabilization.

Disclosures: G. Li: None. **S. Vaidya:** None. **Y. Li:** None. **R.A. Chitwood:** None. **J.C. Magee:** None.

Poster

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Title: A contextual fear conditioning paradigm in head-fixed mice exploring virtual reality

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Abstract: Contextual fear conditioning is a laboratory task used for testing associative memory formation and retrieval. One key to understanding the brain mechanisms involved in memory is the ability to monitor neural activity from the same neuron populations over time. To understand how neurons involved in memory formation contribute to retrieval, it's important to track the activity of the same neurons during both formation and retrieval periods. Multi-photon microscopy techniques allow for this, but they require animals to be head-fixed. However, there

are only a few tasks that test contextual fear conditioning in head-fixed mice. To address this, we developed a contextual fear conditioning paradigm in head-fixed mice using virtual reality (VR) environments. We trained head-fixed mice to navigate these VR environments by running on a treadmill. We designed an apparatus to deliver tail shocks (unconditioned stimulus, US) while the mouse navigated the VR environment (conditioned stimulus, CS). The acquisition of contextual fear was tested when the mice were reintroduced to the VR environment the following day. We observed an increased conditioned fear response, characterized by increased freezing behavior. This was especially prominent during the first trial in the shock-paired VR environment, compared to a neutral environment where the mice received no shocks. Our results demonstrate that head-fixed mice can be fear conditioned in VR, can discriminate between a feared and neutral VR context, and can display freezing as a conditioned response, similar to freely behaving animals. Furthermore, we imaged from large populations of hippocampal CA1 neurons during the task, using a two-photon microscope. Our findings reconfirmed those from the literature on freely-moving animals, showing that CA1 place cells undergo remapping and restructuring following fear conditioning. Thus, this paradigm offers new opportunities for studying neural dynamics using the head-fixed preparation. By enabling examination of cellular and subcellular dynamics, this paradigm will aid in deciphering the mechanisms involved in memory acquisition, consolidation, retrieval, and extinction.

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Poster

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Title: Effects of cell-type specific dentate gyrus inhibition on CA1 place cell stability

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Abstract: Place cells in the hippocampus are the foundation of an internal cognitive map that supports episodic memory, with individual cells firing reliably at the same location within an

environment. Spatial representations within the hippocampus, however, are not fixed. Changes to an animal's external or internal experience produce changes in place cell population activity, either via representational drift over time or remapping across contexts. These characteristics of the hippocampal map facilitate the balance between flexibility and stability, which is necessary for reliable and accurate memory formation and storage. The dentate gyrus (DG) is the first step in the classical trisynaptic circuit and is thought to play an essential role in encoding memories and disambiguating small differences between experiences. Notably, the DG contains two distinct excitatory cell populations: granule cells (GCs) in the granule cell layer and mossy cells (MCs) in the hilus. The sparse firing of GCs is thought to support pattern separation, while MCs can broadly regulate GC activity and may contribute to novelty detection. While DG lesions have revealed effects on downstream place cell activity, it is unclear how individual DG cell types regulate the activity and stability of place cell population activity in CA1, the primary output region of the hippocampus.
We performed two-photon calcium imaging in the dorsal CA1 of head-fixed mice while they traversed virtual linear tracks. Using Drd2-cre and Dock10-cre mice, we evaluated the effect of selective and reversible inhibition of MC or GC activity, respectively, on CA1 circuit dynamics in novel and familiar environments. We recorded CA1 pyramidal cell activity following DREADD-mediated unilateral inhibition of MCs or GCs and on saline-injected control days (separate days in the same mice). MC inhibition selectively reduced place cell correlations between repeated exposures to the novel (but not familiar) environment, suggesting that MC disruption prevents the formation of a stable spatial map of novel contexts. In contrast, GC inhibition selectively increased place cell correlations between repeated exposures to the familiar environment, with no effect in the novel environment. This result indicates that GC activity may be necessary to discriminate between distinct episodes in the same spatial context and that DG pattern separation processes may promote representational drift in CA1. Together, these results reveal specific functions for distinct DG cell populations, with MCs promoting the stability of novel contextual information and GCs promoting flexibility in established spatial maps.

Disclosures: D. GoodSmith: None. **W. Carson:** None. **M.E.J. Sheffield:** None.

Poster

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Program #/Poster #: PSTR094.06/P8

Topic: H.09. Spatial Navigation

Title: Sap: a toolbox for single-channel axon/dendrite preprocessing in calcium imaging

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Abstract: We developed an analysis pipeline for axon or dendrite calcium imaging data collected using 2-photon microscopy. Historically, the challenges with imaging subcellular

activity include low signal-to-noise ratio, inaccurate identification of potential regions of interests (ROIs), potential movement artifacts in the signal, and difficulty with grouping ROIs that belong to the same axon or dendrite. To address these issues, as the first step, we smoothed time-series calcium traces from single ROIs that were identified using Suite2P and then used Fast Fourier Transform (FFT) to convert the traces into the frequency domain. We then identified frequency bands that were most likely associated with calcium transient dynamics. We employed band-pass filtering methods (e.g. 0.05 to 0.12 Hz) to select ROIs that contained frequencies that closely matched the power band of transients. Next, to remove ROIs with noisy step functions caused by Z-drifts in the field of view (FOV), we ranked ROIs by their power at low frequency bands associated with step functions and eliminated ROIs with the largest power. The remaining ROIs, which were highly likely to contain transients with low noise and exhibit minimal Z-drifts, underwent transient peak detection based on their prominence and duration. Finally, to explore the grouping of ROIs that potentially belong to the same axon or dendrite, we employed hierarchical clustering and k-means clustering methods. To confirm our clustering method grouped ROIs belonging to the same axon, we applied this method on a set of axons in the CA1 region of the hippocampus of mice navigating a familiar virtual environment that were then switched to a novel environment. This familiar-to-novel switch causes global remapping in the CA1. We grouped ROIs based on their activity in the familiar environment using hierarchical clustering and k-mean methods and compared the clustering results to an independent grouping method based on high correlation in both environments, which we consider “the ground truth” as only ROIs belonging to the same axon would be highly correlated during global remapping. We found that both axon clustering methods effectively determined the optimal number of clusters in the pairwise ROI correlation matrices and resulted in similar grouping to the ground truth comparison. Visual inspection of ROIs grouped to the same axon on the imaging FOV further confirmed the validity of clustering results. Together, our approach provides a guideline for researchers analyzing the activity of axons and dendrites using 2-photon calcium imaging to help standardize the extraction of physiological signals from sub-cellular structures during behavior.

Disclosures: A. Jiang: None. **C. Zhao:** None. **M. Sheffield:** None.

Poster

PSTR094: Place Cells

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Program #/Poster #: PSTR094.07/P9

Topic: H.09. Spatial Navigation

Title: The estrous cycle modulates hippocampal spine dynamics and spatial coding

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Abstract: The estrous cycle has been shown to exert a strong modulatory effect on the morphology of CA1 neurons in mammalian hippocampus. However, the role of the estrous cycle in hippocampal spatial coding, as well as longitudinal dendritic spine dynamics, remains unknown. To investigate this, we recorded CA1 pyramidal cells in the hippocampus of navigating mice across the estrous cycle using two-photon calcium imaging. We show that dendritic spine dynamics are shaped by hormonal state, with greater spine density during periods of greater estradiol and lower density when estradiol levels decrease. Apical dendritic activity was also highly estrous-modulated, with greater somatodendritic and intradendritic coupling during high estradiol periods. Finally, both greater place cell stability and remapping were observed during periods of high estradiol, spine density, and somatodendritic coupling. Our results suggest that the estrous cycle is a critical modulator of hippocampal spatial representations at multiple levels.

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Poster

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Topic: H.09. Spatial Navigation

Title: Idiosyncratic behavior determines mouse CA1 representational similarity in a multicompartment environment

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Abstract: Much evidence indicates that the extent to which different spaces evoke similar hippocampal representations is a critical determinant of memory outcomes such as interference and generalization (Liu et al., 2012; Grieves et al., 2016; Trouche et al., 2016; Rashid et al., 2016). Understanding the bases of hippocampal similarity is therefore crucial to understanding memory. Some theories suggest that hippocampal similarity is driven by common world features shared between spaces (Barry et al., 2006; Grieves et al., 2016), while other theories suggest that hippocampal similarity is at least in part determined by the idiosyncratic experience of the navigator (Colgin et al., 2010; Stachenfeld et al., 2017; Whittington, et al., 2020). To adjudicate between these possibilities, we imaged large populations of CA1 neurons as mice repeatedly navigated a radial multicompartment environment (a la Marchette et al., 2014), which allowed us to simultaneously characterize the pairwise similarity of four subcompartments over weeks. Contrary to the prediction that common world features alone drive representational similarity, we found that different mice exhibited distinct hippocampal similarity structures - which were accompanied by distinct behavioral trajectories - persisting over weeks when freely navigating. In each case, hippocampal similarity between subcompartments matched the similarity of behavioral trajectories within those subcompartments and/or the frequency of transitions between

those subcompartments. Constraining the movement of the mouse within the environment for one week led to a gradual shift in hippocampal similarity in the direction predicted by the constrained behavior, followed by a gradual return to the original representational structure once constraint was relaxed. These results indicate that hippocampal similarity in multicompartment environments is not driven by featural similarity alone but also the slow integration of idiosyncratic experience, evocative of recent state-transition models of cognitive mapping (Stachenfeld et al., 2017; Whittington, et al., 2020).

Disclosures: S.A. Pecirno: None. **A.T. Keinath:** None.

Poster

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Program #/Poster #: PSTR094.09/P11

Topic: H.09. Spatial Navigation

Title: Hippocampal remapping depends on task demand during context discrimination

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Abstract: When encoding memories, it is often necessary to separate similar experiences to avoid interference between memories. On the other hand, sometimes it is more advantageous to generalize experiences to prevent memory overload. However, it is unclear under what conditions the hippocampus separates memories and how the separation impacts hippocampal signaling. To address these questions, we explore how task demand, such as goal-directed reward retrieval impacts hippocampal computation during a discrimination task. We developed a novel automatized task that is performed in an octagonal-shaped arena, where each wall is equipped with a liquid reward port and with an LED cue. Mice must discriminate between two contexts, that are defined by adjacent LED cue pairs, to obtain reward at two distinct locations. To test the role of task demand, we designed a control task in which mice are rewarded at a single location in both contexts. We trained 14 mice and found that females (8) learned the discrimination task in 9+/-2 days and males (6) in 8+/-1 days (mean+/-SEM). To explore how the output of the hippocampus represents the different contexts, we performed freely moving calcium imaging of CA1 neurons using one-photon miniscope (N=3 mice). We found that 44% +/-1.5% (mean +/-SEM) of the extracted units were spatially tuned. Most strikingly, an increased remapping between the contexts was observed in the discrimination task compared to the control task ($p=0.003$, Wilcoxon rank-sum test). Our preliminary analysis suggests that the remapping cannot be entirely explained by distinct reward locations ($p=0.026$ when activity in the reward zone is excluded), suggesting a task demand dependent remapping in CA1. We currently perform

silicone probe recordings in dentate gyrus and CA3 to explore upstream hippocampal computations and information flow during context discrimination.

Disclosures: G. Tarcsay: None. **N. Masala:** None. **B.L. Boublil:** None. **J. Yi:** None. **M. Igarashi:** None. **U. Redic:** None. **L.A. Ewell:** None.

Poster

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Topic: H.09. Spatial Navigation

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Title: Critical role of normal astrocyte activity in spatial coding of hippocampal place cells

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Abstract: Hippocampal place cells play a critical role in encoding spatial information and are thought to be a cornerstone of the cognitive map for space. Accordingly, dysfunction in these cells has been associated with various cognitive disorders. However, the specific cellular mechanisms that shape place cell properties remain largely unknown. Recent studies highlighted the role of astrocytes in modulating neuronal activity and synaptic transmission, but their involvement in modulating spatial coding via interacting with place cells remains unknown. We hypothesized that hippocampal astrocyte activity plays a crucial role in modulating place cell properties. We used a mouse model where human muscarinic acetylcholine M3 receptors (hM3Dq) were expressed in astrocytes, alongside GCaMP6f expression in pyramidal neurons within the dorsal hippocampus, which allowed us to modulate astrocyte activity and longitudinally monitor calcium activity in place cells using a miniaturized fluorescent microscope, respectively. Initially, we activated astrocyte Gq signaling during the exploration of a familiar arena. Gq activation induced a significant decrease in spatial information scores, accompanied by reduced peak firing rates in place cells, while place field sizes remained unchanged. Subsequently, we activated astrocyte Gq signaling during the exploration of a novel arena. Interestingly, this led to a significant reduction in both place cell proportions and spatial information, alongside increased place field sizes and average firing rates. These findings indicate that maintaining normal astrocyte activity is crucial for precise place coding within the hippocampus in a novel environment. Furthermore, we also found that astrocyte Gq activation impairs object place recognition in mice. Taken together, our study sheds light on the intricate interplay between astrocyte activity and hippocampal place cell properties, emphasizing the importance of astrocytes in spatial cognition.

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Poster

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Topic: H.09. Spatial Navigation

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Title: Computational strategies of rats navigating spatial environments under changing reward conditions

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Abstract: Decision-making in uncertain environments requires a delicate balance between exploiting knowledge about good courses of action and exploring the environment to improve upon this knowledge. Bandit tasks, where decision-makers make repeated choices between n arms for which the average rewards change over time, have been shown as a useful paradigm for studying this trade-off. We considered four decision models addressing bandit tasks with different underlying representational assumptions: (1) a noisy win-stay/lose-shift strategy ("noisy-WSLS"); (2) optimal foraging based on the marginal value theorem ("foraging"); (3) determining choice values through reinforcement learning (RL); (4) balancing reward and information gain through active inference (AI). We compared two 3-armed choice conditions: one with slowly changing reward probabilities (restless bandit) and one with reward probabilities alternating between prioritizing one option selected randomly for 30 trials followed by a low probability of reward on all three arms for 10 trials (discrete bandit). In both conditions, all models showed a significantly higher probability of obtaining a reward than random choice. However, in the restless version, all the models showed similar performance of gaining reward, while in the discrete condition, RL, noisy-WSLS, and Foraging models showed significantly better performance than the AI model.

We then compared the overall performance and the trial-by-trial patterns of choices of simulated agents to rats performing a spatial 3-arm bandit task. Both sets of experiments were conducted on a T-shaped maze with three arms and a home base. Each arm offered some probability of reward, which changed across trials. Rats earned rewards more frequently than chance in both sets of experiments. In the restless condition, all agents showed slightly better performance than rats. However, on the discrete task, rats showed a similar reward distribution to the AI model, while the RL, Foraging, and Noisy-WSLS models gained more reward than the rats. Finally, we examined choice similarities between

rats and all models performing on the same task conditions. None of the models predicted the actual choice of the rats on the restless bandit better than an agent making random choices, while in the discrete version, all four models predicted behavior of the rat better than an agent making random choices. Hippocampal cells show typical place fields in these spatial tasks, including phase precession, theta sequences, and replay, enabling the comparison of representational effects on hippocampal planning and consolidation processes using these spatial bandit paradigms.

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Poster

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Title: Goal-anticipatory firing and phase precession in place cells during rotational scanning on the honeycomb maze

Authors: *C. YU[1,2,4], J. ORMOND[3], C. GRIFFITHS[3], M. SAHANI[4], J. M. O'KEEFE[3], N. BURGESS[2,3];
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Abstract: We analyse electrophysiological recordings of CA1 pyramidal cells in rats during goal-oriented navigation on the honeycomb maze (Ormond & O'Keefe, 2022), which was analysed in the previous study to identify subpopulation of hippocampal neurons that provide a goal-oriented vectorial rate code to support flexible navigation. Noting a general behavioural pattern of the animals during recording trials, we identify "active scanning" periods where the rats often peer over the edge of the platforms while waiting for the raising of adjacent choice platforms, and perform continuous scanning at higher angular speed (> 60 degrees/s) over an extended amount of time (scanning periods lasting > 0.8s, duration mean ± s.d.: 1.595 ± 0.430s). By restricting our analyses to such periods, we found strong evidence indicating goal-oriented anticipatory firing in the place cells. Specifically, by examining the relationship between the combined firing rate of the entire population of place cells and relative direction to the goal, we found that the population firing of place cell is significantly increased in the anticipation of head direction reaching the goal direction, regardless of rotational direction. The circular mean directions of the orientation-dependent firing ratemaps (combined over all place cells) are -83.38

degrees and 89.04 degrees relative to the goal direction for clockwise (CW) and counter-clockwise (CCW) rotations, respectively (Rayleigh uniformity test p-values: $2.09*10^{-7}$, 0.0011). Of all the active cells during active scanning, 18.6% (31 / 167) fire in both orientations whilst exhibiting significant offsets between CW- and CCW-specific ratemaps, 22.8% (38 / 167) and 31.3% (52 / 167) fire only in CW and CCW rotations respectively, with preferred firing direction before reaching the goal direction. The remaining cells do not show goal-oriented anticipatory firing, 7 of which are bi-directional cells where the mean directions of their CW and CCW ratemaps differ by < 30 degrees; and 16 CW and 23 CCW cells that fire at or after the goal direction.Temporal analysis of the “active scanning” periods shows robust theta phase precession on a population level for the cumulative angular displacement along the scanning direction relative to the onset of scanning (circular-r=-0.176, p=0.002). Collectively, these results suggest that hippocampal neurons comprise anticipatory goal-oriented angular-dependent encoding on a population level. This coding scheme is found during “active scanning” periods, indicating behavioural relevance of these findings for encoding of goal-direction.

Disclosures: C. Yu: A. Employment/Salary (full or part-time):; University of Cambridge. **J. Ormond:** A. Employment/Salary (full or part-time):; UCL. **C. Griffiths:** A. Employment/Salary (full or part-time):; UCL. **M. Sahani:** A. Employment/Salary (full or part-time):; UCL. 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.; Simons Foundation. **J.M. O'Keefe:** A. Employment/Salary (full or part-time):; UCL. 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.; Sainsbury Wellcome Centre Core Grant 090843/F/09/Z. **N. Burgess:** A. Employment/Salary (full or part-time):; UCL. 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.; Wellcome Principal Research Fellowship 222457/Z/21/Z, Wellcome Collaborative Award 214314/Z/18/Z.

Poster

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Topic: H.09. Spatial Navigation

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Title: Sleep loss enhances representational drift

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Abstract: Sleep following learning is beneficial for long-term memory. Previous work from our lab has shown that hippocampal cells that represent locations in a novel waking experience continue to reactivate for hours during post-experience rest/sleep. In contrast, sleep loss significantly diminishes the strength and duration of reactivation. Many studies have demonstrated that neuronal spatial representations gradually change over time in the phenomenon of representational drift. Several other studies have indicated that reactivation during sleep improves the stability of place fields across repeated exposures to the same space, but it is unknown how the stability of these representations are affected by the loss of sleep. We performed chronic high-density electrophysiological recordings in region CA1 of the dorsal hippocampus of two male and two female Long Evans rats before, during, and after exposure to a novel linear track (MAZE). Following track exposure, rats were either sleep-deprived (SD, n=5 sessions) via gentle handling for 5 hours, followed by 4 hours of recovery sleep, or allowed to sleep naturally (NSD, n=3 sessions) for the entire duration. Both groups of animals were re-introduced to the same track (reMAZE) 9 hours later. We found that NSD sessions exhibited high correlations between population-level place field firing patterns from MAZE to reMAZE, supporting the idea that sleep promotes place cell stability. In contrast, SD sessions exhibited enhanced representational drift indicated by lower correlations from MAZE to reMAZE compared to NSD sessions. Spatial tunings during MAZE were initially broad, indicative of learning-related plasticity, and sharpened to more spatially specific patterns during reMAZE following NSD sessions. In contrast, spatial tunings following SD remained broad during reMAZE. These results indicate that sleep loss accelerates place cell representational drift and resets the hippocampus to a state where de novo learning occurs even in a previously experienced environment.

Disclosures: N.R. Kinsky: None. **B.K. Giri:** None. **K. Diba:** None.

Poster

PSTR095: Human Timing and Temporal Processing

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR095.01/Q4

Topic: H.10. Human Learning and Cognition

Support: JSPS-KAKENHI #23KK0046
JSPS-KAKENHI #23K22372

Title: Changes in Bayesian properties induced by visual temporal learning in humans

Authors: *B. OSHIMA[1], Y. YOTSUMOTO[2];
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Abstract: We have various mechanisms to stabilize our perception. In time perception, for example, when time estimation is difficult, we tend to bias our estimates toward the average of previously experienced time lengths, which implies the use of prior information. Recent studies suggest that this bias, known as central tendency, might optimize performance in a time reproduction task and explained well by Bayesian models (Jazayeri & Shadlen, 2010). In addition, musicians demonstrated smaller reproduction errors than non-musicians (Cicchini et al., 2012; Aagten-Murphy et al., 2014), but the process underlying such improvements and how learning from a temporal distribution progresses remain unexplored. To address this gap, we tested how Bayesian properties of time perception change through learning and whether learning effects generalize. Fourteen non-musicians participated in a visual time reproduction task over six days. The experiment consisted of pre- and post-tests with three temporal distributions, and four training days with one of these distributions with feedback. We hypothesized that improving temporal perceptual precision through training would result in reduced variability in reproduced durations and decreased central tendency due to increased reliance on current perception. We assessed central tendency using regression index (RI) and errors using BIAS (error related to accuracy) and coefficient of variation (CV, error related to precision). Paired t-test revealed a significant decrease in CV for short ($t(13) = 6.57$, $p < 0.001$, $d = 1.76$), medium ($t(13) = 2.43$, $p = 0.030$, $d = 0.65$), and long distributions ($t(13) = 2.25$, $p = 0.042$, $d = 0.60$) and no significant change in RI and BIAS. The decrease in CV suggests an improvement in temporal perceptual precision through training. However, no decrease in central tendency was observed, perhaps because repeated exposure to the medium distribution in training promoted refinement of prior. This suggests that, in a Bayesian framework, our estimation is optimized by learning in both ways, capturing the statistical properties of the environment to reinforce prior as well as improving perceptual precision to enhance likelihood. In addition, the decrease in CV for the distributions unused in training indicates that mechanisms for improving temporal perceptual precision are not specific to time length.

Disclosures: B. Oshima: None. **Y. Yotsumoto:** None.

Poster

PSTR095: Human Timing and Temporal Processing

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR095.02/Q5

Topic: H.10. Human Learning and Cognition

Title: Estimating the window of subjective simultaneity through illusions.

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Abstract: Conscious experience is typically felt as a continuous stream (James 1890). In the typical conscious experience, sensory inputs are processed smoothly without any discontinuity

except sleeping, coma or other disruptions of the conscious state. There are illusions associated with variabilities in the time course of conscious experience. In the flash-lag effect (Nijhawan 1994), the position of the moving object is consciously perceived not where the flash occurred but at some future position of the moving object, an illusion showing that external information is not necessarily reflected in our consciousness immediately, and that there could be lag or compression of information.In the wagon wheel effect (Purves et al. 1996), a rapidly rotating object, e.g. a tire or propeller, appear to flip its direction of rotation when the speed of the rotation is above certain level. Specifically, such apparent rotation reversal takes place when the time of half-rotation is smaller than the sampling interval, suggesting discrete probing processes of visual sensory information.In the intentional binding effect (Haggard et al. 2002), when a subject acts with an intention, the moment when he/she acts is perceived to be later toward its effect, and the time of the effect is perceived to be earlier and temporarily closer to the action than its actual time of occurrence. Such shifts of perceived time would suggest a process in which multiple events within certain time intervals are integrated as subjectively simultaneous events, in the processing of consciously perceived sensory information.When the subject makes simultaneity judgments under various conditions, the window of subjective simultaneity (WSS) (Poppel 1988) varies depending on the nature of interaction, sensory information, and the active/inactive nature of the subject's behavior (Arikan et al. 2017) . Here we study the consistency and variability of WSS in subjects when they make simultaneity and timing judgments in experimental settings inducing various illusions. We analyze and identify elements correlating with the consistency and variability of WSS across different illusions. We discuss the nature of WSS and the neural mechanism (Shimojo 2014) involved in the construction of a moment of subjective experience.

Disclosures: S. Nozawa: None. **K. Mogi:** None.

Poster

PSTR095: Human Timing and Temporal Processing

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR095.03/Web Only

Topic: H.10. Human Learning and Cognition

Support: JSPS KAKENHI (22H00502)
JSPS KAKEINHI (22K18263)

Title: Effects of stimulus-response compatibility on body-part specific acquisition of multiple prior distributions in human coincidence timing

Authors: *Y. TANAKA[1], N. SHIMADA[1], M. MIYAZAKI[2];
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Abstract: During timing tasks, the brain acquires a prior distribution of the target timing to improve the accuracy and precision of the timing behavior. Multiple events occur in the course of daily activities (e.g., speedball/slowball in ball sports), requiring the brain to acquire multiple prior distributions in real environments. Our research group reported that in a coincidence timing task, two distinct prior distributions can be concurrently acquired by assigning two different motor effectors (e.g., the left and right hands) to the respective priors ("body-part specificity," Matsumura et al. 2024, npj Sci Learn). The body-part-specific prior acquisition was faster when the priors were assigned to anatomically distant body parts (hand/foot) than when they were assigned to nearby body parts (index/middle fingers). Subsequently, we investigated the effects of spatial distance between the hands on body-part specificity (Shimada et al., SfN2022, NEURO2023), and the results suggested that stimulus-response (S-R) compatibility was effective. In this study, we directly investigated the effects of S-R compatibility. Each participant completed 640 trials of the coincidence timing task. Target time intervals were sampled from one of the following two distributions: short prior (424-988 ms, mean: 706 ms) and long prior (1129-1694 ms, mean: 1412 ms). Each prior was assigned to one of the two stimulus locations. In the control group, the target stimuli were presented either on the left or right side of the fixation. In the S-R-incompatible group, the target stimuli were presented either on the upper or lower side of the fixation. In both groups, the participants placed their left and right index fingers on the left- and right-side keys (distance: 3.7 cm), respectively. The participants performed timing responses using their left and right index fingers according to the left and right stimuli in the control group and the upper and lower stimuli in the S-R-incompatible group, respectively. Consequently, the acquisition of two independent priors was achieved in trials 161-320 in the control group but in trials 321-480 in the S-R-incompatible group. Thus, the incompatible stimulus-response arrangement delayed the acquisition of multiple prior distributions. Conversely, our results suggest that a smoother acquisition of multiple prior distributions requires higher stimulus-response compatibility between the targets and motor effectors assigned to the priors.

Disclosures: Y. Tanaka: None. **N. Shimada:** None. **M. Miyazaki:** None.

Poster

PSTR095: Human Timing and Temporal Processing

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR095.04/Q6

Topic: H.10. Human Learning and Cognition

Support: NSF-BCS-PAC-2043318

Title: Preferred Period and Resonance Tuning in a Rhythmic Motor Task: Long-term Stability and Cognitive and Mechanical Contributions

Authors: *H. SERRE[1], M. EDRAKI[2], D. STERNAD[3];
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Abstract: Previous work has shown a preference for certain frequencies in the rhythmic movements of both humans and animals. In the case of pendulum-like movements, these preferred rates closely correspond to the resonance frequencies of mechanical models of the limbs. While these studies provided evidence that humans sense and tune into the resonance properties of their limbs, little attention has been given to the long-term persistence of such behavior and potential interference from other tasks. If there are inter-individual variations, are they consistent over time and cognitive engagement? The aim of the present study was to assess: 1) the *individual* preferred frequency in wrist flexion and extension with respect to resonance, 2) the consistency of these individual preferences over multiple days, and 3) the perturbing effects of performing a concurrent cognitive task. In Experiment 1, 8 participants were instructed to swing a pendulum via wrist flexion and extension. Two pendulums of different lengths and two conditions were compared: 1) moving at preferred rate alone, 2) concurrently counting backwards by 7 aloud. They performed 5 trials (30s each) for each condition with each pendulum (20 trials total). Data were collected for 10 sessions over a two-week time span. Results showed that the swinging frequency was close to each pendulum's natural frequency, albeit slight participant specific deviations consistent across days. Within-participant frequencies were significantly closer to the eigenfrequency of the pendulum during the cognitive condition. To further understand the effect of cognitive load on the ongoing stiffness of the swinging movement, experiment 2 included a grip sensor to record grip force as a proxy of wrist stiffness. Preliminary results showed three interesting characteristics: 1) grip force is applied in a rhythmic fashion in synchrony with the pendulum's oscillations; 2) during the cognitive task, grip force frequency was slightly closer to the pendulum's eigenfrequency; 3) this shift results in higher movement amplitude during the cognitive task. These findings offer fresh insights into the intricate interplay between individual timing preferences and cognitive demands, and the nuanced temporal adjustments in object interaction.

Disclosures: H. Serre: None. **M. Edraki:** None. **D. Sternad:** None.

Poster

PSTR095: Human Timing and Temporal Processing

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR095.05/R1

Topic: H.10. Human Learning and Cognition

Title: Separate, yet hierarchical mechanisms for timing and metacognition in learning of time intervals

Authors: *C. K. DESAI[1], M. WIENER[2];
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Abstract: Interval timing, the perception of elapsed time from hundreds of milliseconds to seconds, is an essential characteristic of cognitive function. In humans and animals, performance on interval timing tasks improves rapidly with learning, with both metacognitively aware of their past history of timing errors, yet relatively little work has been devoted to understanding how interval timing and metacognition are linked through learning. Recently, we have found evidence that timing and metacognitive awareness of timing errors rely on separate brain systems (Bader & Wiener, 2024; Journal of Neuroscience). To test this hypothesis further, we had human participants (n=30) perform a modified temporal reproduction task ("beat the clock") originally developed by Simen and colleagues (2011; Journal of Neuroscience), in which they were required to press a response key before a randomly-selected interval, anchored around 2s, elapsed to earn a monetary reward. Crucially, the same interval would repeat across trials for an unknown number of trials (4 - 20) before changing to a new interval. As an additional measure, after each trial, subjects were required to make a decision about whether or not the target interval had changed. In partial replication of Simen et al. (2011), we found that average participant performance improved linearly for the first 4 trials after a change, but not as fast as previously reported. Similarly, the probability of reporting a change was highest on the first trial after one occurred and declined linearly. Yet, performance on the task and the probability of reporting a change were uncorrelated, suggesting separate mechanisms. Additionally, subjects were more likely to report a change if the target elapsed before making a response than if they responded early. To explain these findings, we applied a learning model of interval timing based on opponent neural populations with a modifiable drift rate (Simen, et al. 2011). Here, we found the model could only accommodate our findings if separate learning rates were adopted for early versus late responses, where late responses were penalized more. Further the model could only replicate changepoint findings by assuming a second noisy process that later tracked the history of previous responses and their difference with the target. These findings support the notion of separate neural populations for measuring and monitoring time, respectively, in line with recent findings (Sarafyazd & Jazayeri, 2019; Science).

Disclosures: C.K. Desai: None. **M. Wiener:** None.

Poster

PSTR095: Human Timing and Temporal Processing

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR095.06/R2

Topic: H.10. Human Learning and Cognition

Support: JSPS KAKENHI (22H00502)
JSPS KAKENHI (19H01087)
JSPS KAKENHI (17KK0004)

Title: Supplementary vocalizations prime the acquisition of multiple prior distributions in human coincidence timing

Authors: *Y. OKUMURA[1], H. MIWA[2], N. ROACH[3], M. MIYAZAKI[2,4];
[1]Grad. Sch. of Integrated Sci. and Technol., Shizuoka Univ., Hamamatsu, Japan; [2]Fac. of Informatics, Shizuoka Univ., Hamamatsu, Japan; [3]Sch. of Psychology, Univ. of Nottingham, Nottingham, United Kingdom; [4]Graduate School of Integrated Science and Technology, Shizuoka University, Hamamatsu, Japan

Abstract: During timing tasks, the brain optimizes task performance by acquiring a prior distribution and integrating it with sensory information. In daily tasks (e.g., ball sports), events can have different temporal statistics (e.g., fastball/slowball). To generate optimal timing behavior in the real environments, it is critical that we can acquire multiple prior distributions. Recently, we reported that supplementary vocalization can facilitate concurrent acquisition of multiple prior distributions (Okumura et al. SfN2023), where participants selectively added a vocalization concomitantly to the dominant-hand timing response for one of the prior distributions. Notably, sport athletes often vocalize before or after their main motor responses. Here, we investigated whether the timing of the supplementary vocalization is critical for enabling concurrent acquisition of multiple prior distributions. Participants (n = 48) performed a coincidence timing task. Three sequential visual stimuli (S1, S2, and S3) were presented to the right or left of a fixation point. The time interval between S1 and S2 was equal to that between S2 and S3 in each trial. Participants attempted to press a handheld switch with their dominant thumb to coincide with S3. Stimulus intervals were randomly sampled from one of two distributions: the short prior (500-980 ms) and the long prior (1100-1580 ms). The two priors were assigned to stimuli presented on the left or right of fixation. Participants voiced “Ba” only when stimuli were presented on one side of fixation (i.e., either of the short or long prior). Separate groups of participants timed their vocal utterance to be either immediately before (*pre-vocalization*), during (*simultaneous-vocalization*), or immediately after (*post-vocalization*) the timing response with their dominant hand. Results revealed more pronounced divergence of the two acquired priors for the pre-vocalization group than for the other groups. Thus, selective pre-vocalization efficiently facilitated the acquisition of the two priors. Our finding suggests that preliminary behavioral contexts are effective for the acquisition of multiple prior distributions.

Disclosures: Y. Okumura: None. **H. Miwa:** None. **N. Roach:** None. **M. Miyazaki:** None.

Poster

PSTR095: Human Timing and Temporal Processing

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR095.07/R3

Topic: H.10. Human Learning and Cognition

Support: JSPS KAKENHI (22H00502)

Title: Invisible Pitch: Testing the Bayesian Estimation Model in Timing Behavior in Baseball Batting

Authors: *J. SUZUKI[1], Y. TANAKA[1], C. KASEGAWA[1], M. MIYAZAKI[1,2], T. KIMURA[3]; [1]Grad. Sch. of Integrated Sci. and Technol., [2]Fac. of Informatics, Shizuoka Univ., Hamamatsu-shi, Japan; [3]NTT Communication Sci. Labs., Atsugi-Shi, KANAGAWA, Japan

Abstract: Based on Bayesian estimation theory, the brain can improve sensorimotor behaviour accuracy by integrating a target's prior distribution with sensory information. Psychophysical studies have indicated that the brain implements Bayesian estimation for timing tasks. Recently, we investigated whether a Bayesian estimation model could be applied to timing behavior in baseball batting using a virtual reality system (Tanaka et al., SfN2023). Consequently, batting timing was biased toward the means of short and long prior distributions (i.e., fastball and slowball). The "central tendency" was thus observed as predicted by the basic Bayesian estimation model. However, the central tendency was greater for the short prior than the long prior, contrary to the predictions of the Bayesian estimation model, including scalar variability (greater sensory variability under longer intervals). Participants reported that they observed slowballs immediately before the balls reached the home base. Under this strategy, the time intervals to be estimated were shorter for the long prior, resulting in smaller scalar variability and central tendency. Based on this report, we hypothesized that if pitched balls are invisible in the middle of the pitch, batting timing responses behave as predicted by the Bayesian estimation model with scalar variability. The participants performed 240 trials of the virtual batting task. The time interval from the start of the ball pitch to the ball reaching the home base was sampled from a short (500-1000 ms) or long (1000-1500 ms) prior distribution. Half of the participants experienced the short prior in trials 1-120 and the long prior in trials 121-240, whereas the other half experienced the priors in the reverse order. When making the pitched balls invisible at half of the pitch, there was no significant difference in the degree of central tendency between short and long priors. Moreover, when making the pitched balls invisible earlier (345 ms after the start of the pitch), the central tendency was greater for the long prior than for the short prior, which was consistent with the predictions of the Bayesian estimation model with scalar variability. These results support our hypothesis. Our results suggest that task-specific strategies should be considered when applying Bayesian estimation models to daily tasks.

Disclosures: J. Suzuki: None. **Y. Tanaka:** None. **C. Kasegawa:** None. **M. Miyazaki:** None. **T. Kimura:** None.

Poster

PSTR095: Human Timing and Temporal Processing

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR095.08/R4

Topic: H.10. Human Learning and Cognition

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Sylvan Adams Sports Institute Grant number 0601133671

Title: A Novel Reaction Time Assessment in Virtual Reality: Advantages Over Computerized Tests

Authors: T. LOUSHY KAY[1], E. BEEN[2], ***C. PICK**[3];
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Abstract: Background: Reaction time (RT) is a fundamental cognitive function impacting daily live and sports activities. Despite the increasing use of virtual reality (VR) for cognitive assessments, its efficacy for RT assessments remains uncertain. We aimed to evaluate VR potential for measuring RT.**Methods:** Thirty participants completed both a traditional computerized RT test (RT-COM) and a new RT test in VR (RT-VR). RT-VR replicated RT-COM, testing simple and choice RTs. Additionally, it introduced complex conditions: clicking a controller in response to static stimuli in a known location and reaching to touch static stimuli in known or unknown locations, or dynamic stimuli in unknown locations. Subsequently, differences between RT-COM and RT-VR tasks were examined.**Results:** Moderate linear correlations were found between the two tests (simple: $r=0.660$, choice: $r=0.646$, $p<0.001$). However, RTs were significantly shorter in the RT-VR compared to RT-COM ($p<0.001$). Significant differences were found among RT-VR tasks ($p<0.001$): reaching out to touch stimuli involved slower RT compared to clicking the controller button. Furthermore, the RT was even slower when stimuli appeared in different and unexpected locations. However, moving stimuli were associated with shorter RT.**Conclusion:** VR is suitable for RT measurement, yet its outcomes should be interpreted within its framework rather than in comparison to computer assessments. Furthermore, VR offers additional possibilities, such as using lifelike stimuli with various spatial and dynamic characteristics and measuring bodily and eye movement parameters. In a follow-up study, we aim to further explore correlations between VR-RT and brain activity across different populations.

Disclosures: T. Loushy Kay: None. **E. Been:** None. **C. Pick:** None.

Poster

PSTR095: Human Timing and Temporal Processing

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR095.09/Web Only

Topic: H.10. Human Learning and Cognition

Title: Could There Be No Oddball Effect in Children? A Study of Subjective Time Dilation

Authors: *B. SIRMATEL BAKRIYANIK[1,2], B. SÖZER[3], H. ÖZÇELIK[4], A. KOLAYLI[5], M. ÇIÇEK[3,2,6];
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Abstract: Could There Be No Oddball Effect in Children? A Study of Subjective Time Dilation Burcu SIRMATEL-BAKRIYANIK[1,2], Batuhan SÖZER[1], Hazal ÖZÇELİK[3], Alperen KOLAYLI[4], Metehan ÇİÇEK[1,2,51]Department of Interdisciplinary Neuroscience, Institute of Health Sciences, Ankara University, Ankara, Turkey[2]Neuroscience and Neurotechnology Center of Excellence (NÖROM), Ankara University, Ankara, Turkey[3]Ankara University School of Medicine, Ankara, Turkey[4]Department of Biological Sciences, Biology Program, Middle East Technical University (METU), Ankara, Turkey[5]Department of Physiology, Ankara University School of Medicine, Ankara, Turkey
In moments of danger, like car accidents or combat, time often feels like it slows down, akin to the ‘slow-motion’ technique in movies. This time dilation is known as the temporal oddball effect, despite the cause of this phenomenon is not fully understood. Several studies in adult populations using the classic oddball experiment design (adapted for measuring time perception), have shown that oddball stimuli lead to the perception of time as longer than reality. We aimed to explore the developmental aspect of the temporal oddball effect by administering a temporal oddball paradigm to children (n = 9; age-range = 10-11) and adult (n = 7; age-range = 20-23) groups. The standard time comparison task was performed as the control. The point of subjective equality (PSE) was determined as the oddball duration at which participants reported the duration as longer than the standard duration (1550 ms) half of the time. PSE for each participant in each condition was calculated as the 50% point using probit analysis of their responses across the oddball durations.Our findings indicate that in the adult group, the mean PSE for oddball durations (1336 ms) was significantly shorter than the mean PSE for control task (1468 ms) ($t(6) = -3.07$, $p = 0.022$). However, in the child group, although mean PSE durations (1296 ms) were notably shorter than the standard, no significant difference was found between the mean oddball PSE and control PSE. While children perceive both oddball stimuli and other time comparisons as longer, adults only tend to perceive the duration of oddball as longer. This difference observed in children may stem not only from the distinct perception of oddball, but also from the possibility that all standard stimuli appear 'oddball-like' and attention-grabbing to them.
The authors declare that there is no conflict of interest. Ethical approval for this study was obtained from Ankara University Faculty of Medicine Human Research Ethics Committee (approval number/ID: İ10-609-22).

Disclosures: B. Sirmatel Bakriyanik: None. **B. Sözer:** None. **H. Özçelik:** None. **A. Kolayli:** None. **M. Çiçek:** None.

Poster

PSTR095: Human Timing and Temporal Processing

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR095.10/R5

Topic: H.10. Human Learning and Cognition

Title: Cnv and p300 amplitude reflect decisions about stimulus magnitude in both space and time

Authors: *E. L. P. MIEULET[1,2], I. KOROLCZUK[3], L. CASINI[2], F. VIDAL[2], J. T. COULL[2]; [1]Aix marseille université, MARSEILLE, France; [2]Ctr. de Recherche en Psychologie et Neuroscience, Aix-Marseille Univ. & CNRS, Marseille, France; [3]Dept. of Pathophysiologie, Med. Univ. of Lublin, Poland, Lublin, Poland

Abstract: EEG studies indicate that duration processing can be indexed by the amplitude of two fronto-central components, the Contingent Negative Variation (CNV) and the P300. If stimulus duration is longer than that of a memorized standard, CNV amplitude increases steadily until a temporal decision can bemade at which point it resolves back to baseline. In parallel, the amplitude of the p300 is smaller for longer stimulus durations. In our EEG study we examined whether these patterns are observed only when duration is being estimated explicitly in a temporal task or whether they might also be observed when duration is processed implicitly in a non-temporal (spatial) control task. Participants viewed two consecutive dots, each of which moved laterally across the screen, and judged the relative duration (temporal condition) or distance (spatial condition) of the second dot's trajectory compared to the first. Results confirmed that both CNV and P300 amplitude reflect temporal decision-making selectively during explicit, but not implicit, estimation of duration in the temporal task. Moreover, these two components were also found to reflect spatial decision-making during explicit estimation of distance in the spatial task. Taken together these results suggest that P300 and CNV amplitudes reflect decisions about the relative magnitude of a task-relevant stimulus feature, in either the temporal or spatial dimension.

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Poster

PSTR095: Human Timing and Temporal Processing

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Program #/Poster #: PSTR095.11/R6

Topic: H.10. Human Learning and Cognition

Support: NIH R01 NS129703

Title: A hierarchy of intrinsic neural timescales in the human speech network revealed by intracranial EEG

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Abstract: The dynamics of neural signals at rest are thought to mirror the temporal diversity of sensory and motor processing by exhibiting a multitude of intrinsic neural timescales (INTs). INTs are proposed to mediate neural computations through preferred timescales that reflect the level of analysis of distinct neural populations. Previous evidence from sensory networks suggests that INTs are spatially organized and show hierarchical gradients of processing. Whether INTs follow discrete anatomical hierarchies within the human speech network, a highly integrative and multimodal system, has yet to be empirically established. We sought to investigate the organization of resting-state INTs in the speech network and examine how these dynamics manifest in neural speech computations. We used intracranial neural recordings (iEEG) across 18 regions of interest (ROIs) implicated in speech to compare INTs at rest with INTs during a speech repetition task. Data was collected from 36 subjects (mean age = 31, 18 female) undergoing inpatient monitoring for surgical treatment of epilepsy. We hypothesized that INTs would 1) differ between ROIs and demonstrate increased INTs along the ascending auditory and descending motor speech pathways, and 2) exhibit task-selective modulation whilst maintaining their hierarchical structure. Preliminary results show that resting-state INTs exhibit a discrete anatomical gradient in support of our hypothesis that INTs differed between ROIs (one-way ANOVA, $F(17) = 11.08$, $p < 0.0001$). In auditory ROIs, INTs were shortest in heschl's gyrus, mid-range in the posterior superior temporal gyrus and the superior temporal sulcus, and longest in the inferior temporal gyrus and the middle temporal gyrus. Motor and sensorimotor ROIs exhibited a complementary gradient, with the longest INTS in the pars triangularis, followed by mid-range INTs in the inferior parietal cortex and the caudal middle frontal gyrus, and finally the shortest INTs in the supplementary motor area, precentral gyrus, and the pars opercularis. We also found that task-state INTs across ROIs were differentially modulated in auditory versus motor speech processing, showing a systematic decrease from rest with a mean 7.15 ms and 9.40 ms reduction, respectively. The spatial gradient remained intact across states, suggesting that INT duration is directly related to neural speech computations. Our findings show preliminary evidence that INTs reflect both the auditory and motor speech network hierarchy, and are selectively modulated by task. Taken together, our work provides evidence that INTs demonstrate a potential computational substrate for speech processing.

Disclosures: N.C. Liddle: None. **A.M. Earle-Richardson:** None. **D. Southwell:** None. **M. Vestal:** None. **G. Grant:** None. **G.B. Cogan:** None.

Poster

PSTR095: Human Timing and Temporal Processing

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR095.12/S1

Topic: H.10. Human Learning and Cognition

Support: CONACYT (CF-263377)

Title: Brain functional connectivity changes after time production training in young adults

Authors: *L. P. RUIZ GÓMEZ[1], J. RAMOS-LOYO[1], A. SANZ MARTIN[2];
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Abstract: The ability to measure the passage of time can be improved by training; this allows for a more efficient use of neural resources. Functional connectivity analysis represents simultaneous activation of different brain regions forming functional networks during specific cognitive processes. These networks are dynamic and can be modified by experience and learning. The present study aims to assess the effects of training in time production on brain functional connectivity. We evaluated 20 healthy young adults who underwent a time production training program. Brain electrical activity was recorded during pre- and post-training sessions. Participants performed a time production task that consisted in voluntarily producing 2.5-second intervals. Each trial started with a fixation point in the center of the screen that switched to a green circle, signaling the interval onset. Participants were instructed to press the spacebar when they considered that 2.5 s had elapsed. Following the pre-training session, participants underwent the training program, which consisted of nine online sessions. Each training session consisted of 150 time-production trials similar to the time-production task, including trial-by-trial feedback. We calculated the coefficient of variation (CV) to measure their responses' precision. We found that participants improved their precision on the time production task after training. Regarding functional connectivity, participants showed a decrement in the local (LE) and global efficiency (GE) in the delta band in the post-training session. Also, theta band showed a lower LE and beta1 a lower GE after training. The training program improved the participant's ability to produce time intervals consistently. It also modified the brain networks that were active during the time production task. These changes might reflect the plastic reconfiguration that the brain underwent during the training. These results contribute to understanding the neural correlates of time production processes and how the brain's functional networks change due to learning.

Disclosures: L.P. Ruiz Gómez: None. **J. Ramos-Loyo:** None. **A. Sanz Martin:** None.

Poster

PSTR095: Human Timing and Temporal Processing

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR095.13/S2

Topic: H.10. Human Learning and Cognition

Support: NCT01273129
NCT04095026

Title: A multiscale representation of temporal context in human anterior temporal lobe

Authors: *I. BRIGHT[1], A. VAZ[3], S. INATI[2], M. W. HOWARD[4], K. A. ZAGHLOUL[5];
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Abstract: Cognitive neuroscientists have proposed that episodic memories are associated with a gradually changing state of temporal context. Temporal context produces a neural recency effect; similarity in brain activity decreases over time. Across experiments, the reported time scale of contextual change varies, ranging from seconds to tens of minutes. Further, the mechanisms that drive contextual change remain unclear. We recorded single units in the anterior temporal lobe of epilepsy patients while they completed a paired associates task. We report a neural recency effect at multiple timescales simultaneously; population activity changes gradually within a trial, within a list, and within a session. Critically, these changes were consistent across repeated experiences, enabling the decoding of trial time and list position. Taken together, these results expand and constrain our understanding of how the brain implements temporal context.

Disclosures: I. Bright: None. **A. Vaz:** None. **S. Inati:** None. **M.W. Howard:** None. **K.A. Zaghloul:** None.

Poster

PSTR096: Connectomics Across Species

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR096.01/S3

Topic: I.03. Anatomical Methods

Support: The Francis Crick Institute

Title: Comparative Connectomics: The Effect of Social Isolation on Brain Wiring

Authors: *A. SEGGEWISSE, L. KIMBLEY, X. CANO FERRER, L. COCHRANE, A. IMBERT, M. WINDING;
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Abstract: Social behaviours are essential for all animals, including humans. A prolonged lack of social isolation impairs social behaviours and is associated with adverse health outcomes. However, the neural circuits in the brain that are disrupted by such isolation, which ultimately lead to distorted neural computations, impacting behaviour and health, are poorly understood. An excellent model that allows to study social-isolation induced changes in neural circuits on a synaptic level and link it back to behavioural dysfunction, is the *Drosophila* larva. The larval

brain is compact enough to permit synapse-resolution electron microscopy imaging for comprehensive mapping of neural circuitry. Individual neurons from these circuit maps have been linked to genetic tools allowing targeted manipulation or recording of functional activity. The larva engages in social behaviours, notably collective digging, where synchronised movements enable more efficient feeding. This project aims to determine how social isolation alters brain wiring and computations underlying social behaviour. To do this, we first developed a behavioural rig to record collective digging behaviour across larvae that were social deprived during early development compared to those exposed to social cues throughout their lives. We developed tools that enable us to track larvae and to quantify their digging behaviour. In line with previous literature, this revealed strong behavioural effects in collective digging between group-reared and socially isolated larvae. How these effects relate to differences in neural wiring, will be further explored using electron microscopy, to generate brain connectomes of both experimental conditions. These connectomes will then be compared in their neural architecture in order to identify isolation-induced wiring aberrations. This project will be the first comparative connectomics study across an entire brain, revealing how developmental adversities can have long-term effects on brain wiring and behaviour.

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Poster

PSTR096: Connectomics Across Species

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR096.02/S4

Topic: I.03. Anatomical Methods

Support: NIH R01NS133654-01
NSF IOS 2227963

Title: 3D EM reconstructions of neurons from the nudibranch Berghia stephanieae reveal novel ultrastructural features

Authors: H. H. SANT[1], S. DEAMICIS[1], K. DHIMAN[1], R. SCHALEK[2], J. W. LICHTMAN[2], ***P. S. KATZ**[1];
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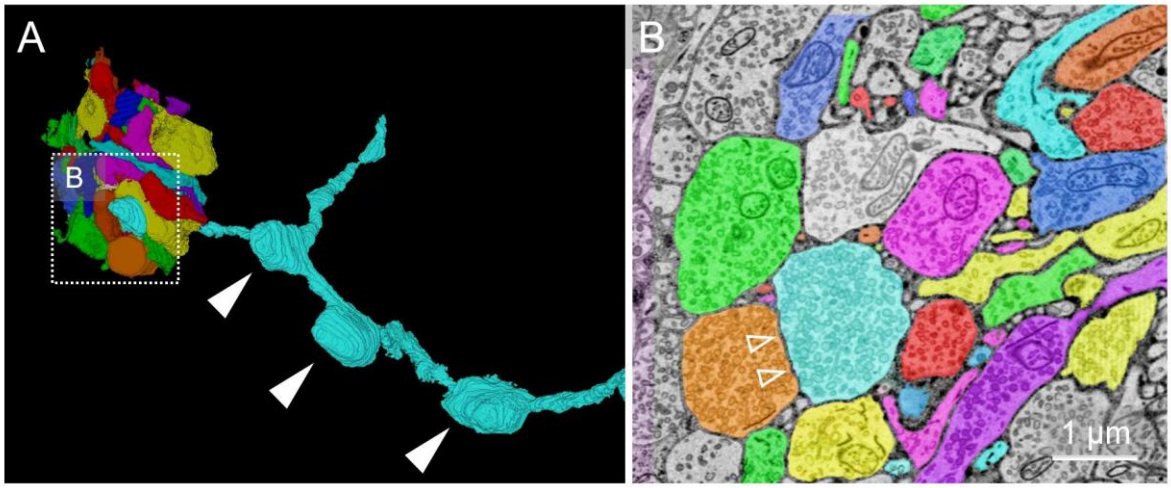
Abstract: Volume electron microscopy (vEM) reveals features of nervous systems that are inaccessible through other techniques. Here we segmented and reconstructed neurons from a vEM dataset obtained from the rhinophore ganglion (rhg) of the nudibranch mollusc, Berghia stephanieae. The *rhg* contains 9000 somata whose functions and axonal projections are not known. Half of the rhg including the connective to the cerebral ganglion (ceg) was serially sectioned at 33 nm thickness and imaged using SEM, generating a dataset of 2,175 sections with 4x4 nm lateral resolution. There were distinct neuropil regions including one receiving axonal

projections from a peptidergic ceg neuron. We reconstructed several neurons, including one that had a soma in the *rhg* and an axon that projected into the connective. Its dendrites lacked vesicles but contacted many vesicle-filled presynaptic boutons. We also reconstructed an axon terminal arbor that branched profusely in the neuropil region occupied by the terminals of the peptidergic ceg neuron, which contained many vesicle-filled varicosities - likely sites of peptide release (Fig. A, arrows). Boutons of neighboring axons made membrane-to-membrane contact with no postsynaptic specializations (Fig. B, open arrowheads). We also found novel structures, namely independent vesicle-filled boutons that were free of axon attachments. Some, but not all of these independent boutons were surrounded by glial cells suggesting that they might be in the process of degradation. The features that we uncovered using vEM reconstruction could help generate hypotheses about the function of this enigmatic ganglion.



Disclosures: H.H. Sant: None. **S. DeAmicis:** None. **K. Dhiman:** None. **R. Schalek:** None. **J.W. Lichtman:** None. **P.S. Katz:** None.

Poster

PSTR096: Connectomics Across Species

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR096.03/S5

Topic: I.03. Anatomical Methods

Support: Francis Crick / Wellcome Trust FC001153 to A.T.S.
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PSI beamtime at cSAXS proposals 20190654, , 20200783 and 20211852
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Francis Crick / MRC to A.T.S. FC001153

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ERC 852455 (BRILLIANCE) to A.P.
ERC 810451 (HERO) to G.A.
SERI-funded ERCStG XrayConnectomics to A.A.W.

Title: 3D-Imaging of synapses in neuronal tissues with synchrotron X-ray ptychography

Authors: *C. BOSCH PIÑOL[1], T. AIDUKAS[2], M. HOLLER[2], A. PACUREANU[3], E. MÜLLER[2], C. PEDDIE[4], Y. ZHANG[1], P. COOK[3], L. COLLINSON[4], O. BUNK[2], A. MENZEL[2], M. GUIZAR-SICAIROS[2,5], G. AEPPLI[2,5,6], A. DIAZ[2], A. A. WANNER[2], A. T. SCHAEFER[1,7];
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Abstract: Wiring diagrams of neural circuits are of central importance in deciphering mechanisms of computation in the brain. To generate these diagrams, the individual parts of neurons - axons, dendrites and synapses - must be densely identified in 3-dimensional volumes of neuronal tissue. This is typically achieved by electron microscopy, which requires physical sectioning of the specimen either before or during the image acquisition process at ultrathin step sizes. Since X-rays penetrate into materials much deeper than electrons, coherent X-ray microscopy has the potential to resolve ultrastructure in tissue without the need of sectioning - and using instead the tomographic principle to obtain 3-dimensional information non-destructively.
Here, we demonstrate that X-ray ptychography, a coherent diffractive X-ray imaging technique, can faithfully provide 3D images of metal-stained mouse brain tissue. Achieving high image quality requires minimising radiation damage to the sample, which we attain by imaging at cryogenic temperatures and using specialised tomographic reconstruction algorithms. A tri-functional epoxy resin renders samples resilient to X-ray doses exceeding 10^{10} Gy. Sub-40 nm FSC resolution allows to densely resolve axon bundles, boutons, dendrites and synapses without physical sectioning. Subsequent imaging of those volumes with focused ion beam scanning electron microscopy shows intact ultrastructure, suggesting that metal-stained neuronal tissue can be highly radiation-stable.
Last, optimal 3D tomographic reconstruction requires cylindrical samples. Instead, using laminography - an imaging modality involving a sample rotation axis that is oblique instead of orthogonal to the beam - the optimal sample geometry is a lamina - a slice. Here we imaged consecutive 5 µm-thick brain slices with ptychographic laminography, and the results demonstrate that this technique can provide synaptic resolution and will therefore be useful for connectomics. We propose that connectomes of samples of arbitrary dimensions can be obtained using X-ray microscopy in principle.
Ongoing improvements in synchrotrons, X-ray optics and detectors, as well as in sample preparation and staining procedures, will lead to substantial improvements in acquisition speed. Alongside complementary X-ray techniques such as nano-holotomography, non-destructive X-

ray imaging of synapses and neural circuits will provide volumes of increasing size - and eventually reach sufficient throughput for routine use in mammalian connectomics and tissue life sciences.

Disclosures: C. Bosch Piñol: None. **T. Aidukas:** None. **M. Holler:** None. **A. Pacureanu:** None. **E. Müller:** None. **C. Peddie:** None. **Y. Zhang:** None. **P. Cook:** None. **L. Collinson:** None. **O. Bunk:** None. **A. Menzel:** None. **M. Guizar-Sicairos:** None. **G. Aeppli:** None. **A. Diaz:** None. **A.A. Wanner:** None. **A.T. Schaefer:** None.

Poster

PSTR096: Connectomics Across Species

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR096.04/S6

Topic: I.03. Anatomical Methods

Support: NSF DMR-2011854
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European Union's Horizon 2020 research and innovation program under grant agreement No 101017902
University of Chicago and the Neubauer Family Assistant Professors Program

Title: Photoemission electron microscopy for connectomics

Authors: *L. LAMBERT[1], K. M. BOERGENS[3], G. WILDENBERG[4], N. B. KASTHURI[2]; [2]Neurobio., [1]Univ. of Chicago, Chicago, IL; [3]Paradromics Inc., Austin, TX; [4]Neurobio., Univ. of Chicago Dept. of Neurobio., Chicago, IL

Abstract: Recently, photoemission electron microscopy (neuroPEEM) has been introduced for connectomics. Previously, in order to image ultrathin brain slices embedded in epoxy at synaptic resolution to reconstruct networks in the nervous system, scanning electron microscopy (SEM) or transmission electron microscopy (TEM) have been used. Because of limitations in these techniques, a full mammalian connectome (i.e. map of every neural connection) has been considered an impossible task. However, neuroPEEM has the potential to allow for considerably faster imaging. Ultimately, heat induced degradation of samples likely limits the throughput of this otherwise revolutionary technique. In order to determine a potential maximum rate for nueroPEEM imaging of ultrathin brain slices, we tested the degradation of sections of tissue embedded in Lx112 and well adhered to a diamond or silicon wafer under lasing conditions similar to what the samples would experience in the neuroPEEM. We found that a conductive

(diamond) substrate is key to increasing the amount of heat an ultrathin brain slice can withstand. Using COMSOL simulation data, we found that an ultrathin brain slice well-adhered to a diamond substrate could support a 3.9 W laser, which could image at a 15.6 Gigahertz pixel rate without significant heating. We estimate then that a mouse brain could be imaged in 5 years with a single PEEM. In order to obtain a more complete understanding of the behavior of these epoxies in the neuroPEEM and adapt wavelength appropriately, we then took UV-Vis spectroscopy measurements of the epoxies and embedded brain tissue. Furthermore, by altering sample collection methods to expand the size of collectable sections, we can take advantage of neuroPEEM's full capabilities. The ability to collect and image large slices will pave the way for a broader utility of neuroPEEM and facilitate new discoveries in connectomics and neuroscience in the near future.

Disclosures: L. Lambert: None. **K.M. Boergens:** None. **G. Wildenberg:** None. **N.B. Kasthuri:** None.

Poster

PSTR096: Connectomics Across Species

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR096.05/T1

Topic: I.03. Anatomical Methods

Title: Visualizing the nervous system across the whole mouse body at micron resolution using high-speed blockface VISoR

Authors: C. XU, ***Y. YAO**, Q. ZHU, P. LAU, G. BI;
Univ. of Sci. and Technol. of China, Hefei, China

Abstract: The nervous system, comprising the central and peripheral components, governs all cognitive and physiological functions in most animals. The past decade has seen remarkable advances in our understanding of the architecture of central neurons at whole-brain scale. The study of the peripheral system, however, has been limited in the scale and resolution due to technical difficulties, especially the lack of 3D microscopy techniques of sufficient resolution and throughput to efficiently resolve cells across large scales. Here, we develop a blockface imaging and sectioning system implementing Volumetric Imaging with Synchronized on-the-fly-scan and Readout (VISoR) technology. Combined with a modified aqueous solution based whole-mouse clearing technique, this system enables imaging the whole-body of an adult mouse within 40 hours at a resolution of $1 \times 1 \times 2.5\ \mu m^3$. After 3D reconstruction, the nervous system of *Thy1-GFP* mice and its entire vasculature labeled by lectin were visualized. By tracking the trajectory of nerves and axons, we reveal fine projection patterns of the trigeminal nerve and characterize the morphological features of individual spinal neurons. With viral tracing, we constructed the 3D structure of the vagus nerve. Further, we established a whole-body immunostaining method to map the structure of the entire sympathetic nervous system. Our

method and pipeline provide efficient tools for mesoscopic structural analysis of the nervous system across the whole mouse body.

Disclosures: C. Xu: None. **Y. Yao:** None. **Q. Zhu:** None. **P. Lau:** None. **G. Bi:** None.

Poster

PSTR096: Connectomics Across Species

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR096.06/T2

Topic: I.03. Anatomical Methods

Support: U19MH114830

Title: Input-output organization of the corticothalamic circuit and its molecular underpinnings

Authors: *S. YAO[1], H. CHOI[5], E. LI[6], N. LUSK[7], M. TAORMINA[1,1], L. NG[9], S. RANSFORD[2], E. GELFAND[3], J. SWAPP[2], B. OUELLETTE[11], C. NAYAN[11], C. GRASSO[11,1], K. NORTH[11], N. DOTSON[11], A. GARY[11], A. RUIZ[8], C. A. POM[8], K. BROUNER[12], T. EGDORF[8], E. LIANG[8], M. REDING[11], K. RONELLENFITCH[11], S. A. SORENSEN[7], A. WILLIFORD[11], M. KUNST[4], C. VAN VELTHOVEN[7], Z. YAO[1], P. A. GROBLEWSKI[9], J. WATERS[9], L. KRUSE[11], B. TASIC[10], Q. WANG[1], S. MIHALAS[9], H. ZENG[1];
[1]Allen Inst. for Brain Sci., Seattle, WA; [2]Allen Inst. for Brain Sci., seattle, WA; [3]Allen Inst. for Brain Sci., settle, WA; [4]Imaging, Allen Inst. for Brain Sci., Seattle, WA; [5]Mathematics, Georgia Inst. of Technol., Atlanta, GA; [6]Georgia Inst. of Technol., ; [7]Allen Inst., Seattle, WA; [8]Allen Inst., ; [10]Cell and Circuit Genet., [9]Allen Inst. For Brain Sci., Seattle, WA; [11]; [12]Everett, WA.

Abstract: Understanding the structure of neuronal circuits is essential for comprehending brain function in both health and disease. We have utilized viral tools to map the anterograde and retrograde connectivity of genetically defined populations across the brain. Leveraging this extensive dataset, we systematically explored the cortical-thalamic connectome and investigated the spatial relationship between detailed connectivity patterns and transcriptomic cell types. Our study elucidated the modular and hierarchical organization of the corticothalamic circuits, detailing their input and output connections throughout the brain. We unveiled specific connectivity patterns across different organizational levels, from the global modular structure to specific areas within each module, to sub-areal or topographic transitions within each area. By comparing spatial patterns of retrogradely labeled input neuronal populations with the spatial transcriptomic cell atlas, we identified specific types associated with connectional specificity across brain regions. In summary, our study provides a high-resolution whole-brain atlas of the cell type-specific input-output connectome and reveals its organizational logic as well as its molecular underpinnings.

Disclosures: S. Yao: None. **H. Choi:** None. **N. Lusk:** None. **M. Taormina:** None. **L. Ng:** None. **S.A. Sorensen:** None. **M. Kunst:** None. **C. van Velthoven:** None. **Z. Yao:** None. **P.A.**

Groblewski: None. **J. Waters:** None. **B. Tasic:** None. **Q. Wang:** None. **S. Mihalas:** None. **H. Zeng:** None.

Poster

PSTR096: Connectomics Across Species

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR096.07/T3

Topic: I.03. Anatomical Methods

Support: NIH Grant MH117820
NIH Grant MH126864

Title: An imaging pipeline for mapping dense axonal projections over large mammalian brains

Authors: *K. TAKASAKI[1], A. GLASER[2], E. E. TURSCHAK[1], A. HELLEVIK[1], X. JIANG[2], S. VASQUEZ[2], M. WOODARD[2], R. TORRES[1], O. GLIKO[1], C. LAUGHLAND[1], W.-Q. YU[1], P. BALARAM[1], S. CHATTERJEE[1], S. J. COOK[1], K. VILLALOBOS[1], J. V. CHANDRASHEKAR[2], K. SVOBODA[2], R. C. REID[1];
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Abstract: Studies of the anatomical organization of mammalian brains across spatial scales have benefitted from recent advances in methods of mapping local and long-distance connectivity. On the microscale, dense anatomical reconstructions from electron microscopy resolve connections between neurons at the level of individual synapses, whereas on the macroscale, imaging methods such as MRI, OCT, and x-ray tomography allow brain-wide mapping of fiber tracts and areal connectivity. We are interested in approaches that bridge these scales by resolving and tracing individual axons from their neurons of origin, but that can be scaled to entire mammalian brains for dense maps of projections over long distances. To this end, we have been developing histological methods based on tissue clearing and expansion microscopy techniques to stain axons throughout thick sections of mammalian brain tissue, as well as computational methods adapted from EM connectomics to align and assemble petascale 3D volumes from images acquired from serial sections. However, the ability to image axons with sufficient resolution for tracing over volumes spanning many cubic centimeters has been hampered by existing microscope technology. Trade-offs between resolution and field-of-view imposed by conventional optics and cameras in the life sciences have limited the feasibility of acquiring images of such large volumes at high resolution. The recent development of a novel light-sheet microscope approach, expansion-assisted selective plane illumination microscopy (ExA-SPIM, Glaser et al. 2023), has enabled fluorescence imaging with sub-micron, near-isotropic resolution over volumes of unprecedented scale. Here, we describe the integration and use of ExA-SPIM in the axonal connectomics pipeline. Our preliminary results with ExA-SPIM demonstrate imaging of axons with 200 nm expanded resolution at acquisition speeds up to 1 gigavoxel per second. Importantly, the microscope was able to accommodate and image large histological sections from non-human primate and human up to 0.5 mm thick, immunolabeled for neurofilament

proteins, and subsequently expanded 4x. Data conversion to the OME-Zarr file format provided a standard entry point to the computational workflow, and we demonstrate image quality sufficient for tile stitching of sections over several centimeters, and segmentation and tracing of individual axons throughout densely labeled white matter. The goal of the program is to trace individual axons from their area of origin, through the white matter, to their destinations, providing a new approach to studying the large-scale organization of connectivity in the primate brain.

Disclosures: K. Takasaki: None. **A. Glaser:** None. **E.E. Turschak:** None. **A. Hellevik:** None. **X. Jiang:** None. **S. Vasquez:** None. **M. Woodard:** None. **R. Torres:** None. **O. Gliko:** None. **C. Laughland:** None. **W. Yu:** None. **P. Balaram:** None. **S. Chatterjee:** None. **S.J. Cook:** None. **K. Villalobos:** None. **J.V. Chandrashekar:** None. **K. Svoboda:** None. **R.C. Reid:** None.

Poster

PSTR096: Connectomics Across Species

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR096.08/T4

Topic: I.03. Anatomical Methods

Support: Stony Brook Research Foundation

Title: A DTI study of diffuse superior longitudinal fasciculus terminations in prefrontal and posterior parietal cortices

Authors: *K. FARBER[1], M. J. AMANDOLA[2], H.-C. LEUNG[3];
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Abstract: The superior longitudinal fasciculus (SLF) is the major fiber tract connecting the prefrontal and posterior parietal areas. Although it is relatively well studied in non-human primates, the organization of the SLF cortical terminations is still not fully clear for humans. Recent studies using probabilistic tractography together with specific pairings of non-overlapping frontal and parietal regions of interest (ROIs) allowed for a clear delineation of SLF into three subcomponents in each hemisphere. Recent tract tracing studies in nonhuman primates have shown the existence of prefrontal diffuse fibers, which spread more widely across posterior association cortices. The purpose of the present tractography study is to examine whether the human SLF is strictly organized into three subcomponents with distinct and entirely separable areas of termination, or whether there is some overlap or diffusivity in its terminations similar to non-human primates. We preprocessed high-resolution 99-direction diffusion images using standard FSL and AFNI pipelines and conducted tractography using FSL's probtrackX. First, we applied literature-based frontal and parietal ROI pairs and were able to reliably recreate the 3

subdivisions of the SLF in 50 healthy subjects (36F/14M, Age=61.43±16.5) from the Human Connectome Project Aging (HCP-A) cohort. We then used mixed pairings of the frontal/parietal ROIs, and found additional terminations that are not explained by the assumed SLF subdivisions in all frontal and parietal areas at 25% threshold (i.e., present in at least 25% of participants). We further quantified each frontal termination of the canonical and mixed signal by calculating its average streamline density per voxel in each corresponding frontal ROI thresholded at 0.5%. We used two-factor repeated measures ANOVAs to assess the main effects of hemisphere and of the frontal/parietal ROI combination on the average termination density within each frontal ROI (superior frontal, middle frontal, and inferior frontal gyrus). The analysis showed significant main effects of ROI pairing for the superior and inferior frontal gyri (p's<0.01), with post hoc tests suggesting the average density of mixed ROI terminations are lower than that of the canonical SLF. The results of the study suggest that although the 3-division organization of SLF identified in previous studies is the main frontoparietal connection pattern, there may be additional crossing or diffuse fibers that are not entirely captured by a restricted ROI approach for mapping SLF organization.

Disclosures: K. Farber: None. **M.J. Amandola:** None. **H. Leung:** None.

Poster

PSTR096: Connectomics Across Species

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR096.09/T5

Topic: I.03. Anatomical Methods

Support: NIH Grant 5DP1DA056668
NIH Grant 1U01NS132161
SFARI Pilot Award #875575
ASF Postdoc Training Award #23-001

Title: Mapping single-neuron projections with improved sensitivity and cell-type specificity using MAPseq2

Authors: *H. KIM[1], C. XU[1], C. WASHINGTON[1], J. M. KEBSCHULL[1,2];
[1]Biomed. Engin., [2]Kavli Neurosci. Discovery Inst., Johns Hopkins Univ., Baltimore, MD

Abstract: Understanding the statistics of single neuron projection patterns of different cell types is critical for deciphering information flow between brain regions. While bulk-level projection data is readily available in the mouse, single-neuron projection data is still more challenging to obtain, as it requires high-resolution whole-brain imagining and neuron reconstructions. Sidestepping these difficulties, we previously developed MAPseq (Multiplexed Analysis of Projections by Sequencing), which uses cellular barcoding and DNA sequencing instead of imaging to rapidly map the projections of thousands of single neurons in individual animals. However, as MAPseq is based on the RNA virus Sindbis, it cannot be used with popular DNA

recombinases such as Cre or Flp to enable cell-type specific projection mapping. To address this shortcoming, here we introduce a new version of MAPseq that allows single-cell projection mapping of specific cell types as defined by recombinase expression. We further improved MAPseq sequencing library preparation to capture fine projections in more neurons, achieving close to 4 times improved sensitivity with 6 times decreased cost per sample simultaneously. We validate our method in the mouse motor cortex and then apply it to uncover the brain-wide projections of midbrain dopaminergic neurons at single-cell resolution.

Disclosures: H. Kim: None. **C. Xu:** None. **C. Washington:** None. **J.M. Kebschull:** None.

Poster

PSTR096: Connectomics Across Species

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR096.10/T6

Topic: I.03. Anatomical Methods

Support: NIH grant 1RF1MH120005

Title: Correlative molecular, anatomy, and activity mapping in mouse primary visual cortex

Authors: *T.-W. KUO[1], J. G. LETNER[2], H. JIANG[3], H.-H. HUANG[4], M. CUI[5], D. CAI[6]; [1]Univ. of Michigan, Ann Arbor, MI; [2]Biomed. Engin., Univ. of Michigan, Ann Arbor, MI; [3]ECE, Purdue Univ., West Lafayette, IN; [4]Taipei Veterans Hosp., Taipei, Taiwan; [5]Purdue Univ., West Lafayette, IN; [6]Cell and Developmental Biol., Michigan Neurosci. Inst., Univ. of Michigan, Ann Arbor, MI

Abstract: Large-scale functional and anatomical mapping of neural circuits presents a persistent challenge in contemporary neuroscience research. The current state-of-the-art electron microscopy (EM) reconstructions of neural networks offer unparalleled spatial and connection resolution. However, the extensive data acquisition and analysis resulting from these experiments pose challenges in their adaptation to routine neuroscience research. In addition, molecular information is difficult to discover from the EM sample, which limits its utilization in disease mechanism studies. Addressing this challenge, here we introduce a novel light microscopy-based imaging paradigm that enables correlative molecular, anatomy, and activity mapping (coMAAP) of the mouse brain. We applied coMAAP to the primary visual cortex (V1) to delineate the local functional circuits. By integrating a suite of advanced techniques, including correlative two-photon live calcium imaging and expansion Brainbow imaging, multiplex mRNA/protein profiling, and semi-automatic morphology reconstruction, coMAAP offers a comprehensive approach to efficiently characterize 1-10% of V1 neurons in multiple mice within a few months. Our results suggest that the coMAAP pipeline holds promise as a powerful tool for mapping brain-wide networks across physiological conditions within a practical timeline, paving the way for accelerated progress in understanding brain structures and functions.

Disclosures: T. Kuo: None. **J.G. Letner:** None. **H. Jiang:** None. **H. Huang:** None. **M. Cui:** None. **D. Cai:** None.

Poster

PSTR096: Connectomics Across Species

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR096.11/

Topic: I.01. Molecular, Biochemical, and Genetic Techniques

Support: Glaucoma Research Foundation CFC4
McKnight Foundation
NIH R00EY028625

Title: Evolution of the vertebrate retina : Insights from single-cell genomics

Authors: *K. SHEKHAR;
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Abstract: Advances in DNA sequencing have been pivotal in illuminating the evolutionary history of genes. Recent breakthroughs in single cell profiling have motivated a related enterprise focused on the evolution of cell types, the functional units of complex tissues. In this talk I will describe single cell analyses of cell type evolution in the retina, the thin film of neurons in the eye where vision begins. The retina is as complex as any other brain region, but its compactness and accessibility make it an ideal system to address conceptual and technical challenges associated with cell type evolution. I will discuss our recent integrative analysis of retinal atlases across 20 species, which suggest that many of the cell types and circuits thought to be unique to mammals have ancient evolutionary origins beyond the Devonian (>420 million years ago). As a specific case studies, I will describe (1) how an ancient cell type substrate has massively expanded in the primate retina to enable vision at high spatial resolution; (2) how the mammalian rod bipolar pathway is present in fish; and (3) the origins amacrine cell diversity. I will make some speculative connections between the co-evolution of the retina and the cerebral cortex, which has massively expanded in humans. Beyond furthering our basic understanding of the evolution of vision, these results have important implications for improving existing animal models for blinding diseases.

Disclosures: K. Shekhar: None.

Poster

PSTR096: Connectomics Across Species

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR096.12/T8

Topic: I.03. Anatomical Methods

Support: 1U01NS126054-01

Title: Brain-wide mapping of prefrontal cortex projections

Authors: *T. KIM[1], C. MAGNUS[1,2], S. M. STERNSON[1,2];
[1]UCSD, San Diego, CA; [2]HHMI, Chevy Chase, MD

Abstract: Prelimbic cortex encodes the outcome of the need-state based decisions between hunger and thirst through different ensemble activities. Cell-type specific wiring diagram of the prelimbic cortex can aid the understanding of functional circuits that guide a choice selection in diverse behavioral states. To achieve this, we developed retrograde viral vectors that express unique barcode transgenes and designed their oligonucleotide probes for a selective detection of individual barcode transgenes. Each barcode virus was injected and expressed in multiple different projection sites across the brain. Then, we reconstructed and compared the cytoarchitecture of the prelimbic cortex to neighboring prefrontal subregions with spatial organization of endogenous marker genes and projection patterns via EASI-FISH technique, a multiplexed gene detection method in a thick tissue. Our results show a brain-wide cell-type specific wiring information in mouse medial prefrontal cortex.

Disclosures: T. Kim: None. **C. Magnus:** None. **S.M. Sternson:** None.

Poster

PSTR096: Connectomics Across Species

Location: MCP Hall A

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Program #/Poster #: PSTR096.13/T9

Topic: I.03. Anatomical Methods

Support: Dr. Miriam and Sheldon G. Adelson Medical Research Foundation (LAH)
New York State Spinal Cord Injury Research Board (LAH)

Title: Mapping of the sacral ventral root projectome in rhesus macaques to refine neuromodulation strategies

Authors: *L. HAVTON[1], P. BARTMEYER[1], G. BORTOLANCA CHIAROTTO[2], Y. SIM[2], Y. BESHAY[3], J. NIETO[2], M. P. WARD[4], N. P. BISCOLA[2];
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Abstract: Sacral anterior root stimulation (SARS) and sacral nerve stimulation (SNS) represent two forms of neuromodulation by electrical stimulation of peripheral axons with the goal of

overcoming lower urinary tract (LUT) dysfunction in the clinical setting of traumatic myelopathies or a non-neurogenic overactive bladder. Clinical outcomes to SARS and SNS may vary extensively between subjects and mechanisms of action are not well understood. There is a need for a detailed characterization of the fascicular and sub-fascicular organization of nerve fibers in sacral nerve roots to better predict nerve fiber recruitment and guide functionally-selective and refined neuromodulation strategies. We have developed a model system for high resolution mapping of the organization of the sacral nerve root projectome in rhesus macaques. During spine surgery for lumbosacral ventral root avulsion injury, proximal segments of the L6-S3 ventral roots (VRs) were procured and processed for light microscopy (LM) and transmission electron microscopy (TEM). Ultrastructural imaging of entire VRs is followed by digital segmentation of all myelinated and unmyelinated axons for detail analyses. Individual S1 VRs may consist of a single or multiple fascicles. The fascicles are populated by myelinated axons of varied sizes and by a cohort of unmyelinated axons. The myelinated axons exhibit a diameter distribution with three peaks of 0-4 μm, >4-10 μm, and >10 μm, corresponding to preganglionic parasympathetic fibers, γ-motor fibers, and α-motor fibers, respectively. The relative proportions of the three different functional groups of myelinated fibers vary between animals. The myelinated fibers showed heterogeneity with regards to their 2-dimensional distribution within fascicles, and the degree of clustering was higher in the setting of a larger proportion of small preganglionic parasympathetic fibers. The small myelinated and unmyelinated axons also appeared to cluster together within the endoneurial space. A heuristic action potential interpreter (HAPI) was introduced to provide predictions of evoked compound nerve action potentials (CNAPs) with inclusion of all myelinated and unmyelinated axons within each VR fascicle. Physiologic heterogeneity was shown with a broad range of CNAP responses and included two or three peaks corresponding to known morphological subtypes of nerve fibers. Our findings highlight the value for detailed mapping of the sub-fascicular VR organization to better predict nerve fiber recruitment and guide new SARS and SNS refinement strategies. Possible targeting of select fascicles and fiber populations may help to augment therapeutic outcomes.

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Poster

PSTR096: Connectomics Across Species

Location: MCP Hall A

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Program #/Poster #: PSTR096.14/T10

Topic: I.03. Anatomical Methods

Support: NIH Grant R21NS125372
Pennsylvania Department of Health Commonwealth Universal Research Enhancement (C.U.R.E.) Tobacco Appropriation Funds SAP 4100083102

Title: An Integrated MRI-Histology Atlas of the Marmoset Cerebellum

Authors: *M. LIN[1], A. C. BOSTAN[1], D. SZCZUPAK[1], M. FRUM[1], M. HANADA[1], S.-H. CHOI[1], M. KLASSEN[2], P. L. STRICK[1], D. J. SCHAEFFER[1], A. C. SILVA[1];
[1]Neurobio., Univ. of Pittsburgh, Pittsburgh, PA; [2]Ctr. for Functional and Metabolic Mapping, Western Univ., London, Ontario, OH, Canada

Abstract: The common marmoset (Callithrix jacchus) has proven to be a tractable model species for studying neuroanatomical and physiological features of the primate brain, as well as an emerging key model species for understanding the pathology of neurodegenerative and neuropsychiatric disease. The marmoset brain includes evolutionally divergent features that are primate-specific, such as an elaborated, granular frontal cortex and a relatively large cerebellum that is structurally expanded when compared with rodents. Due to the extensive foliation of the cerebellar cortex, combining detailed anatomical labelling with digital 3D cartography has been a technical challenge. Here, we bridged a traditional histological brain mapping approach with modern ultra-high- resolution MRI to produce a highly accurate and detailed representation of the marmoset cerebellum. We developed a new registration method that accurately combines ultra-high- resolution anatomical MRI at 25um isotropic resolution and 20um serial tape-transfer Nissl histology. This approach allowed us to manually annotate and digitize a comprehensive true 3- dimensional marmoset cerebellar atlas. This resource comprises 45 discreetly labelled and color-coded anatomical regions, including individual sub-folia across all cerebellar lobules, individually separated at the granular and molecular layer levels, as well as the cerebellar nuclei. Manual annotations were performed on individual MRI sections sampled every 40 um in the sagittal plane. Our nomenclature is based on that of Larsell (1970), to facilitate correspondence and relevance to the human and other large non-human primate cerebellum studies. Further, we developed a novel method optimized to identify the cerebellar surface curvature and represent it in a 2-dimensional space (Flatmap). This approach accurately reflects the anatomy of the cerebellum and maintains the native topology with minimal distortion. This Flatmap allows for accurate multimodal data (e.g., fMRI, lesion/injection map, neuroanatomical tracing) visualization and comparison. This resource is publicly available for on-the-fly viewing and/or download at marmosetbrainconnectome.org/cerebellum.

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Poster

PSTR096: Connectomics Across Species

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Support: National Key R&D Program of China (No. 2022YFA1603604)
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the National Science and Technology Innovation 2030 Major Program (No. STI2030-2021ZD0200100)
the Scientific Instrument Developing Project of CAS (No. YJKYYQ20190052)

Title: Single-cell spatial transcriptome atlas and whole-brain connectivity of the macaque claustrum

Authors: Y. LEI[1], Y. LIU[2], M. WANG[3], N. YUAN[4], L. DING[5], Z. ZHU[5], Z. WU[6], C. LI[7], Y. HOU[8], Y. SUN[9], M.-M. POO[10], J. YAO[6], W. WEI[11], H. KENNEDY[12], ***Z. SHEN**[10];
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Abstract: Claustrum orchestrates brain function via its connectivity with numerous brain regions, but its molecular and cellular organization remains unclear. Single-nucleus RNA sequencing of 227,500 macaque claustral cells identified 48 transcriptome-defined cell types, with most glutamatergic neurons similar to those in deep-layers of insular cortex. Comparison among macaque, marmoset, and mouse transcriptomic data revealed primate-specific glutamatergic and GABAergic cell types. Retrograde tracer injections in 59 cortical areas and 7 subcortical structures defined four distinct distribution zones of retrogradely labeled claustral neurons. Joint analysis of whole-brain connectivity and single-cell spatial transcriptomes revealed the claustral zones contained distinct compositions of transcriptome-defined glutamatergic cell types, preferentially connected to specific brain areas with a strong ipsilateral bias. Notably, several primate-specific glutamatergic cell types in distinct ventral and dorsal claustral zones were selectively connected to hippocampus/entorhinal cortex and putamen/motor cortex, respectively. These data contribute to elucidating the molecular and cellular organization underlying diverse claustrum functions.

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Poster

PSTR096: Connectomics Across Species

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR096.16/T12

Topic: I.03. Anatomical Methods

Title: A cellular-resolution sympathetic projectome of zebrafish

Authors: *M. ZHENG[1,2], H. WAN[1], R. WANG[1], X. DU[1,2];
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Abstract: The sympathetic division of the autonomic nervous system is indispensable for body homeostasis. It controls diverse physiological processes through innervating peripheral organs and tissues throughout the body. Although the study of sympathetic nerve has a long history, we lack a cellular-resolution projection map for understanding the organization, integration and coordination of diverse sympathetic outputs. Here, taking advantage of the larval zebrafish in building single-neuron morphology atlas, we systematically mapped the sympathetic projectome at the whole-body level. We constructed a larval zebrafish (at 6 - 7 dpf) whole-body 3D average template with brain and internal organ parcellations for data integration. According to transgenic labeling, we defined all sympathetic ganglions and traced postganglionic axon tracts that innervate end organs, such as eye, skin, swim bladder, and intestine. Using sparse labeling, we further reconstructed over 300 postganglionic sympathetic neurons and created a single-neuron projectome atlas by aligning them with the reference template. We then presented a 3D digital projectography to illustrate the connectivity between neural clusters in specific sympathetic ganglia with known end organs, yielding insights into topological, divergent, and convergent projection properties. This cellular-resolution sympathetic wiring diagram stands as a structural foundation for the understanding of the sympathetic motor output system.

Disclosures: M. Zheng: None. **H. Wan:** None. **R. Wang:** None. **X. Du:** None.

Poster

PSTR096: Connectomics Across Species

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Program #/Poster #: PSTR096.17/U1

Topic: I.03. Anatomical Methods

Support: NIGMS: R35GM142566

Title: Mapping the neural basis for individual differences in the risk-taking behavior of adult zebrafish.

Authors: *N. RAJPUT[1], K. PARIKH[2], D. KANANI[2], A. SQUIRES[2], K. FIELDS[2], B. D. FONTANA[3], J. W. KENNEY[4];
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Abstract: Mapping the neural basis for individual differences in the risk-taking behavior of adult zebrafish.

Neha Rajput, Kush Parikh, Dea Kanani, Ada Squires, Kailyn Fields, Barbara D. Fontana, and Justin W. Kenney

Individual differences in behavior have been observed across a wide range of taxa, including humans, rodents, and fish. One significant axis of behavioral variation is risk-taking, where animals displaying a greater willingness to take risks are classified as bold, while those exhibiting less inclination are characterized as shy. While biological factors are known to contribute to this variation, the underlying mechanisms are not yet fully understood. To investigate the neural mechanisms underlying these behavioral differences, we employ adult zebrafish as a model. We assess behavioral differences in zebrafish by subjecting them to the novel tank test and quantifying their exploration of the new environment. Our findings reveal that bold individuals explore a larger area of the tank and spend most of their time near the top, whereas shy individuals exhibit limited exploration and spend most of their time towards the bottom of the tank.To gain a better understanding of the neural basis of bold and shy behavior types, we developed tools for whole-brain activity mapping. We used *in situ* hybridization chain reaction (HCR) to detect the expression of *c-fos*, an immediate early gene, as a means of labeling active neurons. To visualize brain-wide *c-fos* expression, we combined tissue clearing technique with light sheet microscopy to generate whole brain images. For automatic detection of *c-fos* positive cells, we employed CellFinder, a deep learning-based cell identification approach integrated into the BrainGlobe computational environment. The images were then registered to our recently created adult zebrafish brain atlas (AZBA) using advanced normalization tools (ANTs). We successfully trained CellFinder to identify *c-fos* positive cells with an accuracy of 96% and found that *c-fos* expression peaks at 15-30 minutes following exposure to a novel tank. With this approach, we identified distinct patterns of *c-fos* activity within the subpallium region of the telencephalon, associated with bold and shy behavior type.

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Poster

PSTR096: Connectomics Across Species

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Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR096.18/U2

Topic: I.03. Anatomical Methods

Support: NSF (2203119)
Vannevar Bush Faculty Award (ONR N000142012828)

Title: Connectome of the endodermal nerve net of Hydra vulgaris

Authors: *S. ZHANG[1], N. OFER[1], R. SCHALEK[2], X. WANG[2], C. DUPRE[1], A. YAKOBE[1], D. WEI[3], J. W. LICHTMAN[2], R. YUSTE[1];
[1]Columbia Univ., New York, NY; [2]Harvard Univ., Cambridge, MA; [3]Boston Col., Boston, MA

Abstract: The cnidarian *Hydra vulgaris* is a small freshwater polyp with a nervous system of few hundred neurons belonging to a dozen cell types, organized in two nerve nets, one in the endoderm and one in the ectoderm, and without cephalization or ganglia. Using this simple "chassis", Hydra can maintain a stable repertoire of behaviors, even performing complex fixed-action patterns, like *somersaulting* and feeding. How such a simple nervous system can generate a stable and relatively complex behavioral output remains a fascinating mystery. The morphology, connectivity, neuronal subtypes, and means of communication in this simple nervous system are still poorly understood. As a first step to understanding this, we have focused on studying the endodermal nerve net, which is smaller than the ectodermal one and has only three transcriptomic neuronal cell types. We have used serial EM of high-pressure freezing fixed samples to reconstruct all the endodermal neurons and their connectivity, characterizing their distinct morphologies, with the ultimate goal of linking the connectome with the cell types. In our initial results, we often find interneuronal morphological specializations ("handshakes") where neurites from one neuron end inside the neurites of another neuron. We also reconstructed all vesicles, both dense core and clear ones, present in neurons using deep learning autosegmentation and manual proofreading. We find that most vesicles in neurons are located far from other neurons. This fact, together with the reconstruction of one neuron which is physically isolated from the rest of the nerve net, suggests that *Hydra* neurons communicate with each other mainly through volume transmission as opposed to synaptic transmission.

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Poster

PSTR096: Connectomics Across Species

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Program #/Poster #: PSTR096.19/U3

Topic: I.03. Anatomical Methods

Support: NIH/BRAIN Initiative (U01MH117079)
CHDI Foundation, Inc (Research Contract)

Title: Dendritome Mapping Reveals Medium Spiny Neuron Morphological Variations Linked to D1/D2 Genetic Types and Striatal Domains

Authors: *X. YANG[1], C. PARK[1], H. DONG[2], N. FOSTER[3];
[1]UCLA, Los Angeles, CA; [2]Neurobio., UCLA, Los Angeles, CA; [3]Univ. of California at Los Angeles, Los Angeles, CA

Abstract: For over a century since the age of Cajal, dendrite morphology is considered one of the cardinal features of mammalian neurons, as it defines the domain and input of each neuron and a primary cellular site for neural computation in the mammalian brain. Despite the importance of dendrites in understanding the mammalian neurons and their diseases, there is

currently a lack of a generalizable systems-biology approach to analyze the intact dendritic arbors of genetically-defined mammalian neurons at large-scale, from labeling and imaging to registration onto reference brain atlas and quantitative analysis. Here, we introduce a generalizable and scalable pipeline from genetic sparse and bright labeling of the complete dendritic trees of single-neurons using MORF3 mice (Veldman et al. Neuron 2020, PMID:32795398), 3D-imaging of cleared thick brain sections, customized multi-scale reference map registration, semi-automated single-neuron reconstruction, grid-mapping of the whole brain, interactive morphometric and box-based analyses, and brain-wide single-neuron visualization. We applied such large-scale single-neuron dendritic mapping (i.e. "dendritome" mapping) approach to develop a reference dendritic morphological map for 2402 D1- and D2-MSNs in P56 mouse brains. We verified and extended prior findings on the morphological differences between the two MSN genetic types. Moreover, using a novel reference box-based analysis of MSN morphologies, we discovered that distinct MSN morphometric features are localized to specific striatal domains and correspond to functional domains. Finally, we applied dendritome analysis to over 1000 MSNs from 12-month-old wildtype and Huntington's disease mice, and uncover both age- and HD-related morphological changes. By building a suite of generalizable, scalable and sharable genetic, imaging and computational tools, our study provides a proof-of-concept on dendritome mapping as a new systems biology approach to study genetically-defined single-neuron morphology, which can advance in vivo brain cell biology and understanding of disease pathogenesis.

Disclosures: X. Yang: None. **C. Park:** None. **H. Dong:** None. **N. Foster:** None.

Poster

PSTR096: Connectomics Across Species

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Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR096.20/U4

Topic: I.01. Molecular, Biochemical, and Genetic Techniques

Support: ZIC MH002903 NIMH-IRP

Title: Specificity of neuronal cell-cell communication using single-cell RNA sequencing data

Authors: *P. NARNUR[1], A. SCHULMANN[2], Y. PATEL[3], D. KIM[3], P. K. AULUCK[4], **S. MARENCO**[3];
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Abstract: Background: Cell-cell communication (CCC) regulates neuronal activity through interactions between ligands and cognate targets (interaction pairs). We used NeuronChat to predict CCC from the expression of ligands and targets in specific cell types measured with single cell RNA-seq (scRNA-seq) in mouse and single nucleus RNA-seq (snRNA-seq) in

human. We hypothesized that some interaction pairs would be specific to cell type pairs and conserved across cortical regions. We focused on interneuron-interneuron communication under the assumption that local reciprocal connectivity of interneurons is conserved across neocortical regions.
Methods: We used a scRNA-seq dataset with 13 adult cortical regions (Yao et al. 2021) for mouse and a snRNA-seq dataset with 33 cortical regions for human (Siletti et al. 2023). We curated a database of 2272 neuronal interaction pairs for mouse and 2058 interaction pairs for human. For each interaction pair, NeuronChat generated estimates of probability of connection (ligand * target abundance) for each of 25 cell type pairs derived from VIP, SST, PVALB, LAMP5 and SNCG cell types. Variance partitioning was used to test whether the variance of a given interaction pair was explained more by cell type pair or regional differences. For each region, we calculated the specificity of interaction pairs to cell type pairs. We compared highly specific interaction pairs between species.
Results: We found 29 interaction pairs in mouse and 99 in human to be most specific to one interneuron cell type pair across all cortical regions (e.g. Penk-Oprl1 for VIP to SST in mouse and Tac-Tacr1 for PVALB to LAMP5 in human). In addition, some interaction pairs were markers for several cell type pairs (e.g. Nrxn1-Nlgn3 for VIP to SST, SNCG to SST, and VIP to SNCG) in mouse. The median proportion of variance explained by cell type pair was much larger than for region of interest (0.55 vs. 0.04 for mouse and 0.32 vs. 0.04 for human). Comparison of markers for cell type pairs across species revealed some conserved pairs (e.g. Sema3a-{Nrp1_Plxna4} for SST to VIP), and some species-specific interaction pairs (e.g. Cdh2-Cdh2 for SNCG to SNCG in mouse and for SST to SST in humans).
Conclusion: We identified a group of interaction pairs consistently specific to one interneuron-interneuron pair across mouse cortex and human cortex. Preliminary comparisons of mouse and human cell-cell communication reveal both conserved and divergent patterns of interneuron-interneuron signaling. These findings could pave the way for efficient discovery and validation of cell-cell connectivity and circuitry in human brain.

Disclosures: P. Narnur: None. **A. Schulmann:** None. **Y. Patel:** None. **D. Kim:** None. **P.K. Auluck:** None. **S. Marenco:** None.

Poster

PSTR096: Connectomics Across Species

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR096.21/U5

Topic: I.03. Anatomical Methods

Support: Nebraska Research Initiative Collaboration Grant
NIH R21MH128123
NIH R21MH134678
NIH P20GM130447
NIH P20GM103480

Title: Mapping Brain Molecular Connectivity Using CEST MRI

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Abstract: The mapping of brain metabolic and neurotransmitter connectivity provides "molecular level" information that augments the "system level" knowledge of brain functional and structure connections measured using functional MRI and diffusion tensor imaging (DTI), respectively. Positron emission tomography (PET) has been extensively tested to map brain molecular connectivity based on regional radiotracers uptake maps. The radiotracer uptake maps acquired by PET is "static", and therefore multiple subjects have to be used to identify the patterns of the covariation of regional radiotracer uptake in the subjects. In other words, subject series PET data are used to detect inter-subject connectivity. We here tested a novel brain molecular connectivity mapping technique in mice using MRI based on the chemical exchange saturation transfer (CEST) contrasts of biomolecules. CEST contrast-based MRI provides specific detection of biomolecules including metabolites and neurotransmitters at high spatial resolutions. In this study, we estimated the molecular connectivity based on the CEST contrasts of glutamate as a prototype. The acquisition time of CEST data is relatively long. To achieve connectivity mapping within a single mouse (intra-subject analysis), we employed an innovative connectivity modeling approach that builds molecular connectivity based on CEST data sets acquired with varying radiofrequency (RF) saturation. The neurophysiological basis underlying this approach is the CEST contrast of glutamate is influenced by local pH, temperature and other biological effects, and show regional variations in response to saturation RF. Regions with covarying CEST contrast in RF belong to the same network. CEST data in mice (C57BL/6, n = 10) were acquired on a 7 T scanner using a RARE sequence with 15 slices to cover the whole brain, 51 frequency offsets from -5 to 5 ppm with a step = 0.2 ppm. A recently published scheme was used to shorten scanning time, in which the 1st saturation RF length = 3 s followed by 0.5 s saturation RF for each readout. Six CEST data sets were acquired with RF magnitude = 1 - 6 μT, respectively, and each data set was acquired in 11 mins. Seed-based correlations were calculated using FSL with left hippocampus as the seed. Brain regions that significantly ($p < 0.05$, $Z > 3.0$) correlated with the left hippocampus included somatosensory cortex, auditory cortex, gustatory cortex, and secondary motor area, amygdala and colliculus. This proof of concept study demonstrates the technical feasibility using RF-varying CEST data to estimate brain molecular connectivity. We plan to use ICA and graph theoretic analysis to further test the CEST data based approach.

Disclosures: M.G. Uberti: None. **A. Bhattarai:** None. **C. Samaraweera:** None. **D. Peng:** None. **Y. Liu:** None.

Poster

PSTR096: Connectomics Across Species

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR096.22/U6

Topic: I.03. Anatomical Methods

Support: The Francis Crick Institute

Title: Linking a synapse-resolution connectome to behaviour

Authors: L. KIMBLEY[1], L. COCHRANE[1], A. SEGGEWISSE[1], X. CANO FERRER[1], C. SHAND[1], A. STRANGE[1], A. IMBERT[1], A. CARDONA[2], M. ZLATIC[2], ***M. WINDING**[1]; [1]The Francis Crick Inst., London, United Kingdom; [2]MRC Lab. of Mol. Biol., Cambridge, United Kingdom

Abstract: Comprehensive synaptic circuitry—the connectome—is required to understand how brains generate behaviour. It provides all pathways of information flow through the brain. However, this information alone is not enough. We need to know which circuits and circuit elements have a causative role in behaviour. Here, we generated the first synapse-resolution map of an insect brain using volume electron microscopy, including 3016 neurons and 548,000 synaptic sites. We used this information to simulate how signals propagate from sensory to premotor neurons across an entire brain. We found extensive multimodal integration, recurrent connectivity, and robust signal integration across brain hemispheres. Patterns of brain-wide circuitry mirrored cutting-edge AI architectures, suggesting much can be learned by comparing artificial and biological neural networks. To determine the role of observed network features in behaviour, we linked individual circuits elements from the connectome to a library of genetic tools allowing us to manipulate their activity. Using these tools, we designed a set of behavioural paradigms that allow us to selectively inhibit individual neurons and determine their role in social behaviours. This study lays the foundation for converting connectivity data into testable hypotheses about behaviour and neural dynamics across an entire brain.

Disclosures: L. Kimbley: None. **L. Cochrane:** None. **A. Seggewisse:** None. **X. Cano Ferrer:** None. **C. Shand:** None. **A. Strange:** None. **A. Imbert:** None. **A. Cardona:** None. **M. Zlatic:** None. **M. Winding:** None.

Poster

PSTR097: Network Models I

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR097.01/U7

Topic: I.06. Computation, Modeling, and Simulation

Support: UB SPARC Award

Title: Using dynamic network embeddings to distinguish distinct brain network trajectories

Authors: *J. HARTZ[1], S. E. MULDOON[2];
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Abstract: The brain is a dynamic system whose structure is constantly evolving through learning, aging, and disease. Unfortunately, due to both individual differences among people and noise in neuroimaging techniques, brain network data is inherently noisy. This presence of noise in the data can hamper our ability to detect and quantify changes or differences in network structure. This problem is particularly relevant when studying networks that can evolve from a single initial state to multiple final states. In such cases, one would like to be able to identify a network's trajectory, or path, and therefore predict its final state. Here, we develop a methodology to quantify and predict a network's evolution over time. Our approach is based on novel dynamic brain network embeddings to encode local network properties and track their divergence over time. Additionally, we incorporate statistical techniques to determine when a network's trajectory is significantly changing above noise levels. We provide initial examples of how this technique can be applied to simulated brain network trajectories that model the evolution of a traumatic brain injury (TBI). These techniques will be especially important in developing personalized medicine treatment strategies in populations where subgroups of patients follow different trajectories of the same disease that can be linked with different clinical outcomes.

Disclosures: J. Hartz: None. **S.E. Muldoon:** None.

Poster

PSTR097: Network Models I

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR097.02/U8

Topic: I.06. Computation, Modeling, and Simulation

Support: NIH R01NS117405

Title: Transcranial magnetic stimulation evoked responses in a mesoscale spiking network model of primate motor cortex with patchy connectivity

Authors: *G. J. YU[1], M. A. SOMMER[2], A. V. PETERCHEV[1], W. M. GRILL[2];
[1]Psychiatry & Behavioral Sci., Duke Univ., Durham, NC; [2]Biomed. Engin., Duke Univ., Durham, NC

Abstract: The motor cortex is a model system for investigating the cortical response to transcranial magnetic stimulation (TMS) because its output can be measured from the corticospinal tract without being obfuscated by the stimulus artifact. Such measurements revealed a stereotyped TMS-evoked response pattern called I-waves. Understanding the mechanisms of I-wave generation in motor cortex serves as a building block for understanding the cortical response to TMS more generally.

Prior computational modeling studies revealed that conduction delay is an important factor in determining the neuron types that contribute to peaks of I-waves. However, these models represented a small volume of cortex that excluded conduction delays relevant to the temporal window for I-waves. Expanding this volume would add longer range intracortical dynamics and delays, but for primates would also require the addition of intracortical projections that are not observed in rodents, called patchy connectivity. We developed a mesoscale spiking network model of primate motor cortex to account for conduction delays relevant to I-waves that incorporated anatomical constraints across the laminar and horizontal axes for the intracortical circuit, extracortical afferents, and patchy connectivity.
To generate the local connectivity, spatial probability distributions of dendrites and axons were measured from morphological reconstructions. Dendritic distributions and synapse count estimates were used to generate synaptic locations, and the axonal distributions were used as weights to compete for synapses. Patchy connectivity was constrained based on anterograde tracer studies that measured features such as numbers of patches, inter-patch distance, and patch size. Calculations of conduction delays included axonal and somatodendritic conduction and synaptic transmission.
Responses of the model to single pulse TMS demonstrated that the long-range monosynaptic projections of the patchy connectivity system allow more neuron types to contribute to later I-waves than in smaller-volume and patchless models. These findings suggest that patchy connectivity is an important feature for investigating responses evoked by cortical stimulation and spatial propagation of stimulation-evoked activity in models of primate cortex.

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Poster

PSTR097: Network Models I

Location: MCP Hall A

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Program #/Poster #: PSTR097.03/U9

Topic: I.06. Computation, Modeling, and Simulation

Support: NSF 2209872
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Title: Flexible tool for constructing cell types distributions for computational models from transcriptomics data in brain atlases.

Authors: S. CHOCKALINGAM[1], S. ITO[2], K. DAI[3], D. WANNIPURAGE[1], S. MARRU[1], A. ARKHIPOV[3], *G. KRISHNAN[1];

[1]Georgia Inst. of Technol., Atlanta, GA; [2]SCIPP, Allen Inst., Seattle, WA; [3]Allen Inst., Seattle, WA

Abstract: Brain atlases have become more extensive and detailed, yet using brain atlases for the construction of computational models remains a challenge. In particular, single-cell transcriptomics data allow for identifying diverse cell types. Further, spatial transcriptomics data allows for regional and layerwise distributions of the different cell types. Current approaches for incorporating these data into computational models require constructing complex workflows. In this work, we developed a flexible and extendable tool that allows queries over transcriptomics data from brain atlases and applies transformations over transcriptomics datasets. The results of such processing can be directly incorporated within the computational models described using SONATA format. We provide various examples of this tool for the construction of detailed regional and whole-brain mouse and human models. The tool, accessible via neuroscience.cybershuttle.org, offers extensibility and flexibility for diverse applications, supporting executions on various computational resources. The open-source code is accessible to the community under the Apache framework.

Disclosures: S. Chockalingam: None. **S. Ito:** None. **K. Dai:** None. **D. Wannipurage:** None. **S. Marru:** None. **A. Arkhipov:** None. **G. Krishnan:** None.

Poster

PSTR097: Network Models I

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR097.04/U10

Topic: I.06. Computation, Modeling, and Simulation

Title: Exploration of structure-function relationships with personalized brain network models in developing readers

Authors: *A. NGUYEN[1], S. E. MULDOON[2];
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Abstract: Developmental dyslexia is a learning disability that affects reading ability and is characterized by disruptions in processing orthographic and phonological information from written language. While dyslexia has been studied using a host of neuroscientific methods, network modeling work on dyslexia is relatively limited, despite the implication that dyslexia involves disruptions of communications within the sensory processing network of the brain, and more specifically, the reading network. Here, we analyze an archival dataset of developing readers, containing individual diffusion MRI scans and performance data on a rhyming judgment task, which varied in the sensory modality and lexicality of stimulus presentation. We extract individual tractography networks and build personalized computational brain network models, which simulate brain dynamics. This study therefore identifies cognitive systems of the brain that

functionally vary as a result of individual differences in brain white matter structure. We then use these models to examine the effects of auditory and visual stimulation on the brain, and how resultant functional connectivity correlates with individual rhyming judgment performance measures. Specifically, we systemically apply stimulation to visual and auditory nodes in each brain network model, and observe changes in functional correlation in subnetworks associated with various cognitive systems, as well as a specific reading network. We find that the simulated functional connectivity within and between specific cognitive systems (auditory, medial default mode, visual and cerebellar) is significantly associated with measures of accuracy and response time for certain conditions of the rhyming judgment task. These functional differences correlate with performance on a verbal task that can potentially distinguish between strong and weak developing readers. This provides a preliminary exploration of the complex connectivity differences thought to underlie developmental reading proficiency.

Disclosures: A. Nguyen: None. **S.E. Muldoon:** None.

Poster

PSTR097: Network Models I

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR097.05/U11

Topic: I.06. Computation, Modeling, and Simulation

Support: Ontario Graduate Scholarship

Title: Stratifying depression patients using in-silico EEG biomarkers of SST interneuron inhibition

Authors: *F. MAZZA[1,2], M. HASSAN[3], A. T. GUET-MCCREIGHT[4], E. HAY[1,2];
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Abstract: Depression is a leading cause of disability with a large proportion of patients being treatment-resistant. Recent postmortem studies in depression patients have implicated cellular mechanisms of reduced cortical inhibition by somatostatin-expressing (SST) interneurons. However, establishing the link between the cellular changes and diagnostic brain signals such as electroencephalography (EEG) is currently not possible in living humans. To overcome the experimental limitations, we characterized in-silico EEG biomarkers of SST interneuron inhibition using detailed models of human cortical microcircuits. We simulated models of human cortical microcircuits in health and depression with varying severities of reduced inhibition, and trained an artificial neural network (ANN) to estimate inhibition from the ground-truth simulated data. The ANN estimated inhibition and classified depression versus healthy microcircuits with high accuracy. We then applied the ANN to estimate patient inhibition from the EMBARC depression dataset. We identified a subset of depression patients exhibiting high estimated

reduced SST interneuron inhibition consistently, which was also significantly higher than the estimated low inhibition for healthy controls. We showed that the estimated inhibition correlated strongly with depression severity score and cognitive symptoms thought to be linked to reduced SST interneuron inhibition. Our study pioneers estimating cell-specific inhibition from patient EEG, overcoming experimental limitations using machine learning and in-silico biomarkers, which will serve to improve mechanistic stratification of depression patients.

Disclosures: F. Mazza: None. **M. Hassan:** None. **A.T. Guet-Mccreight:** None. **E. Hay:** None.

Poster

PSTR097: Network Models I

Location: MCP Hall A

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Program #/Poster #: PSTR097.06/U12

Topic: I.06. Computation, Modeling, and Simulation

Support: NIH Grant R01EB029813
NIH Grant R01NS122742
NIH Grant U24NS124001
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Title: Advancements in the Bio-realistic Mouse V1 Model: Incorporating New Connectivity Data

Authors: *S. ITO[1], D. HAUFLER[1], K. DAI[1], J. AMAN[1], J. GALVÁN FRAILE[2], G. CHEN[3], C. MIRASSO[2], W. MAASS[4], A. ARKHIPOV[1];
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Abstract: We have advanced our bio-realistic model of the mouse primary visual cortex (V1), building upon the foundational work by Billeh et al. (Neuron, 2020). The new model integrates the results of extensive analysis of the new synaptic physiology data from Campagnola, Seeman et al. (2022; portal.brain-map.org/connectivity/synaptic-physiology) and detailed connectomics from the IARPA MICrONS dataset (www.microns-explorer.org). These new data have refined the model's connectivity structure and synaptic dynamics. Notable improvements are seen in the representation of receptor properties, degree distributions, and synaptic weight distributions. The resulting model exhibits stable activity patterns prior to optimization.
Moreover, we have implemented TensorFlow-based optimizations to systematically refine model parameters, ensuring alignment with physiological data, including Neuropixels recordings. This method allows automated tuning of the model to achieve specific empirical targets such as firing rates and the level of orientation selectivity.
The enhancements in this iteration of the model not only deepen our understanding of cortical

processing but also enhance its utility as a research tool, which will be shared publicly to facilitate future research in the community.

Disclosures: S. Ito: None. **D. Haufler:** None. **K. Dai:** None. **J. Aman:** None. **J. Galván Fraile:** None. **G. Chen:** None. **C. Mirasso:** None. **W. Maass:** None. **A. Arkhipov:** None.

Poster

PSTR097: Network Models I

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Program #/Poster #: PSTR097.07/U13

Topic: I.06. Computation, Modeling, and Simulation

Support: NIH NINDS R01NS129622
NIH NINDS K23NS112339

Title: Short-term synaptic depression regulates excitability onto the edge of stability

Authors: *T. J. RICHNER[1], B. N. LUNDSTROM[2];
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Abstract: Excitability is defined by neural responses to stimuli, but in many ways remains poorly defined. However, abnormal excitability can clearly lead to events such as epileptic seizures. We aimed to understand how excitability is dynamically regulated to maintain a homeostatic level of neural activity. Without dynamic regulation, stimuli can propagate through the highly recurrent neural network of the brain and either diminish or amplify exponentially, depending on the strength of network connections. We hypothesized that short-term synaptic depression (STD) regulates excitability in a dynamic fashion to maintain normal excitability. STD is characterized by temporary decreases in synaptic strengths in response to repeated presynaptic inputs.

To investigate the contribution of STD to the regulation of excitability, we constructed a neural network with STD modeled as a multiplicative gain that decreases over time (i.e., it adapts) when driven presynaptically. We quantified excitability as the rate by which the network outputs dampen or grow exponentially. Since STD has a multiplicative nonlinearity, we used Wolf's method to measure the largest Lyapunov exponent (L1). We found that STD dynamically regulates excitability such that the L1 is near zero with transient excursions positive and negative, i.e., the response will neither grow nor decay over time. Instead, the spike rates of the neurons evolve along a parallel trajectory through state space, maintaining an encoding of the stimulus over an extended period.

STD dynamically rebalanced the network, keeping it on the edge of stability. Notably, we found that STD regulated excitability onto the edge of stability across a wide range of network connectivities. Therefore, STD largely mitigates the dependence of stability on connectivity, providing distributed learning rules (e.g., Hebbian learning) greater flexibility without requiring

careful connection tuning for stability. These results suggest that quantifying mechanisms of neural adaptation, especially STD, may be critical for understanding neural excitability.

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Poster

PSTR097: Network Models I

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR097.08/U14

Topic: I.06. Computation, Modeling, and Simulation

Support: NSF DBI 2015317

Title: Segmented Neural Model for Control and Adaptation of Peristaltic Locomotion

Authors: *S. RIDDLE[1], C. JACKSON[2], H. J. CHIEL[3], K. A. DALTORIO[2], R. D. QUINN[2]; [1]Case Western Reserve Univ., Cleveland, OH; [2]Mechanical Engin., Case Western Reserve Univ., Cleveland, OH; [3]Biol., Case Western Res. Univ., University Heights, OH

Abstract: Animals rely on their nervous systems to generate and coordinate muscular control for locomotion. In earthworms, *Lumbricus Terrestris*, the locomotion control network is housed in the ventral nerve cord (VNC). Due to the presence of ganglion nodes located at each body segment along the VNC, the earthworm neuronal system is thought to consist of daisy-chained compartmentalized subnetworks. It is believed that each node houses an oscillator, which provides intra-segment control and coordination of the circular and longitudinal muscle activations [1]. The worm nervous system also provides for inter-segment coordination between neighboring nodes to produce whole-body peristaltic behavior. However, it is not known how this inter-segment coordination is achieved or what underlying mechanisms influence each segment's individual control network. This work proposes one possible methodology for peristaltic coordination via inter-segment couplings of adjacent segments' oscillator networks. Our neural network model uses non-spiking leaky-integrator neurons and conductance-based synapses to form a half center oscillator for single-segment muscle contraction patterns. The inter-segment coupling between these oscillators consists of a group of neurons tuned to perform edge detection, sending a signal to propagate the wave to the posterior segment when the anterior signal switches from contraction to retraction. The control network was tested on a soft robotic worm simulation for validation and successfully demonstrated coordinated peristaltic movement in a variety of environments. We also examined how intra and inter-segment control alters locomotion in response to external stimuli. For this, we approximated sensory neurons using

stretch and contact sensors and fed these signals back into the network at various points. We aim to understand the underlying mechanics of how the worm adapts its movement by identifying what sensory capabilities and parts of the network are vital to adapting locomotion and how they interact to improve movement in adverse environments. [1] - Prosser, C. Ladd. “The Nervous System of the Earthworm.” *The Quarterly Review of Biology*, vol. 9, no. 2, 1934, pp. 181-200. *JSTOR*, http://www.jstor.org/stable/2808407. Accessed 24 Apr. 2024.

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Poster

PSTR097: Network Models I

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Program #/Poster #: PSTR097.09/U15

Topic: I.06. Computation, Modeling, and Simulation

Support: NSF Grant 2123781

Title: Efficient multi-objective optimization of high-dimensional neural dynamical systems by joint learning of objectives, constraints, and sensitivities

Authors: *F. GRESSMANN[1], I. RAIKOV[2], P. MOOLCHAND[3], S. KIM[4], G. UPADHYAY[5], T. KHANDAKER[6], M. GAZZOLA[4], L. RAUCHWERGER[6], I. SOLTESZ[7];
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Abstract: Biophysical models of neurons and neuronal networks are described by dynamic equations with numerous parameters that often cannot be directly determined experimentally and must be constrained with optimization techniques that iterate through the parameter space in order to determine which combinations of parameters recapitulate experimentally measured features of neural activity. These optimization techniques are time consuming and incur high computational cost.
We present a novel, scalable multi-objective optimization framework that combines surrogate modeling, constrained sampling, and sensitivity-guided evolutionary optimization to significantly reduce the number of computationally expensive model evaluations during optimization. The joint modeling of the problem objectives and constraints allows us to compute a gradient that points to sensitive regions in the search space that are not only of higher objective value but also more likely to meet all problem constraints.
We demonstrate that our optimization approach can used with neuron models based on the Pinsky-Rinzel formalism to quantitatively reproduce key experimentally-obtained

electrophysiological features of several major hippocampal neuron classes, specifically input resistance, frequency-current relationship, interspike interval adaptation, and spike amplitude. Although ion channel kinetics for the target neuron classes are not known, our approach can generate several suitable models for each neuron type, exhibiting feature variability that is consistent with the experimental data. We further demonstrate that our approach can be applied to constraining the synaptic conductances in a large-scale CA1 neuronal network model in order to recapitulate LFP oscillatory frequencies and mean firing rates for each neuron type that have been observed experimentally in rats during awake behavior.
While the results we present are focused on hippocampal neuron types and networks, our strategy is broadly applicable to nonlinear chaotic, tightly-coupled dynamical and complex systems. Our optimization method is flexible, can efficiently utilize distributed computational resources, and does not rely on trial-and-error tuning of hyperparameters. This enables a more automated data-driven approach to optimize high-dimensional and highly constrained input spaces where the shape of the functional relationship between inputs and outputs cannot easily be visualized and understood.

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Poster

PSTR097: Network Models I

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Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR097.10/U16

Topic: I.06. Computation, Modeling, and Simulation

Title: Sampling-based Bayesian inference in a balanced network with internally generated variability

Authors: *X. YANG[1], W. ZHANG[2], B. DOIRON[3];
[1]Univ. of Pittsburgh, Pittsburgh, PA; [2]UT Southwestern Med. Ctr., Dallas, TX; [3]Univ. of Chicago, Chicago, IL

Abstract: The spiking responses of cortical neurons are characterized by large response variability. Traditionally, such variability is viewed as deleterious to neural information processing, in that it makes neural representation less reliable. Previous theoretical studies suggest that spiking response variability could arise from a balance between excitatory and inhibitory synaptic inputs in a strongly connected recurrent circuit. This raises the question of why recurrent circuits would use strong recurrent connections since they generate such prominent response variability. Under the assumption that the brain performs Bayesian inference to interpret the external world, we propose a recurrent balanced network model that uses internally generated variability to perform sampling-based Bayesian inference so as to compute the posterior of stimuli in the world. Compared with traditional balanced networks with only

random connections, in our network the recurrent connections between excitatory (E) neurons also have a weak structured component depending on the tuning similarity between E neurons. The strong random connections set the network in balanced state and internally generate Poissonian response variability to drive sampling. The weak structured connections between E neurons create the selectivity of E neurons, and form a one-dimensional stimulus subspace in neuronal response space to represent stimuli. Optimal sampling-based inference on the stimulus subspace collectively emerges from the interplay between weak structured connections and strong random connections within the network. Through this model, we illustrate that a neural circuit of coupled neuron populations with fixed connections can sample multivariate stimulus posteriors with varying uncertainties, utilizing a Gibbs-like algorithm. Our study provides novel insight into how circuit based population variability contributes to overall neural computation.

Disclosures: X. Yang: None. **W. Zhang:** None. **B. Doiron:** None.

Poster

PSTR097: Network Models I

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR097.11/U17

Topic: I.06. Computation, Modeling, and Simulation

Support: National Institute Of Biomedical Imaging And Bioengineering of the National Institutes of Health: Award Number R01EB029813
National Institute of Neurological Disorders and Stroke of the National Institutes of Health: Award Numbers R01NS122742 and U24NS124001
National Institute Of Mental Health of the National Institutes of Health: Award Number U01MH130907

Title: Biorealistic modeling of the human superior temporal gyrus for investigating speech comprehension

Authors: *D. HAUFLER[1], X.-P. LIU[2], S. ITO[1], J. GALVÁN FRAILE[3], K. DAI[1], B. E. KALMBACH[4], J. AMAN[1], D. XU[5], C. MIRASSO[6], G. CHEN[7], W. MAASS[8], E. LEIN[4], E. F. CHANG[9], M. K. LEONARD[10], A. ARKHIPOV[1];
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Abstract: Speech comprehension, a hallmark feature of human cognition, involves successive processing stages that transform basic auditory coding into high-level representations of semantic meaning. Despite widespread interest, the neural underpinnings of speech processing

are still poorly understood. To this end, we have developed a large-scale biorealistic model of the human superior temporal gyrus (STG), a structure situated at the interface between primary and higher-level associative areas related to language, to simulate cortical speech processing and identify putative neuronal contributions. Our model simulates a 1.5 mm cylindrical volume of cortical tissue using point-neuron models fit to distinct neuronal subtypes. Network construction is based on multiple publicly available datasets characterizing neuronal composition [h01-release.storage.googleapis.com/landing.html; portal.brain-map.org/atlases-and-data/rnaseq], electrophysiology [celltypes.brain-map.org/], and synaptic properties [portal.brain-map.org/connectivity/synaptic-physiology] of the human temporal lobe. Using a TensorFlow implementation of the model to enable automated tuning of synaptic weights, and STG input based on an auditory version of BMTK's Filternet [alleninstitute.github.io/bmtk/] we target STG neuron response properties characterized using Neuropixels recordings from subjects presented with spoken sentences [Leonard et al, 2024]. This combination of data-driven modeling and automated connectivity refinement aims to elucidate cell-type-specific contributions to human speech processing. We anticipate that this model will serve as a novel platform for the broader research community to explore human cortical circuitry.

Disclosures: D. Haufler: None. **X. Liu:** None. **S. Ito:** None. **J. Galván Fraile:** None. **K. Dai:** None. **B.E. Kalmbach:** None. **J. Aman:** None. **D. Xu:** None. **C. Mirasso:** None. **G. Chen:** None. **W. Maass:** None. **E. Lein:** None. **E.F. Chang:** None. **M.K. Leonard:** None. **A. Arkhipov:** None.

Poster

PSTR097: Network Models I

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR097.12/U18

Topic: I.06. Computation, Modeling, and Simulation

Support: MRC grant MC_UU_00003/1

Title: Phase-locked deep brain stimulation: model-based predictions validated in Parkinsonian rats

Authors: *N. MIRKHANI[1], C. G. MCNAMARA[2], G. OLIVIERS[1], A. SHAROTT[1], B. DUCHET[1], R. BOGACZ[1];
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Abstract: Neuromodulation can serve as a treatment in conditions such as movement disorders, where it interferes with pathological neural activity. While various stimulation strategies have proven successful in alleviating symptoms, achieving finely controlled interactive modulation remains challenging due to technical limitations and incomplete theoretical understanding. Mathematical modelling, complemented by statistical techniques can usher in insights for

efficient modulation of neuronal oscillations addressing the question of when to stimulate and when not to. We seek to achieve this goal by testing predictions of the Kuramoto model of coupled oscillators in phase locked stimulation against experimental data from a previous study collected in Parkinsonian rats. In this modelling framework, interacting oscillators undergo cycles of activity and their mean-field behaviour is represented in terms of mean phase and synchrony level which linearly translates to the oscillation amplitude from a neuronal population. Ideally, the timing of stimulation could be optimized with regards to these macroscopic quantities of the ongoing oscillations, i.e. phase and amplitude. The first prediction concerns the effect of phase on the network oscillation described by phase response curve (PRC) and amplitude response curve (ARC). The model predicts that the derivative of PRC determines whether stimulation at a specific phase has suppressing or amplifying effects. This relationship between the ARC and PRC is validated by the experimental data where all subjects except one exhibited strong correlations ($R > 0.8$). In addition, we show that this correlation holds consistently whenever there is a statistically significant effect of the phase on the response. The second prediction elucidates the role of oscillation amplitude on the magnitude of suppression/amplification attainable by stimulation at each phase. While both suppression and amplification levels peak at some intermediate values of the network synchrony, they follow different characteristic curves. Model fitting enables us to extract the dominant range of synchrony in networks leading to the measured local field potentials in subjects. Considering the relatively low levels of synchrony (0.1-0.2) in these networks, the model predicts stronger amplification compared to suppression and overall smaller effects at lower ends of oscillation amplitudes. Investigation of the experimental data confirms the presence of these trends in subjects. Taken together, this study demonstrates the validity of predictions made by this modelling approach which offers an opportunity to enhance stimulation efficiency.

Disclosures: N. Mirkhani: None. **C.G. McNamara:** None. **G. Oliviers:** None. **A. Sharott:** None. **B. Duchet:** None. **R. Bogacz:** None.

Poster

PSTR097: Network Models I

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR097.13/Web Only

Topic: I.06. Computation, Modeling, and Simulation

Support: NSF DBI2015317

Title: Modelling local modulation of neural circuits and muscles in the framework of Synthetic Nervous Systems

Authors: *Y. LI[1], V. A. WEBSTER-WOOD[2], H. J. CHIEL[3], R. D. QUINN[4];
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Abstract: Neurotransmission and neuromodulation are two main methods by which neurons convey information and implement computation intracellularly. Neurons can realize fast synaptic transmission by neurotransmission. To excite or inhibit postsynaptic neurons, they release chemicals called neurotransmitters that bind to specific postsynaptic receptors. On the other hand, they can influence the activity of other neurons, or even muscles, by secreting chemicals called neuromodulators that diffuse over a longer distance and modulate the properties of groups of neurons, or muscles, over long time scales. Neuromodulation can change synaptic strengths to reconfigure the wiring diagram of the network. It can also modulate the intrinsic conductance of neurons to alter their excitability. However, despite its critical role in the motor control of animals, traditional research in modeling nervous systems and building artificial neural networks (ANNs) mainly focuses on neurotransmission. In this work, we introduced neuromodulatory mechanisms into Synthetic Nervous Systems (SNSs) which are dynamic models inspired by the biophysics of neuronal elements and their functional roles in computation. SNSs have been applied as biologically plausible models of neural circuits and to control robots. In most previous SNS networks, each neuron was modeled as a single compartment with membrane capacitance, leak conductance, synaptic conductances, and other ion channels. To capture the modulatory effects on the excitability of neurons, we allowed presynaptic neurons to modify the activation function of postsynaptic neurons in SNSs. Specifically, the activities of presynaptic neurons provide synaptic inputs (neurotransmission) and can scale the activity of postsynaptic neurons (neuromodulation) through a first-order system with a time delay. We used such an SNS network to model the modulation of I3 muscle in the sea slug, *Aplysia californica*. Head-to-head comparison between the model output and animal data demonstrated that the computational model generated similar output enhancements and enhancement decays owing to the neuromodulatory mechanisms. These results suggest that the model reflects the dynamics of the local neuromodulation in *Aplysia* feeding control to some extent. In addition, SNSs with modulatory mechanisms have the potential to contribute to intelligent robotic grasper control.

Disclosures: Y. Li: None. **V.A. Webster-Wood:** None. **H.J. Chiel:** None. **R.D. Quinn:** None.

Poster

PSTR097: Network Models I

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR097.14/U19

Topic: I.06. Computation, Modeling, and Simulation

Title: Network diversity lowers the effective dimension of population covariability

Authors: *G. TIAN[1], O. ZHU[1], V. SHIRHATTI[2], C. M. GREENSPON[3], J. E. DOWNEY[4], D. J. FREEDMAN[5], B. DOIRON[1];
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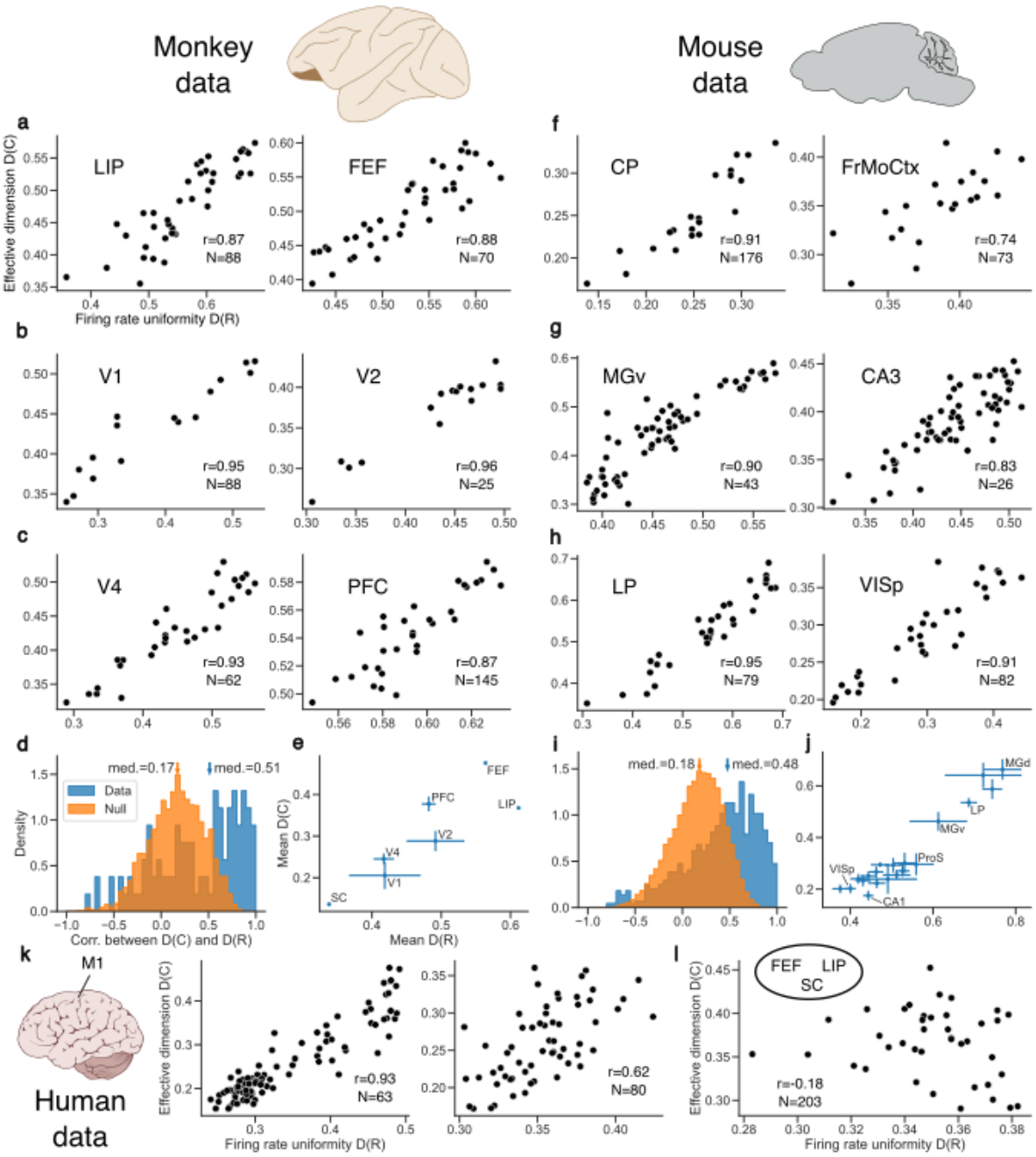
Abstract: Both trial-averaged population activity and its trial-to-trial fluctuations are critical aspects of neural representation. A diverse trial-averaged response among neurons confers a myriad of benefits on neural computation, which has been extensively studied under the framework of sparse coding (Olshausen & Field, 2004). At the same time, trial-to-trial fluctuations of neural activity that are concentrated around a low-dimensional subspace orthogonal to the informative subspace have been shown to facilitate linear decoding downstream (Averbeck et al., 2006). Here we link these two aspects of neural representation using a recurrent circuit model and derive the following relation: the more diverse the distribution of trial-averaged responses, the lower the effective dimension of population trial-to-trial covariability. This surprising prediction is tested and validated using multiple population datasets from numerous brain areas in non-human primates, mice, and humans (see attached figure). We verify in simulation that indeed a sparser code leads to better fine discrimination performance through a lowering of the dimension of population covariability. In line with this result, we show that neural populations across the brain exhibit both more diverse mean responses and lower-dimensional fluctuations when the brain is in more heightened states of information processing. In sum, we present a key organizational principle of neural population response that is widely observed across the nervous system and acts to synergistically improve population representation.



Disclosures: G. Tian: None. **O. Zhu:** None. **V. Shirhatti:** None. **C.M. Greenspon:** None. **J.E. Downey:** None. **D.J. Freedman:** None. **B. Doiron:** None.

Poster

PSTR097: Network Models I

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR097.15/U20

Topic: I.06. Computation, Modeling, and Simulation

Support: 2013 07699-0
CAPES

Title: Exploring Dynamic Behaviors of the KTH Neuron: Revelations from Computational Neuroscience

Authors: *S. RHAMIDDA[1,2], O. KINOUCHI[3], M. GIRARDI-SCHAPPO[4];
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Abstract: Neuronal modeling, including Hodgkin-Huxley DEs and discrete-time maps, offers insights into dynamic behaviors. This study delves into the KTH neuron's behaviors, akin to cardiac cells, revealing insights crucial for biopotential research. Through computational analysis, we explore parameter effects on action potential dynamics, shedding light on excitable cell behavior. The KTH neuron exhibits behaviors such as excitability, tonic spikes, cardiac spikes, tonic bursts, chaotic bursts, and twenty other behaviors akin to Izikevich [1]. Similar to the KTZ map model, the single KTH neuron displays cardiac-type firing, which is not trivial. Based on this, we demonstrate some specificities of this behavior type that are important within the scope of computational neuroscience. Despite their simplicity, single-compartment neurons are capable of executing fundamental information processing tasks individually. The map equations, since the variables are represented by V[t+1], Y[t+1] and Z[t+1]. The excitable cell dynamical variables are the membrane voltage V(t), the auxiliary variable Y(t), the slow current Z(t), and the input current I(t). The cardiac excitatory cells exhibit common oscillatory behavior similar to any ex- citable neuron, given the action potential. Thus, what we are demonstrating is that within the framework of the KTH model, we can study the polarization and depolar- ization of the cell as an electrical activity in the heart. For a practical explanation, we propose that the KTH can replicate the action potential of cardiomyocytes, which has characteristics common to excitable cells and an oscillatory system. The analysis of model parameters (K, T, H) coupled with the understanding of variables (V, Y, and Z) is crucial for comprehending the action potential. Our study begins with varying one parameter at a time to observe how the parameters affect the potential. This task was initially performed manually, isolating one parameter after another , and subsequently the activity was repeated computationally but more robustly . Not surprisingly, differences in behavior were confirmed in both analysis methods. In these procedures, we found potentials that can be approximated for studies of cardiac cells. What we can observe is that as soon as the voltage generates a peak, the membrane potential increases and other ionic channels become active, contributing to the formation of the plateau described above at different stages. It is a fact that the coexistence of these regimes may indicate the presence of a memory effect in the dynamics of excitable cells. The memory results from a transient in the subsystem.

Disclosures: S. Rhamidda: None. **O. Kinouchi:** None. **M. Girardi-Schappo:** None.

Poster

PSTR097: Network Models I

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR097.16/U21

Topic: I.06. Computation, Modeling, and Simulation

Support: NIH Grant 1R01NS130919

Title: Fitting a dynamical network model to simultaneous recordings from cortical and thalamic regions during texture discrimination task

Authors: *M. G. MOORE[1], A. GILAD[2], M. REIMERS[3];
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Abstract: We study combined neural recordings and behavioral videos from mice trained on a texture discrimination task. The neural recordings consist of a single hemisphere of wide field calcium imaging combined with an array of 32 optical fibers inserted into thalamic nuclei and the amygdala. Behavior is monitored by a body-camera and a second camera recording whisking and licking. We have developed a pre-processing pipeline that includes corrections for motion and bleaching artifacts, alignment, and normalization of the calcium data, together with Deeplabcut processing and alignment of the behavioral videos. Our goals are to combine these recordings with anatomical connectome data and study the network dynamics of the thalamocortical circuits. In particular, we aim to study trial-to-trial variations in network dynamics and how these can be related to trial outcomes, initial brain states, and the spontaneous behaviors of the animals.
Most commonly-used network analysis techniques rely on cross-correlations between brain regions. These methods are unable to distinguish between direct and indirect (common cause) causation. We are developing a model-based approach where we fit a feed-forward dynamical regression model and extract connectivity parameters using optimization methods. The model is fit with Alternating Direction Method of Multipliers optimization using non-negativity constraints and L1 regularization for sparseness, yielding a network structure that is significantly different from that obtained by correlation-based methods. In a preliminary analysis of network dynamics during a texture discrimination task, we see a decrease in inferred connection strengths between auditory, motor, and parietal association areas with respect to the other cortical and thalamic regions, particularly during “hit” trials where the animal actively seeks a reward. Strong changes in network dynamics are observed during licking (water reward) behavior. Attentive task-oriented behavior is accompanied by an increase in inferred connection strengths between cortical motor areas and a subset of thalamic nuclei.

Disclosures: M.G. Moore: None. **A. gilad:** None. **M. Reimers:** None.

Poster

PSTR097: Network Models I

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR097.17/U22

Topic: I.06. Computation, Modeling, and Simulation

Support: 5U01EB025830

Title: Synaptic Integration and Granule Cell Activation following Extracellular Electrical Stimulation: A Multi-Scale Computational Model to Investigate Hippocampal Electrical Stimulation

Authors: *S. FARZAD[1], T. WEI[2], J.-M. C. BOUTEILLER[3], T. W. BERGER[3], G. LAZZI[2]; [1]USC, LOS ANGELES, CA; [3]Biomed. Engin., [2]USC, Los Angeles, CA

Abstract: Recent advancements in neuroprosthesis systems offer promising potential for both monitoring and electrically stimulating the hippocampal formation, which may enhance and restore memory functions. However, significant challenges stem from the intricate architecture of neural tissue and the incomplete understanding of how electrical stimulation impacts hippocampal networks. We have developed a computational model that precisely simulates hippocampal stimulation. This model is designed to optimize the placement and configuration of electrodes and determine the most effective stimulation parameters. It aids in identifying the most effective stimulation strategies, enhancing our understanding of the factors that influence neural responses to electrical stimulation. In 2018, Bingham et al. created a computational model to simulate the effects of electrical stimulation on a 400um thick hippocampal slice. The present model extends the model and accurately depicts the septal to temporal spread of the dentate gyrus, focusing on granule cell (GC) neurons and their dendritic structures. Simulation stages are: (1) a 3D model of the hippocampal tissue calculates the electric field distribution resulting from bipolar electrode stimulation;(2) this field is used to model neural activity. The admittance method determines the field distribution, while neural network simulations are performed using the NEURON platform. Of importance, the model incorporates detailed 3D reconstructions of the rat dentate gyrus based on thin histological sections (Ropireddy and Ascoli, 2012). The network model also includes the dentate gyrus GCs and axon arbors from the entorhinal cortex (EC), connecting to the GCs through the perforant path, with realistic axon arbor configurations generated using the Ruled-Optimum Ordered Tree System (ROOTS) algorithm. This multi-scale computational model has facilitated research into synaptic integration between the myelinated EC axons and GCs. Our findings indicate that initiating an action potential in GCs requires at least 1600 synapses from both medial and lateral EC axons. Additional investigations aimed at exploring the effects of various electrical stimulation parameters to determine the minimum required current to activate GCs. Our results indicate that a current amplitude of 500 µA (1ms cathodic-first biphasic pulse), applied at the infrapyramidal blade, is sufficient to activate GCs. Our investigations also focus on varying electrode positions, such as the crest and suprapyramidal, shedding some light on their impact on axonal activation and subsequent granule cell activation.

Disclosures: S. Farzad: None. **T. Wei:** None. **J.C. Bouteiller:** None. **T.W. Berger:** None. **G. Lazzi:** None.

Poster

PSTR097: Network Models I

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR097.18/U23

Topic: I.06. Computation, Modeling, and Simulation

Support: R21MH120801

Title: Flexible network dynamics across brain states is associated with task performance and internalizing symptoms.

Authors: *H. PUSHKARSKAYA;
Yale Univ. Sch. of Med., New Haven, CT

Abstract: Motivation/Problem Statement: Most fMRI analyses focus on brain function within a single epoch, often not even considering the order of tasks. However, cognitive/affective states do not occur in isolation; they build on prior states. The brain is a complex dynamic system. A dynamic system's defining feature is that the current state generates a successor state by a dynamic rule. We examine the dynamic rules governing the brain's transition from a pre-task 'resting state' to active engagement in a task and how it predicts task performance and clinically relevant characteristics. **Methods/Approach:** The Default Mode Network interference hypothesis (DMN-ih) predicts that dynamic coordination between the Default Mode Network (DMN) and the Salience Network (SN) at rest shapes how the brain connectome changes from rest to a subsequent task, affecting task performance. DMN-ih posits that DMN-SN anticorrelation at rest should lead to greater rest-to-task attenuation in DMN-VS coupling and better task performance. We tested this hypothesis in adults with obsessive-compulsive disorder (OCD, N = 18) and matched healthy individuals (HC, N = 20), using functional connectivity analysis among key nodes in the DMN (ventromedial prefrontal cortex, vmPFC), SN (right anterior insula, rAI), and reward network (ventral striatum, VS). The dataset included a resting-state scan (6 min) immediately followed by a reward-based fMRI task (the Risk and Ambiguity task). **Results:** Dynamic Structural Equation Modeling (dSEM) confirmed the DMN-ih predictions: greater vmPFC-rAI anticorrelations and vmPFC-VS positive connectivity at rest predicted a greater increase of vmPFC-VS anticorrelations from rest-to-task ($\beta std=-0.30 <0.01$ and $\beta std=0.64$ $p<0.01$, respectively), which in turn predicted better task performance (lower randomness of choices: $\beta std=-0.61$ $p<0.01$) and lower OCD symptoms ($\beta std=-0.47$ $p<0.01$). Dynamic causal modeling of concatenated rest-to-task timeseries, using a fully connected vmPF-rAI-VS model, supported these findings. The change in dynamic coordination among the networks of interest from rest to task predicted both the task performance and obsessive compulsive symptoms more accurately than the coordination among the networks at rest and/or task. **Conclusion/Implications:** Studying the brain as a dynamic system, focusing on the rule of change from state to state rather than individual states, can overcome limitations of current, more static methods. This approach has the potential to improve our understanding of brain function in both healthy and clinical populations.

Disclosures: H. Pushkarskaya: None.

Poster

PSTR097: Network Models I

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR097.19/U24

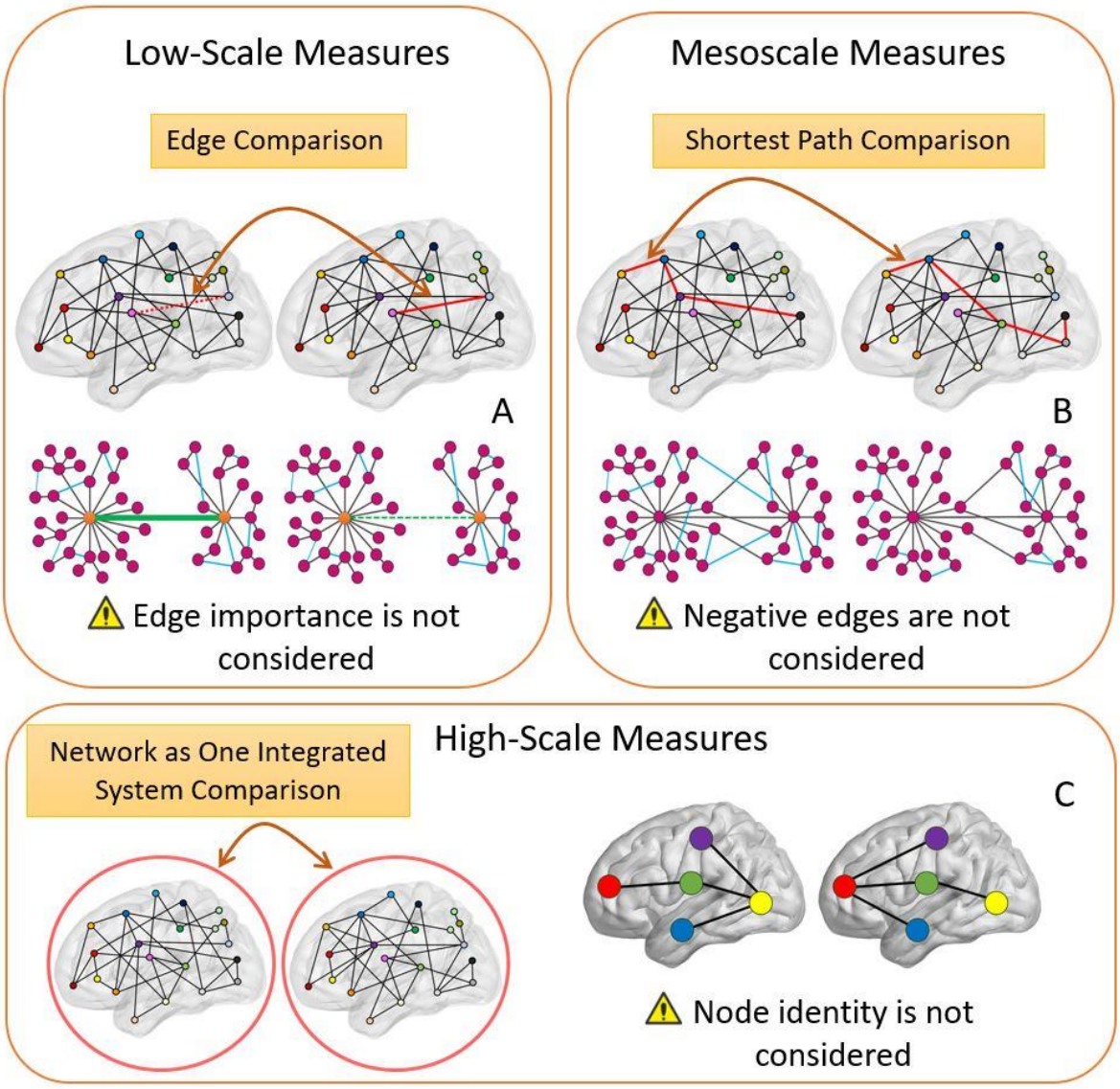
Topic: I.06. Computation, Modeling, and Simulation

Support: P50 AA026117

Title: Redefining brain network comparison with a novel multiscale distance measure

Authors: *M. KHODAEI, S. L. SIMPSON, H. SHAPPELL, P. J. LAURIENTI;
Wake Forest Univ. Sch. of Med., Winston Salem, NC

Abstract: In 2021, neurological disorders ranked as the leading cause of disability-adjusted life-years (DALYs), affecting 3·40 billion individuals. Functional connectivity brain networks have demonstrated their ability to capture valuable insights about neurological disorders. However, no comprehensive network distance metric is available for comparing these brain networks. Here, we proposed a multiscale distance measure that considers the node and edge identities of corresponding brain areas. At the low scale, information concerning individual edges is captured. The mesoscale captures topological information driven by interactions between nodes. The high-scale information captures features of the network as an integrated entity. Our distance measure consists of three components, each corresponding to a distinct scale of information. In all component of the distance measure, the Jensen-Shannon divergence is used for comparison between the distributions. For the low-scale component, the distribution of edge weights is compared between the two networks. The mesoscale component utilizes the shortest paths between all pairs of nodes in the networks. Nodes that are one step, two steps, and up to N-steps away from each other are identified. The distribution of average weights for each N-step away neighborhood is compared using JSD to find the distances for the N-step away variation. The average distance of the M-1 neighborhoods is then computed. The high-scale component compares the spectral representations of the two graphs by comparing eigenvalues and the distributions of eigenvectors of their Laplacian matrices. Our simulation analyses illustrated that each component of our distance measure can capture specific types of information not captured by the other measures, highlighting the multilevel storage of information in brain networks.



Disclosures: M. Khodaei: None. **P.J. Laurienti:** None.

Poster

PSTR098: Human Data: MRI, Image, Video and Other Database

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR098.01/U25

Topic: I.07. Data Analysis and Statistics

Support: NIH Grant F32EY033625 to MLE
Boston University startup funding to RND

Title: Multivoxel decoding of rapidly presented sequential stimuli in fMRI

Authors: *M. L. EPSTEIN, R. N. DENISON;
Psychological & Brain Sci., Boston Univ., Boston, MA

Abstract: Motivation: Functional magnetic resonance imaging (fMRI) has low temporal resolution due to the slow time course of hemodynamic responses. This limitation has traditionally precluded the use of fMRI to measure separate signals from sequentially presented stimuli. Here we present a novel method that uses multivoxel pattern analysis (MVPA) to individually and separately classify the orientations of two stimuli separated by only hundreds of milliseconds. Methods: While recording fMRI data, participants viewed sequential pairs of grating stimuli with a stimulus-onset asynchrony of 250 ms while performing a discrimination task. Importantly, the orientations of the first stimulus (T1) and the second stimulus (T2) were independent, ensuring that when a classifier was trained using labels for one stimulus, the orientation of the other would be random and thus could not impart any information to the classifier. We collected fMRI data across two sessions. Separate run-wise general linear models were calculated for T1 and T2 orientations. Beta coefficient values for each orientation and target time were extracted from V1, V2 and V3 maps drawn from a separate population receptive field mapping session. Linear support vector machine classifiers were trained and tested using leave-one-run-out cross-validation separately for T1 and T2. Classification accuracy for each condition was tested against chance (50% accuracy). Results and conclusion: We found classification of stimulus orientation to be significantly above chance for each stimulus, T1 and T2, across visual areas. The decoding technique developed here provides a method to analyze the signal strength specific to each stimulus in a rapidly presented sequence, opening new avenues for investigating the brain dynamics involved in tasks previously thought unsuitable for fMRI.

Disclosures: M.L. Epstein: None. **R.N. Denison:** None.

Poster

PSTR098: Human Data: MRI, Image, Video and Other Database

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR098.02/Web Only

Topic: I.07. Data Analysis and Statistics

Support: NIH U19 AG078109

Title: Pi-2620 tau pet signal and off-target binding

Authors: *M. W. HAND[1], N. LEE[2], S. O'BRYANT[3], B. T. CHRISTIAN[4], A. W. TOGA[5], M. N. BRASKIE[6];
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Med., USC, Los Angeles, CA; [3]Inst. for Translational Res., Univ. of North Texas Hlth. Sci. Ctr., Fort Worth, TX; [4]Univ. of Wisconsin Madison, Madison, WI; [5]USC Stevens Neuroimaging and Informatics Inst., USC, Los Angeles, CA; [6]Keck Sch. of Med., USC, Los Angeles, CA

Abstract: *Introduction:* Meningeal off-target binding in [18F]-PI-2620 tau-Positron Emission Tomography (PET) scans may influence signal in adjacent regions. We tested two alternative methods to reduce effects of off-target binding on mean lateral parietal (LP) signal, a region adjacent to the meninges: 1) median LP signal, which is less influenced by outliers and 2) LP signal after eroding the perimeter of the region to minimize spillover from the meninges. *Methods:* We included 1355 Hispanic, non-Hispanic Black, and non-Hispanic white adults with available PI-2620 scans (990 cognitively unimpaired, 292 mild cognitive impairment, and 73 dementia; 817 female; mean age 64.3 ± 8.7) from the Health & Aging Brain Study-Health Disparities. We used T1-weighted MRIs to create: 1) a FreeSurfer-derived LP mask, 2) an eroded LP mask, and 3) a LP border mask capturing meningeal signal. To create the eroded LP mask, we eroded a full brain mask (FSL erode kernel sphere 3) and multiplied it by the FreeSurfer-derived LP mask. To create the LP border mask we dilated each person's LP mask (kernel box 6), subtracted a full brain mask, and thresholded at 0. Standardized reuptake value ratios (SUVR) used inferior cerebellar gray matter, without corrections, as a reference. We assessed differences between mean LP SUVR and the two alternative methods. We used linear regression to relate tau binding in the LP border mask to SUVR change (between the mean and alternative methods). We also related these methods to 1) medial temporal lobe (MTL) SUVR, which is unaffected by meningeal signal, 2) age, and 3) two cognitive tests (Digit symbol substitution [DSST] and Logical memory AB), covarying for age, education, sex, and cognitive diagnosis. *Results:* Higher LP border signal was related to greater LP SUVR changes in both eroded (β= 0.85, p<0.01) and median (β= 0.69, p<0.01) methods. Higher MTL SUVR was related to higher LP SUVR (original β= 0.51, p<0.01; eroded β= 0.57, p<0.01; median β= 0.51, p<0.01). Higher LP SUVR was associated with worse performance on the DSST (original β= -0.14, p<0.01; eroded β= -0.15, p<0.01; median β= -0.13, p<0.01) and Logical memory AB (original β= -0.12, p<0.01; eroded β= -0.13, p<0.01; median β= -0.11, p<0.01). Age was correlated with SUVR for the eroded β= 0.16, p<0.01, and median β= 0.09, p<0.01, but not the mean SUVR β= 0.04, p=0.15. *Conclusion:* Higher signal from the LP border mask was associated with greater change between original and alternative methods, indicating that the removed signal was likely off-target contamination. Cognition and age were more strongly associated with LP SUVR in the alternative methods, with similar effects that were slightly stronger for the eroded method.

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Poster

PSTR098: Human Data: MRI, Image, Video and Other Database

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR098.03/U26

Topic: I.07. Data Analysis and Statistics

Support: NSF Award #2239654
Fellowship Award from Canadian Institute for Advanced Research

Title: A meta-study of whole-brain causal connectivity during decoded neurofeedback

Authors: *F. ARAB[1], A. GHASSAMI[3], M. A. PETERS[4], E. NOZARI[2];
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Abstract: Neurofeedback (NF) offers a unique method for modulating neural dynamics in conditions such as anxiety and substance use disorders. Decoded NF (DecNef) is a specific form of NF that enables the manipulation of neural activity tied to specific cognitive processes or behaviors without participants' explicit awareness. DecNef induces changes in various behaviors, including visual sensitivity, fear memory, perceptual confidence, and facial preference. However, a significant challenge in neurofeedback is the variability in participants' ability to alter their target brain activity. To understand the neural mechanisms of DecNef interventions, we explored whole-brain causal connectomes from five DecNef studies (n = 45 subjects) using our newly-developed CaLLTiF (Causal Discovery for Large-scale Low-Resolution Time-Series with Feedback) method. These studies targeted distinct areas for NF induction, from early visual to prefrontal, allowing us to extract common mechanisms attributable to NF. For each subject, we used fMRI data from 4 sessions: 1 decoder construction (DC) session originally used to train the DecNef decoder, and 3 NF sessions. We computed one causal graph for each session using an adapted version of CaLLTiF designed to handle the very slow sampling in this data (TR = 2s).
We analyzed partial correlation values for each edge identified by CaLLTiF, comparing NF and DC graphs. Both revealed predominantly excitatory connections. However, the bilateral visual subnetwork appears more excitatory (less inhibitory), while bilateral somatomotor and attention subnetworks show higher inhibition (less excitatory) in NF graphs compared to DC graphs. We observed greater similarity in causal graphs from neurofeedback sessions across datasets, subjects, and sessions than those from decoder construction sessions, suggesting brain network convergence during the reinforcement process. This motivated assessing the average causal graph during the NF sessions of all studies. We observed robust connectivity within and between the Somatomotor, Dorsal Attention, and Ventral Attention subnetworks and substantial directional influence from the left to the right hemispheres in the average NF graph. When compared to DC graphs, on the other hand, we observed significantly higher causal connectivity (degree of the causal graph) in the bilateral limbic network, significantly higher causal flow (more source-ness) in the left ventral attention network, and significantly lower causal flow (more sink-ness) in the right visual network. These findings show how using causal discovery in DecNef enhances understanding of neural dynamics in decoded neurofeedback.

Disclosures: F. Arab: A. Employment/Salary (full or part-time):; University of California Riverside. **A. Ghassami:** A. Employment/Salary (full or part-time):; Boston University. **M.A. Peters:** A. Employment/Salary (full or part-time):; University of California Irvine. **E. Nozari:** A. Employment/Salary (full or part-time):; University of California Riverside.

Poster

PSTR098: Human Data: MRI, Image, Video and Other Database

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR098.04/U27

Topic: I.07. Data Analysis and Statistics

Support: Austin Faculty Funds
NARSAD Young Investigator Award
NIH Grant P50 HD105353
NIH Grant T32 NS105602
NIH Grant T32 CA009206
NIH Grant T32 GM140935

Title: Improved consistency of brainstem nuclei delineation using combined structural and diffusion MRI processing

Authors: *A. BLOCK[1], N. ADLURU[2], J. GUERRERO-GONZALEZ[3], M. DURAN[4], S. KECSKEMETI[5], A. ALEXANDER[5], D. DEAN[5], B. TRAVERS[6], G. KIRK[5];
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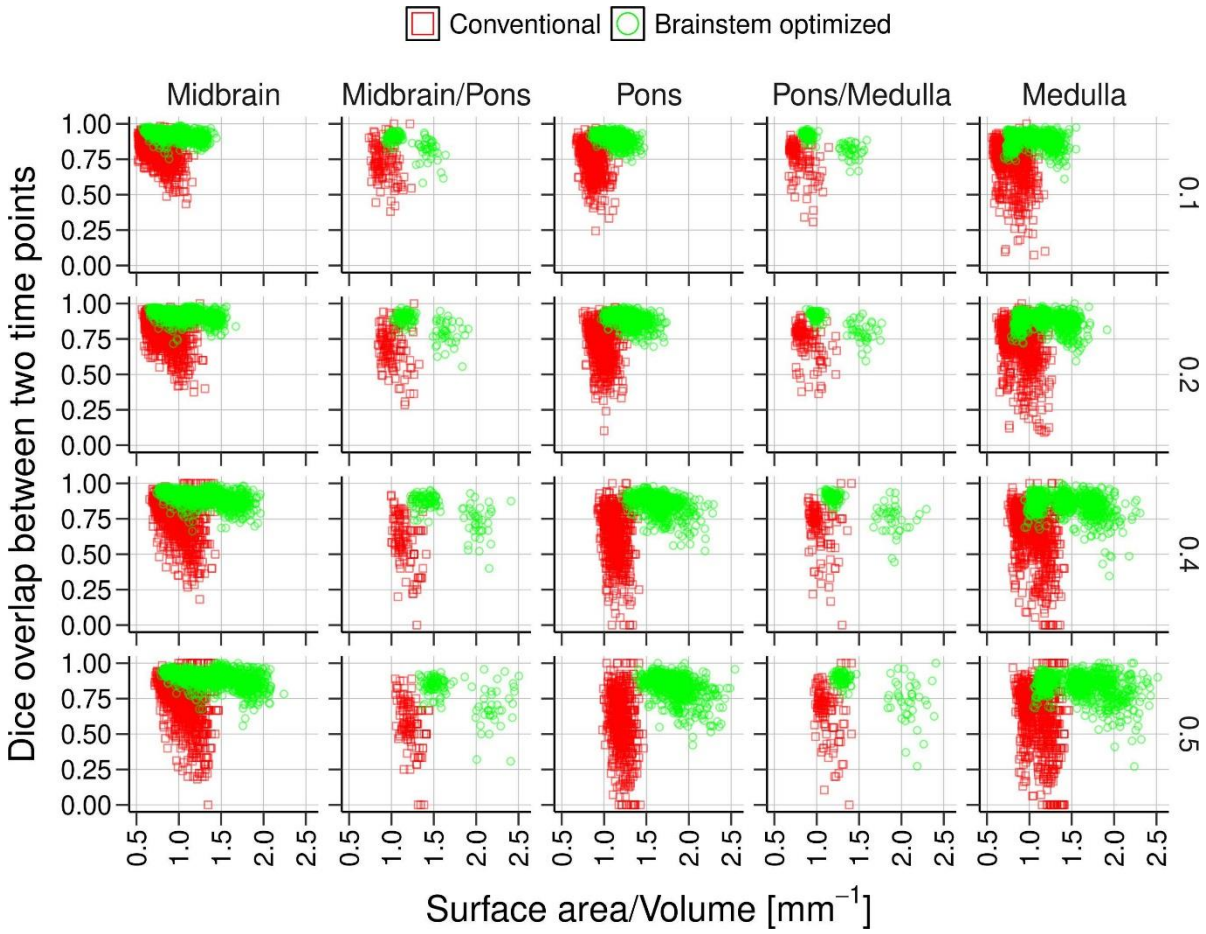
Abstract: Reliably distinguishing gray and white matter properties from typically acquired MRI data in the brainstem is highly relevant for understanding the role of brainstem's reticular formation in autistic behaviors (Rimland et al., 1964). Previously, it was shown that brainstem optimized MRI acquisition combined with post-processing techniques that align structural and diffusion data reduced the coefficient of variation of microstructural measures and enhanced the biological plausibility of their associations with age in several brainstem/cerebellar regions (Guerrero-Gonzalez et al., 2022). However, it is unclear if this method will also improve images in conventionally acquired MRI. Thus, the purpose of this study was to quantitatively assess the improvements in shape consistency of brainstem regions at an individual level with optimized post-processing applied to conventionally acquired MRI. T1- and diffusion-weighted imaging with typical acquisition at two time points (6-8 weeks apart) from n=39 participants (n=20 ASD, age: 15.6+/-1.4; n=19 TD, age: 15.0+/-1.5) were analyzed. The brainstem's autonomic, pain, limbic, and sensory nuclei (Singh et al. 2022) were extracted using both conventional processing and brainstem-optimized processing. Fig. 1 presents the Dice similarity coefficient between the two time points for the nuclei in midbrain, pons, and medulla regions as well as those in the overlapping regions. We found that the optimized post-processing offers significant improvements (higher Dice overlap scores) across different probability thresholds and surface-area-to-volume ratios. These data suggest that optimized post-processing combining structural and diffusion images can improve the consistency of brainstem nuclei delineation even in typically acquired MRI, assuming the brainstem is present in the field-of-view. This reduces the shape induced variability in the gray and white matter measures of the nuclei and opens the possibility of large-scale analysis of the brainstem regions using publicly available datasets from studies on autism.



Disclosures: A. Block: None. **N. Adluru:** None. **J. Guerrero-Gonzalez:** None. **M. Duran:** None. **S. Kecskemeti:** None. **A. Alexander:** None. **D. Dean:** None. **B. Travers:** None. **G. Kirk:** None.

Poster

PSTR098: Human Data: MRI, Image, Video and Other Database

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR098.05/U28

Topic: C.05. Tauopathies, Synucleinopathies, and Other Related Diseases

Support: Author's research is funded by a company that produces a product or service related to the work being reported.

Title: Enabling Rapid and Convenient Human Immune Profiling in Fresh and Long-Term Stabilized Whole Blood Samples With CyTOF Flow Cytometry

Authors: N. ZABINYAKOV, S. LI, *S. HASAN, C. LOH;
Standard BioTools, Markham, ON, Canada

Abstract: Changes in cellular composition of blood and associated peripheral immune markers provide a potential window into the pathogenesis of neurodegenerative diseases. Whole blood (WB) is best processed for analysis within 24 hours of collection to capture clinically relevant blood-based biomarkers. But WB collection and cytometric analysis are often performed at different sites, which can lead to significant delays. Fixation of WB with stabilizer reagents can overcome these challenges. However, not all antibody panels are compatible with these reagents. The Human Broad Immune Profiling CyTOF® Panel, 20 Antibodies was created to be compatible with commercial WB stabilizers and enable fast and convenient human immune profiling. CyTOF flow cytometry uses metal-tagged antibodies and has multiple advantages over fluorescence-based cytometry. Spectral compensation is not required since CyTOF flow cytometry has low signal spillover and no autofluorescence. Panels with more than 50 markers can be rapidly designed and conveniently stained and acquired in a single tube. The Human Broad Immune Profiling CyTOF Panel contains 20 liquid antibodies. For customization, there are more than 30 open channels to easily drop-in and analyze markers of interest. The panel is compatible with both fresh and stabilized WB samples, and with different staining and acquisition workflows. To demonstrate the flexibility of the panel with different WB staining and stabilization workflows, samples from three healthy donors were assessed using two stabilization workflows with Proteomic Stabilizer PROT1 and Cytodelics Whole Blood Cell Stabiliser. Antibodies in the panel were pooled together and frozen at -80 °C as single-use aliquots to reduce technical variability from staining throughout the course of the study. In addition, samples were barcoded and acquired as a single tube to reduce variability from sample acquisition. The panel successfully identified more than 30 immune cell populations in fresh and stabilized multiplexed WB samples. Thus, the Human Broad Immune Profiling CyTOF Panel overcomes analysis challenges caused by logistical delays as WB samples can be frozen during different steps of sample processing. Furthermore, freezing antibody cocktails is a unique feature of CyTOF flow cytometry, ensuring staining consistency. Together, CyTOF workflows enable fast and convenient cytometry of WB samples and can facilitate the study of blood-based biomarkers of neurodegenerative diseases. For Research Use Only. Not for use in diagnostic procedures.

Disclosures: N. Zabinyakov: A. Employment/Salary (full or part-time):; ull-time employee of Standard BioTools. 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.; Author's research is funded by a company that produces a product or service related to the work being reported. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Author has ownership interest with Standard BioTools. **S. Li:** A. Employment/Salary (full or part-time):; Full-time employee of Standard BioTools. 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.; Author's research is funded by a company that produces a product or service related to the work being reported. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Author has ownership interest with Standard

BioTools. **S. Hasan:** A. Employment/Salary (full or part-time):; Full-time employee of Standard BioTools. 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.; Author's research is funded by a company that produces a product or service related to the work being reported. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Author has ownership interest with Standard BioTools. **C. Loh:** A. Employment/Salary (full or part-time):; Full-time employee of Standard BioTools. 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.; Author's research is funded by a company that produces a product or service related to the work being reported. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Author has ownership interest with Standard BioTools.

Poster

PSTR098: Human Data: MRI, Image, Video and Other Database

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR098.06/U29

Topic: I.07. Data Analysis and Statistics

Support: NIA 1R56AG080816-01
AHA #16BGIA27250047

Title: Including Women of Color in Functional Near Infrared Spectroscopy (fNIRS) Studies: Developing Recruitment & Retention Approaches to Combat Neuroracism

Authors: *S. L. GORNIAK[1], L. POLLONINI[2];
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Abstract: Introduction: Our lab has been working to develop a more inclusive approach to fNIRS measurement in individuals who are typically excluded from fNIRS studies—specifically women of color. We present our approach as well as future work in this area to improve recruitment and retention of women and persons of color in fNIRS studies. **Methods:** Inclusive approaches to fNIRS involve a combination of changes to researcher behaviors before and during fNIRS assessments. Prior to data collection, our lab has taken the following steps to prepare a more inclusive approach to fNIRS data collection: (1) active recruitment of women and persons of color, (2) integration of questions regarding hair type and skin tone into self-report questionnaires, (3) development of an fNIRS cap that has shown improved signal-to-noise ratios across diverse self-reported hair types, (4) explaining to potential participants how fNIRS data will be collected using pictures with the actual fNIRS device, (5) discussion and explanation of why participants will not be able to wear wigs or hair extensions during testing, (6) scheduling

fNIRS data collections to accommodate hair appointments as needed, and (7) flexibility in date and time of fNIRS sessions to accommodate work schedules and childcare/eldercare responsibilities. During data collection, our lab has taken the following steps: (1) inquiring about fNIRS cap comfort, (2) using an internally illuminated crochet hook or ear curette to gently move hair/braids/locs away from optodes and detectors, and (3) provide shower opportunities for participants to wash their hair after testing. **Results:** To date, we have had significant success in recruiting and retaining women, particularly women of color, in our fNIRS studies due to the inclusive approach described above. Our current study focusing on fNIRS imaging in women of color has retained all 20 participants initially recruited for the study. Our data has also shown improved signal-to-noise ratios in our sample as compared to prior studies in our lab which included women of color. **Conclusion:** Our approach to inclusivity in fNIRS research has resulted in improved recruitment and retention of women of color in our studies along with improved signal-to-noise ratios. Future work in this area will include development of mathematical models to incorporate hair type, skin tone, age, adiposity measures, and sex in additional improvement of signal-to-noise ratios during data post-processing.

Disclosures: S.L. Gorniak: None. **L. Pollonini:** None.

Poster

PSTR098: Human Data: MRI, Image, Video and Other Database

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR098.07/Web Only

Topic: I.07. Data Analysis and Statistics

Title: Machine learning exploration of neuroanatomical correlates in human sensory perception

Authors: *B. JARRAHI;
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Abstract: Previous investigations have implicated the neuroanatomical basis of sensory systems; however, definitive neuroimaging biomarkers remain elusive. The present study employs machine learning techniques to probe the relationship between brain morphological features and sensory measures of audition, olfaction, taste, and visual contrast sensitivity using a large dataset from the publicly available Human Connectome Project (HCP; n = 874). Structural MRI measures of the brain, including cortical and subcortical volumes, cortical thickness, and surface area across various brain regions, were incorporated as morphological features. These data were processed using the FreeSurfer pipeline customized for analyzing HCP data. The dataset was split into a training set (80% of subjects) and a test set (20% of subjects) through random splitting. Various regression algorithms, such as Linear Regression, Support Vector Machines, and Decision Trees, were tested. Hyperparameters were fine-tuned using GridSearchCV to optimize model performance. Evaluation metrics including Root Mean Squared Error (RMSE), Mean Absolute Error (MAE), and Pearson r correlation were utilized. Robustness was ensured through two cross-validation methods: k-fold cross-validation (k = 5) and leave-one-out cross-

validation (LOOCV). Feature selection techniques like Random Forest, SelectKBest, Recursive Feature Elimination (RFE), and SHapley Additive exPlanations (SHAP) were employed to identify significant features. Binary classification via machine learning was also conducted to distinguish individuals with high vs. low sensory test scores based on brain morphological features. For the olfaction test, the ExtraTreesClassifier model had a satisfactory testing accuracy of 67.43%, while the RandomForestClassifier model achieved a testing accuracy of 70.86% for visual contrast sensitivity tests. In conclusion, the integration of machine learning with high-dimensional neuroimaging data provided new perspectives on understanding the neural correlates of sensory performance. These findings suggest unique neuroanatomical features related to each sensory domain, potentially aiding in the advancement of predictive models for sensory measures.

Disclosures: B. Jarrahi: None.

Poster

PSTR098: Human Data: MRI, Image, Video and Other Database

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR098.08/U30

Topic: I.07. Data Analysis and Statistics

Support: R01 AG057234

Title: Latino American adult brain atlas based on a multi-center MRI dataset.

Authors: *P. A. REYES[1,5], R. GONZALEZ-GOMEZ[7], H. SANTAMARIA-GARCIA[2,3,6], A. M. IBANEZ, Sr.[8], D. L. MATALLANA[4];
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Abstract: Various human brain templates have been proposed and extensively employed in prior research studies, including templates like the Tailarach, Montreal Neurological Institute, International Consortium for Brain Mapping, Causasian and chinese Brain, Colin-27 and French template. Latino American template is an urgent necessity to enhance neuroscience research and facilitate clinical applications relevant to the underrepresented communities from Latin America. A diverse cohort of Latin American adults spanning various age brackets were extracted from preexisting data and RedLAT databases based on multiple centers across the region. Data Compilation and Preprocessing: Structural MRI data collected from the multiple centers was compiled and the structural images from MRI acquisition of healthy controls will be selected. We removed the face with scripts based on blurring to deidentify the subjects. Quality assurance involved assessing all participants' neuroimaging using the MRIQC toolkit. To preprocessing we

corrected the intensity of field homogeneity with N4bias algorithm apart from traditional schemes, such as resolution, orientation and matrix size. Atlas Construction: We developed 2 templates spanning ages from 50 to 65 years and 65 to 80 years. The symmetric image normalization (SyN) algorithm within the ANTS (Advanced Normalization Tools) software has been utilized to execute the image registration process. Results: A provisional template was constructed using the normalized images with 450 healthy controls. After the contruction of the template we will comparisons between our proposal of templates and MNI, ICBN, and, Chinese 20. Validation and Interpretation: The constructed brain atlases will undergo validation processes to ensure accuracy and reliability. Subsequently, these atlases will be interpreted to delineate and comprehend the variations in neuroanatomy across distinct age groups in the Latin American population.

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Poster

PSTR098: Human Data: MRI, Image, Video and Other Database

Location: MCP Hall A

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Program #/Poster #: PSTR098.09/U31

Topic: I.07. Data Analysis and Statistics

Support: National Science and Technology Council, Taiwan: NSTC 112-2321-B-A49-021
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Dr. Albert C. Yang was supported by he Ministry of Education (Aim for the Top University Plan), Taipei, Taiwan

Title: Identifying subtypes of bipolar disorder using structural MRI with machine learning methods

Authors: *Y.-T. HSU[1], A.-C. YANG[1,2,3,4];
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Taipei, Taiwan; [3]Department of Medical Research, Taipei Veterans General Hospital, Taipei, Taiwan; [4]Brain Research Center, National Yang Ming Chiao Tung University, Taipei, Taiwan

Abstract: Background: Bipolar disorder (BD) is a common affective disorder characterized by recurrent episodes of depression and mania or hypomania. Individuals with BD could be categorized into type I and type II based on manic or depressive episode. Few studies have investigated the differences between the two subtypes of BD through the brain images. Previous studies have used magnetic resonance imaging (MRI) images to analyze the volumetric differences between BD subtypes, however, no statistically significant differences were found. We aim to use the slight volumetric differences in gray matter between BD subtypes to develop machine for differentiating BD subtypes. Methods: The demographic data, structural MRI of 112 participants with BD (56 with BD type I and 56 with BD type II) from UK Biobank dataset were analyzed. First, each MRI data was parcellated into 90 brain regions based on AAL atlas for all participants. Second, we calculated the gray matter volume of each brain region and whole brain gray volume as features. Next, with these features, we trained CatBoost machine learning models to differentiating BD subtypes. At the same time, we calculated the importance of each feature in the model then extract the top 15 features and the features with importance value > 0. CatBoost would undergo hyperparameter optimization for enhancing the accuracy, and 5-fold cross-validation for obtaining a more reliable estimate of the model's performance. Results: The models, the accuracy was 74% with whole structural features, 51% with the top 15 feature, and 61% with the features with importance value > 0. Most critical brain regions located in the frontal lobe, thalamus, the olfactory cortex, and the temporal pole. Conclusion: This study demonstrates the potential of machine learning algorithms in differentiating BD subtypes using brain structural features derived from MRI data.

Disclosures: Y. Hsu: None. **A. Yang:** None.

Poster

PSTR098: Human Data: MRI, Image, Video and Other Database

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR098.10/U32

Topic: I.07. Data Analysis and Statistics

Support: DGAPA-PAPIIT UNAM grant IN207923 (FB)
CONAHCyT grant CB255462 (FB)

Title: Development of brain template and atlases for African Americans populations

Authors: *P. ROSALES ZALDÍVAR[1], D. ATILANO-BARBOSA[2], A. HERNANDEZ[1], F. A. BARRIOS[3];
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Abstract: In the field of neuroimaging, structural brain templates are commonly used as they provide a standardized 3D coordinate framework for analyzing data from diverse subjects. This can be applicable for morphological analysis of a specific population with certain age range and geographical location, in order to reduce bias in neuroimaging studies focused on populations with diverse ethnic and racial backgrounds. In this research study, the construction of a brain atlas was carried out using a T1 structural magnetic resonance imaging template with voxel sizes of 0.7 mm and 1 mm from an African American population (n=167), obtained from the Human Connectome Project database. The AFNI make template dask.py script was used for template creation. The process for generating the brain atlas involved using atlases generated in FreeSurfer containing cortical parcellations for identification and analysis of different brain regions. As a result, atlases based on FreeSurfer parcellations corresponding to the Desikan-Killiany Atlas and Destrieux Atlas were obtained. The template and atlases can be implemented in the field of neuroimaging to improve healthcare for African Americans, as it can be applied for appropriate disease diagnosis and treatment.**Keywords**brain atlases, brain templates, cortical parcellations, neuroimaging

Disclosures: P. Rosales Zaldívar: None. **D. Atilano-Barbosa:** None. **A. Hernandez:** None. **F.A. Barrios:** None.

Poster

PSTR098: Human Data: MRI, Image, Video and Other Database

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Program #/Poster #: PSTR098.11/U33

Topic: I.07. Data Analysis and Statistics

Support: NSF NCS-FO 2023985

Title: Variation in high amplitude events across the human lifespan

Authors: *Y. JO[1], J. TANNER[2], C. SEGUIN[2], J. FASKOWITZ[3], R. BETZEL[4];
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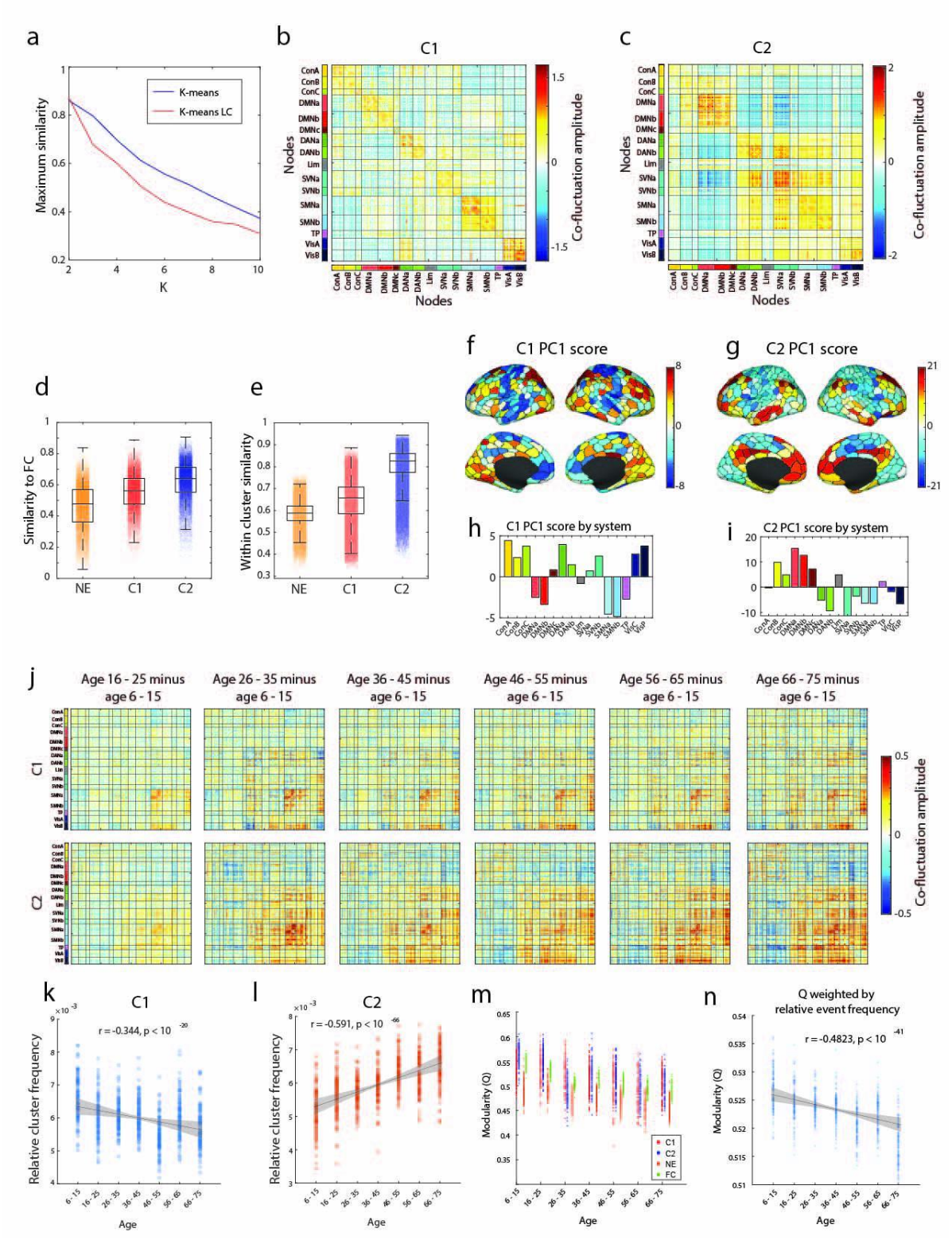
Abstract: Edge time series (eTS) decompose functional connectivity (FC) into their time-varying contributions. Studies have shown that global, instantaneous, high-amplitude co-fluctuations in eTS or “events” disproportionately contribute to FC. However, how these events change throughout the human lifespan is unknown. Here, we investigate event patterns and characterize their changes with age. We calculated the eTS using rsfMRI data from the NKI dataset (n = 537; ages 6-75 years). In brief, we detected “events” in eTS by comparing co-fluctuation magnitudes against a statistical threshold based on a null distribution of circularly shifted surrogate time series. To match group sizes across age, we binned our data (bin = 7) and sampled matching numbers of subjects and event frames per age bin. We then performed k-

means clustering on these events for K = 2-10, and the sampling and clustering processes were repeated 100 times. We determined the optimal K by calculating the similarity of pairs of runs using the Hungarian algorithm.With the optimal K's partition, we measured the frequency of each cluster relative to the total scan length for each age group across all runs and the modularity of the event patterns.

We found patterns of global events across all age groups and the maximum similarity across 100 runs using the Hungarian algorithm at K = 2-10. Maximal similarity was achieved at K = 2 (Fig.1a) and all results regarding cluster 1 (C1) and cluster 2 (C2) were aligned to the optimal centroid (Fig.1b, c). Our results showed that C2 is much more similar to themselves and to static FC than C1 events (Fig.1d, e). Also, the first principal components of C1 and C2 showed that C2 was largely positively weighted in task-negative networks whereas the weights in C1 were mixed for task-positive, -negative networks (Fig.1f, g, h, i). Next, we found that event patterns (Fig.1j), their frequencies (Fig.1k, l), and modularity (Fig.1m, n) vary across age groups.

Our results demonstrate that moments of high-amplitude co-fluctuations in rsfMRI show distinct clusters that systematically change across the human lifespan.



Disclosures: Y. Jo: None. **J. Tanner:** None. **C. Seguin:** None. **J. Faskowitz:** None. **R. Betzel:** None.

Poster

PSTR098: Human Data: MRI, Image, Video and Other Database

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR098.12/U34

Topic: I.07. Data Analysis and Statistics

Support: Bill & Melinda Gates Foundation INV-015711
NIMH R01 MH104324
NIMH U01 MH110274
T32-NS109604
NSF-GRFP 2237827
NSF-GRFP 2020295366

Title: Baby Open Brains Repository: An open-source resource of manually segmented infant brain segmentations

Authors: *S. STOYELL[1], E. FECZKO[2], L. MOORE[3], M. BAGONIS[4], T. CHAMBERLAIN[5], B. A. CHODKOWSKI[6], T. K. DAY[1], D. D. GORADIA[7], A. GRAHAM[8], A. HOUGHTON[9], O. KARDAN[10], E. A. KIFFMEYER[11], E. LEE[9], J. LUNDQUIST[9], A. MUMMANENI[12], P. REINERS[9], M. A. STYNER[13], J. L. WISNOWSKI[14], E. S. YACOUB[9], C. SMYSER[15], M. D. ROSENBERG[16], D. A. FAIR[17], J. ELISON[1];
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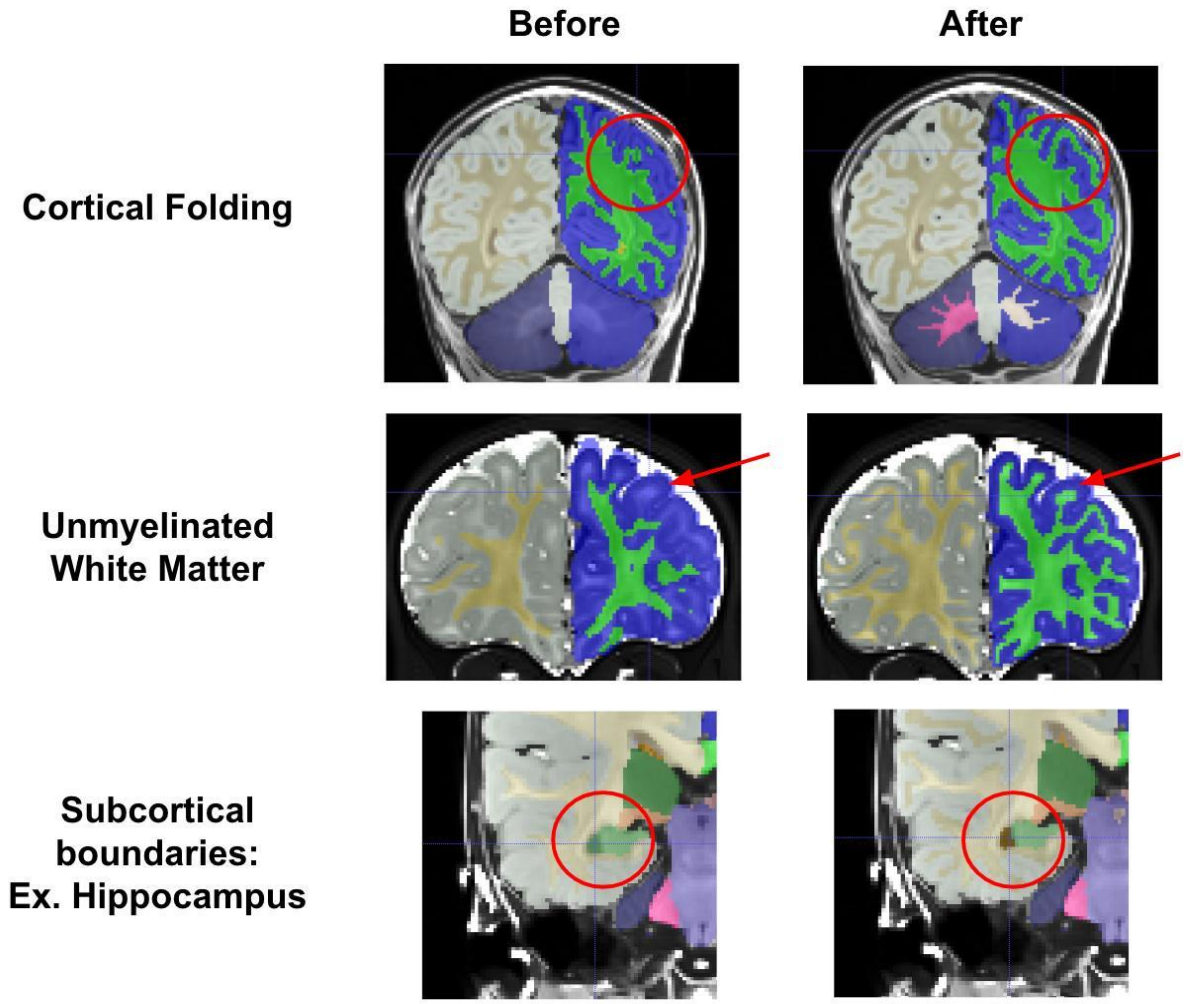
Abstract: Reproducibility of neuroimaging research on infant brain development remains limited due to highly variable protocols and processing approaches, including varied brain tissue segmentation atlases. Addressing this core limitation, we constructed the Baby Open Brains (BOBs) Repository, an open source resource comprising manually curated and expert-reviewed infant brain segmentations. Markers and expert reviewers manually segmented anatomical MRI data from 71 infant imaging visits across 51 participants, using both T1w and T2w images per visit. Anatomical images showed dramatic differences in myelination and intensities across the 1 to 9 month age range, emphasizing the need for densely sampled gold standard manual segmentations in these ages. These manual segmentations are publicly available through the BOBs repository, which links AWS S3 for storage transfer, Datalad for version control, and BrainBox for visualization. This repository represents an open-source model, where new

additions and changes can be added, enabling a community-driven resource that will improve over time and extend into new ages and protocols. These manual segmentations and the ongoing repository provide a benchmark for evaluating and improving pipelines dependent upon segmentations in the youngest populations. As such, this repository provides a vitally needed foundation for early-life large-scale studies such as the upcoming HEALthy Brain and Child Development (HBCD) Study.

Figure 1. Manual segmentations show massive improvements over initial segmentations.



Disclosures: S. Stoyell: None. **E. Feczko:** None. **L. Moore:** None. **M. Bagonis:** None. **T. Chamberlain:** None. **B.A. Chodkowski:** None. **T.K. Day:** None. **D.D. Goradia:** None. **A. Graham:** None. **A. Houghton:** None. **O. Kardan:** None. **E.A. Kiffmeyer:** None. **E. Lee:** None. **J. Lundquist:** None. **A. Mummaneni:** None. **P. Reiners:** None. **M.A. Styner:** None. **J.L. Wisnowski:** None. **E.S. Yacoub:** None. **C. Smyser:** None. **M.D. Rosenberg:** None. **D.A. Fair:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); FIRMM software; Turing Medical Inc. **J. Elison:** None.

Poster

PSTR098: Human Data: MRI, Image, Video and Other Database

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR098.13/U35

Topic: I.07. Data Analysis and Statistics

Support: CONACYT-grant CF-2019-6390

Title: Heritability of the Heschl Gyrus morphology.

Authors: *G. ROBLES RODRÍGUEZ[1], D. RAMÍREZ GONZÁLEZ[1], I. ESPINOSA MÉNDEZ[1], T. V. ROMAN-LOPEZ[1], A. E. RUIZ-CONTRERAS[2], M. E. RENTERIA[3], S. ALCAUTER[1];
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Abstract: The auditory cortex is located in the temporal lobe, specifically within Heschl's gyrus (HG). HG morphology varies significantly among individuals and hemispheres, with anatomical variations including unique and duplicated HG. Duplicates are categorized as a HG with an intermediate sulcus dividing half of the gyrus (CSD) and complete posterior duplications where two gyri are formed (CPD). These variations have been associated with various abilities and conditions such as musical and linguistic skills, cognition, schizophrenia, and bipolar disorder. However, the significance of genetic factors in shaping HG remains unclear. Heritability, which quantifies the proportion of variance attributed to genetics, can be estimated through twin studies, comparing monozygotic twins (Mz, 100% shared DNA) and dizygotic twins (Dz, 50% shared DNA). Heritability may vary among populations, particularly in genetically admixed populations like the Mexican population. This study aims to estimate HG morphology heritability. 188 twins (124 Mz, 64 Dz) from the Mexican Twin Registry underwent preprocessing and parcellation using FreeSurfer's recon-all pipeline. TASH and MCAI were employed to delineate HG morphology and obtain cortical thickness (CT), surface area (SA), and volume measurements. Heritability was assessed in both hemispheres adjusting the ACE/ADE model, which estimates the proportion of variance attributable to additive genetic (A), common environmental (C), non-shared environmental (E) and genetic dominance factors (D). Concordance rates (CR), which indicate the probability that both twins in a pair share a specific characteristic or condition, were evaluated for the anatomical variation assessment. The fitted ACE/ADE model, controlled for age and sex, indicated CT heritability D of .52 and environmental influence E of 0.47 for the left HG, and D of 0.57 and E of 0.42 for the right. For SA, E was .70 and C was .29 for the left HG, and E was .75 and C was .25 for the right. Volume exhibited E of .75 and C of .24 for the left HG, and E of .77 and C of .23 for the right. CT emerged as the most heritable feature, with non-shared environmental factors predominantly influencing SA and volume. The concordance rates were higher for Dz twins in both hemispheres, thus explaining that the morphology of the HG does not explain its variability due to genetic factors. The study suggests that non-shared environmental factors play a more

significant role than genetics in explaining HG anatomical variations and morphometrics measurements.

Disclosures: G. Robles Rodríguez: None. **D. Ramírez González:** None. **I. Espinosa Méndez:** None. **T.V. Roman-Lopez:** None. **A.E. Ruiz-Contreras:** None. **M.E. Renteria:** None. **S. Alcauter:** None.

Poster

PSTR098: Human Data: MRI, Image, Video and Other Database

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR098.14/Web Only

Topic: I.07. Data Analysis and Statistics

Support: Rural and Tribal Medicine Research Award

Title: Utilization of antipsychotic interventions for ASD among medically underserved patients in southern california after COVID-19

Authors: *J. B. TUSCHHOFF[1,2], D. S. BHANDAL[1,2], D. M. DAVIES[1], K. NGUYEN-NGO[2], C. S. COLWELL[3], C. A. GHIANI[2];
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Abstract: In the United States, most children with pervasive developmental disorder (PDD), and in particular autistic spectrum disorders (ASD) receive behavioral, pharmaceutical, or a combination of therapies. Antipsychotics such as Risperidone and Aripiprazole are approved for use in the management of agitation, irritability, and self-injurious behaviors in children and adults diagnosed with ASD. In the two years immediately following the COVID-19 pandemic, a disproportion in the interruption in the delivery of such interventions as well as of community services was observed, that well correlated with socioeconomic risk factors, such as low income or underserved communities. As we enter the fourth year since the pandemic, there are few studies which continue to track this disruption. Our study aimed at assessing the levels of delegation of resources for ASD patients under medical care at UCLA Health across socioeconomic levels, comparing before and after the COVID-19 pandemic. Using UCLA i2b2 Center records, we looked at the management of ASD and comorbid diagnoses of individuals living in 9 counties in Southern California in the five years prior to the lock down in 2020 (March 2015- March 2020) and in the four years since the start of COVID-19 (March 2020 to March 2024). We were interested in correlating the behavioral and/or pharmacological management used with socioeconomic factors including family income, self-described race/ethnicity, and medically underserved areas (MUA) versus medically served areas (MSA) between these two periods. Unfortunately, the rate of behavioral interventions recorded in the database did not allow such correlations. Our findings show that approximately 1 in 5 individuals with ASD living in southern california have been and are treated with antipsychotics. When

looking at the rate of prescription by racial category, Hispanic individuals were less likely to be given prescriptions than non-hispanic individuals; while, Asian and Middle Eastern patients were less likely to be given prescriptions than white and black patients. Such disparities were more pronounced if individuals lived in MUA. In addition, there was a difference in the rate of prescription before and after COVID-19. While there was a temporary increase in the percentage of individuals being prescribed Risperidone and Aripiprazole after the lockdown started in Los Angeles; overall, the percentage of individuals with PDD with prescriptions went down after the pandemic. Our findings suggest socioeconomic factors play an important role in the rate of antipsychotic prescriptions.

Disclosures: J.B. Tuschhoff: 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.; HRSA. **D.S. Bhandal:** 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.; HRSA. **D.M. Davies:** 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.; HRSA. **K. Nguyen-Ngo:** None. **C.S. Colwell:** None. **C.A. Ghiani:** None.

Poster

PSTR098: Human Data: MRI, Image, Video and Other Database

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR098.15/V1

Topic: I.07. Data Analysis and Statistics

Support: Ministry of Electronics and Information Technology (Meity) 4(16)/2019-ITEA

Title: Altered thalamocortical functional connectivity in COVID-19 recovered patients

Authors: *S. MISHRA[1], T. K. GANDHI[1], B. B. BISWAL[2];
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Abstract: The long-term neurological impact of COVID-19, highlighted by symptoms like brain fog, inattention, memory issues, and fatigue, may be reflected in the functional connectivity (FC) in the brain. We hypothesize that these symptoms in COVID-recovered patients (CRPs) may be linked to abnormalities in the thalamocortical (TC) network, due to its widespread projections in the cortex. Therefore, we present a cross-sectional study investigating the resting state FC in the TC Networks of CRPs. We acquired T1-w MRI and resting-state fMRI scans for 72 CRPs and 48 Healthy Controls (HCs). After pre-processing the fMRI scans, we extracted the TCFC maps with 6 thalamic nuclei as seeds, specified using a spherical region of interest (ROI) of radius 8 mm centered at the respective MNI coordinates. The right and left Mediodorsal (MD) nuclei,

pulvinar (PUL) nuclei, and ventral lateral (VL) nuclei were studied. The BOLD time-series for each seed were obtained by averaging the voxels within the ROI. The TCFC of a nucleus with all other voxels was quantified using the Pearson correlation coefficient, followed by Fisher-z transformation, to generate a TCFC map for each seed. For statistical comparison of TCFC between the cohorts, permutation testing was used, and multiple comparison errors were corrected using voxel-based thresholding ($p_{corr} < 0.05$). Upon statistical comparison, the following regions exhibited significant alterations in TCFC maps for CRP > HC contrast. With the seeds in the right and left MD nuclei, significant clusters were observed in the left white matter callosal body, left putamen, and left frontal pole. Further, the right lateral occipital cortex, anterior cingulate gyrus, left sub-callosal orbitofrontal cortex, and the right Heschl's gyrus showed enhanced FC with the PUL nuclei in the CRPs. No significant changes were observed in TCFC maps with the VL nuclei. The MD nuclei relay the input from the basal ganglia and the limbic system to the prefrontal association areas and are primarily involved in higher cognitive processes including memory and attention. The PUL nuclei connect the visual cortex with association areas in the posterior parietal and temporal cortex. The medial PUL also connects with the cingulate and is implicated in multisensory integration. Abnormal FC in the TC circuits of the MD and PUL nuclei in the CRPs can be linked to symptoms like brain fog, memory loss, fatigue, and inattention. In this study, we observed that vital TC circuits involved in memory, planning, and attention show abnormal FC in CRPs, hinting at possible damage in this network. These findings aim to direct future research on the neurological substrates of long-term COVID-19.

Disclosures: S. Mishra: None. **T.K. Gandhi:** None. **B.B. Biswal:** None.

Poster

PSTR098: Human Data: MRI, Image, Video and Other Database

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR098.16/V2

Topic: I.07. Data Analysis and Statistics

Support: NIH NICHD Grant R03HD107124
Massachusetts Life Science Center Bits to Bytes Grant
Author Support: Stefanie Perrier - Banting Postdoctoral Fellowship (Canadian Institutes of Health Research)

Title: Using big data to study nutritional impacts on neurodevelopment: Identification of over 50 international birth cohorts and exploration of research trends

Authors: *S. PERRIER[1,2,4], A. KESRI[1,2], A. N. FOSTER[1,2], F. NASSIWA[1,3], S. SAWANT[1,3], R. VYAS[1,2], P. GRANT[1,2,3,4], S. U. MORTON[1,2,4], Y. OU[1,2,3,4];
[1]Fetal-Neonatal Neuroimaging and Developmental Sci. Center, Boston Children's Hospital, Harvard Med. Sch., Boston, MA; [2]Newborn Med., [3]Radiology, Boston Children's Hosp., Boston, MA; [4]Pediatrics, Harvard Med. Sch., Boston, MA

Abstract: Beginning in early fetal stages and peaking within the first 1000 days of life, brain development is a metabolically demanding and sensitive process known to be influenced by external factors, including availability and abundance of nutrients. Indeed, maternal nutrition during both pre- and post-natal periods (i.e., pregnancy and lactation) can impact infant brain development and later neurocognitive outcomes. Studying this impact requires complex longitudinal data collection from sufficiently large sample sizes. As such, birth cohort studies are designed to follow children from early life onwards, collecting data on external factors influencing health and development. Since birth cohort studies are conducted in various international locations, the joint analysis of multiple cohorts offers an opportunity to study a large and diverse dataset, providing greater statistical power. In this study, we aimed to identify a set of large international birth cohorts (>1000 participants each) that collected data on (1) nutrient intake in early life (e.g., maternal nutrition during pregnancy/lactation, child breastfeeding frequency, and/or child nutrition) and (2) neurodevelopmental outcome measures in childhood and/or adolescence. We identified over 50 birth cohorts encompassing >1 million total participants across 30 countries on 6 continents. Most birth cohort studies were performed in more developed nations, with the majority conducted in European countries. Among these identified cohorts, we sought to investigate the most studied research domains by performing a PubMed database query to extract MeSH keywords from publications citing each initial cohort profile publication. Among >3500 keywords, the top 20 most frequent keywords associated with research-related categories were within the study areas of: (1) exposures and effects (e.g., *Risk Factors, Prenatal Exposure Delayed Effects, Smoking, Socioeconomic Factors, Environmental and Maternal Exposures*), (2) weight and diet (*BMI, Birth Weight, Obesity, Diet, Breastfeeding*), (3) genetics (*DNA Methylation, Single Nucleotide Polymorphism, Genetic Predisposition to Disease*), and (4) neurological disorders (*Depression and Attention Deficit Disorder with Hyperactivity*). To explore closely studied research areas, we also conducted keyword co-occurrence analysis using a correlation matrix to generate graph networks and schemaball diagrams. In sum, these cohorts present an opportunity to develop a combined large dataset to study the impact of early life nutrition on later neurodevelopmental outcomes, and further inform dietary recommendations to optimize brain health.

Disclosures: S. Perrier: None. **A. Kesri:** None. **A.N. Foster:** None. **F. Nassiwa:** None. **S. Sawant:** None. **R. Vyas:** None. **P. Grant:** None. **S.U. Morton:** None. **Y. Ou:** None.

Poster

PSTR098: Human Data: MRI, Image, Video and Other Database

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR098.17/V3

Topic: I.07. Data Analysis and Statistics

Support: NIH R01MH130415
NIH R01AG076227
NIH P20GM103645
Carney Institute for Brain Sciences Zimmerman Innovator Award

Title: Deconstructing the event-based waveform through the lens of MEG beta

Authors: *D. W. ZHOU, S. R. JONES;
Neurosci., Brown Univ., Providence, RI

Abstract: Transient beta-band (15-30 Hz) activity in electrophysiological recordings, known as beta events or bursts, has been implicated in a wide range of cognitive and disease processes (Shin et al. 2017). Recently, time-domain features of these signals are beginning to attract attention, and have been shown to correlate with resting-state activity and behavior (Brady et al. 2020; Brady and Bardouille 2022). Traditional time-domain analyses of beta waveforms involve computing time-locked means and standard error over many observations. This approach, similar to common analytical approaches to analyzing event-related potentials, obscures the waveform structure of individual events in unaveraged data. In this study, we describe a data-driven approach to deconstruct single-trial beta-event waveform features contributing to averaged signals of interests, such as peaks and troughs. This approach can interchangeably incorporate different techniques for extracting time-domain features, such as cycle-by-cycle analysis and convolutional dictionary learning. The empirical distributions of the features can be modified and new waveforms can be generated synthetically through resampling in order to test hypotheses about comparative influences of key feature characteristics on the mean waveform. We applied our approach to beta-events in resting-state MEG data from the open-source Cam-CAN repository in order to investigate the origin of waveform differences between subjects of different ages (400 in 20s, 40s, 60s, and 80s age deciles). Previous studies have shown that averaged beta event waveforms exhibit increases in peak-to-peak times and larger amplitudes across age (Brady and Bardouille 2022). In the averaged signals, the amplitudes of peaks and troughs taper away (i.e. decrease in amplitude and increase in duration) both before and after the "central" trough, defined as the deepest trough within each event. Our analysis revealed that differences in morphology near peaks and troughs in the mean waveform result from statistical differences in amplitude and timing of these features in the non-averaged signal. Increases in the timing between peaks/troughs explain lower beta event frequency, whereas variance in timing between peaks/troughs influences tapering at the start and end of the mean waveforms. Our results define statistically significant changes on trial-level event characteristics that lead to known changes in the waveform of beta events. Our approach may generalize to uncovering feature-based differences in waveforms of other oscillatory events and/or event-related potentials.

Disclosures: D.W. Zhou: E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Work disclosed in patent filing 63/464,340. **S.R. Jones:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Work disclosed in patent filing 63/464,340.

Poster

PSTR098: Human Data: MRI, Image, Video and Other Database

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR098.18/V4

Topic: I.07. Data Analysis and Statistics

Title: Pupillometry and geometrical characteristics parameters during visual and oculomotor tasks

Authors: *P. M. DAYE[1], P. POUGET[2];
[1]P3Lab, UMons, Louvain-la-Neuve, Belgium; [2]Inst. du Cerveau (ICM), Paris, France

Abstract: Pupillometry is a field of research that is mainly concerned with the measurement of two important geometrical characteristics of the pupil: pupil size and pupil location with respect to other anatomical structures of the eye. In general, pupil size determines the amount of light falling on the retina and defines the optical characteristics of the eye. There are two common deficiencies in current video-based pupillometers. First, they measure the location of the pupil as a proxy of the eye position. Second, the pupil size is reported using an arbitrary unit (e.g. the number of pixels within the pupil). In terms of parameter estimation, using the pupil center in reference has two practical consequences: the measurements of the pupil size and direction vary with light level changes, and, more importantly, displacement of the eye generates profile distortions of the recorded image of the pupil and their parameter extraction. Here, we propose to compute a normalized pupil size with respect to the lymbus size. We show that this normalized measurement is less sensitive to the eye orientation to the distance between the eye-tracker and the subject eyes. In addition, we demonstrate that there is a relative motion between the extracted center of the lymbus and the extracted center of the pulpil. These findings have important consequences for clinical and neuroscientific studies using pupil parameters as assets of cognitive and/or visual processes.

Disclosures: P.M. Daye: A. Employment/Salary (full or part-time):; NeuroClues by P3Lab. **P. Pouget:** F. Consulting Fees (e.g., advisory boards); NeuroClues by P3Lab.

Poster

PSTR098: Human Data: MRI, Image, Video and Other Database

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR098.19/V5

Topic: I.07. Data Analysis and Statistics

Title: Association between depression and memory in Hispanic participants from the NACC dataset and implications for Alzheimer's Disease and brain health

Authors: *I. PEREZ[1], L. PENA[2], E. I. ALANIZ[3], M. GIL[4], N. ALLIEY-RODRIGUEZ[5];
[1]Psychological Sci., Univ. of Texas Rio Grande Valley, Brownsville, TX; [2]Dept. of Neurosci., Univ. of Texas Rio Grande Valley, Harlingen, TX; [3]Clin. Psychology, The Univ. of Texas Rio Grande Valley, Brownsville, TX; [4]Dept. of Psychological Sci., The Univ. of Texas Rio Grande Valley, Brownsville, TX; [5]Neurosci., The Univ. of Texas Rio Grande Valley, Harlingen, TX

Abstract: Title: Association between depression and memory in Hispanic participants from the NACC dataset and implications for Alzheimer's Disease and brain healthAuthors: Ismael Perez1, Luis Pena Márquez2, Esperanza Zacarias1, Mario Gil, PhD1,2, Ney Alliey-Rodriguez, MD2Affiliations: 1. University of Texas Rio Grande Valley (UTRGV) Department of Psychological Science, 2. UTRGV School of Medicine Institute of Neuroscience
Background: Studies that analyze depression and memory have found inconsistencies on how self-reported depression affects memory (Vanderhill et., 2010). Hispanics face many challenges, among them higher-than-average adverse health outcomes such as increased obesity, hypertension, neurodegenerative diseases, and poor healthcare access which increases risk of developing depressive symptoms and also memory problems (Sadule-Rios, 2012). The current study aims to analyze self-reports of depression within the last two years and their associations in a Hispanic population. Methods: The present study utilized data from +47,000 individuals in the National Alzheimer's Coordinating Center (NACC) dataset to conduct a linear regression analysis to analyze whether self-reports of depression within the last two years predict memory problems. The factors of education, heartrate, and weight were controlled. Results: The result of a linear regression revealed that in a Hispanic sample of the NACC dataset, there was a significant association between self-reported depression in the past two years and memory problems ($F(4, 901) = 17.212$, $p < .001$, $R2 = 0.071$). The individual predictors were examined further and indicated that education ($t = -4.815$, $p < .001$),), and weight ($t = -2.083$, $p = .038$) were significant predictors in the model. The variable of heart rate ($t = 0.582$, $p = 0.561$) was not significant. Conclusions: The NACC dataset provides valuable information of health outcomes of older adults in the United States of America. Although the current study provided some information into the relationship between self-reported depression and memory, the proportion of the variance between these variables could not be explained. To our knowledge, this is the first study that has controlled for the effects of weight and heart rate with how depression is related to memory in a Hispanic sample. With the rise of diabetes in the United States, the study of how weight and heart rate affect depression and memory is needed, as research has shown that diabetes affects the brain's metabolic activity (Garcia-Serrano et al., 2020). Future plans are to analyze whether this can be achieved with other ethnic groups.

Disclosures: I. Perez: None. **L. Pena:** None. **E.I. Alaniz:** None. **M. Gil:** None. **N. Alliey-Rodriguez:** None.

Poster

PSTR098: Human Data: MRI, Image, Video and Other Database

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR098.20/V6

Topic: I.07. Data Analysis and Statistics

Support: RS-2023-00208884
RS-2023-00265824
Kumoh National Institute of Technology (2023)

Title: Development of deep learning-based brain segmentation technique for effective neurological disease research

Authors: *H. KIM, J. LEE;
Kumoh Natl. Inst. of Technol., Gumi, Korea, Republic of

Abstract: Brain imaging provides crucial information for diagnosing neurological diseases such as brain tumors, strokes, and Alzheimer's disease. Depending on the diseases, there are differences in the primary features to be examined. In the case of brain tumors and strokes, the location and volume of lesions are primarily important, while in Alzheimer's disease, the volume of brain tissue and specific areas are key. These features require the expertise of skilled professionals due to the ambiguity of boundaries, making the process time-consuming. Therefore, this study aims to develop a deep learning-based segmentation model that can achieve sufficient performance with one model despite the differences in disease-specific features in brain imaging. T1-weighted imaging data were used for this study. We proposed two models based on the nnUNet, which has shown good performance in image segmentation. The first model, called nnSeUNet (nnUNet + SE (squeeze and excitation)), incorporates the SE module, which calculates the importance of extracted feature maps during learning operations. The second model, nnSeResUNet (nnUNet + SE + Residual), adds a module that passes residual feature maps through skip connections. One model was simultaneously utilized for the segmentation of brain tumors, stroke lesions, and Alzheimer's disease tissue and areas. Additionally, the region volumes of Alzheimer's disease patients and healthy subjects were compared. In brain tumor segmentation, the base model achieved 90.91%, nnSeUNet achieved 90.60%, and nnSeResUNet achieved 90.41%. In stroke lesion segmentation, the base model achieved 59.43%, nnSeUNet achieved 60.08%, and nnSeResUNet achieved 63.70%. For Alzheimer's disease patients' brain tissue and area segmentation, the base model achieved 85.71%, nnSeUNet achieved 85.72%, and nnSeResUNet achieved 86.07%. When statistically comparing the volume of regions between healthy individuals and Alzheimer's disease patients, the largest differences were observed in the amygdala and hippocampus. In brain stroke lesion segmentation, the relatively low performance metrics were due to differences at the voxel level, and visually, it was possible to confirm sufficiently good results for research assistance. The proposed model outperformed the base model and demonstrated high generalizability when applying the same model to patients with different conditions. Additionally, the inference time was around 10 seconds per brain image, significantly faster compared to manual segmentation by experts. It is expected that the proposed model will serve as a helpful adjunct tool for rapid and accurate diagnosis of brain disease patients.

Disclosures: H. Kim: None. **J. Lee:** None.

Poster

PSTR098: Human Data: MRI, Image, Video and Other Database

Location: MCP Hall A

Time: Sunday, October 6, 2024, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR098.21/V7

Topic: I.07. Data Analysis and Statistics

Title: Vancomycin Area Under Curve Estimated Using Trough Only Data In Adult Intensive Care Unit Patients

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Abstract: In the 2020 therapeutic guidelines, Area Under Curve (AUC) guided dosing and monitoring were recommended as the most accurate way to manage vancomycin (VCM) therapy to predict clinical efficacy, the objective of this work was to explore the relationship between VCM trough concentration and the ratio AUC24/MIC in patients with MRSA bacteremia and head injury and as second goal, to evaluate the use of pharmacokinetics programs using Bayesian analysis in the clinical setting to obtain pharmacokinetics parameters. Data were collected retrospectively, over three years, from the intensive care unit (ICU) at The Instituto Nacional de Neurología y Neurocirugía; the study was approved by the Ethics Committee of the Instituto Nacional de Neurología (56/09), 23 patients (Male 12/Female 11) with an age and body weight range of 14-72 years and 42-117 Kg respectively were included. Following clinical protocol in the Institution, patients received VCM in a dosage regimen of 1g IV during 1 h infusion for a 12 h interval. Patients were categorized according to the Glasgow Coma Scale (GCS), and the MIC for VCM was determined by Test for antimicrobial susceptibility testing. The plasma levels of VCM were determined by a validated HPLC method. The AUC24 was determined based in a total daily dose and predicted using a pharmacokinetic system program with Bayesian analysis, (DoseMe, PKS System, and VancoCalc). A wide inter-individual variability of plasma levels was observed ranging from 3.1-24.9 mg/L, the patients with a Cmin > 15 mg/L, represented 30% (n = 7), those patients that achieved AUC24/MIC values >400 were approximately 23% of the population with a MIC<2. In 40 percent of the patients, the AUC24/MIC ratio was above 400. No significant differences (P<0.05) were found among the mean AUC24 value predicted by all pharmacokinetic programs and the AUC24 mean value determined based in a total daily dose. The comparison of the dosage regimen following clinical protocol with that predicted by the Bayesian analysis showed that only 13% of the patients did not show change. The interindividual variability of VCM serum concentrations for a fixed-dosage regimen could justify TDM. Consequently, the use of population pharmacokinetics programs for the dose adjustment can be an adequate alternative for optimizing treatment.

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Poster

PSTR098: Human Data: MRI, Image, Video and Other Database

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Title: High throughput analysis of human CA1 neuron morphometry using U-Net cell segmentation for the identification of insulin resistance pathology

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Abstract: Although amyloid-β plaques and tau neurofibrillary tangles are diagnostic factors in Alzheimer's disease (AD), an increasing body of evidence indicates that brain insulin resistance can promote AD pathogenesis. IRS-1 pS616 is a neuropathological marker of insulin resistance found in AD brains, in which it is almost exclusively limited to cell nuclei in hippocampal field CA1 of normal humans but accumulates prominently in neuronal cytoplasmic microdomains in AD dementia (ADd; Talbot et al. 2012). To reliably differentiate nucleic and cytoplasmic pathologies in large-scale hippocampal tissue sections from multiple brain banks, we used a convolutional neural network (CNN) deep-learning image analysis system based on U-Net architecture to identify cellular boundaries and determine key neuronal nuclei morphometry. Using these nucleic morphometrics, we quantified the cellular density of cytoplasmic IRS-1 pS616 pathologies in the CA1 hippocampus of cognitively impaired individuals.
Methods: Formalin-fixed, paraffin-embedded blocks from sex- and age- (within 5y) matched normal (n=81), mild cognitively impaired (n=57), and ADd (n=80) cases were selected from 3 brain banks. Coronal 6 um sections were cut from each tissue block and labeled for IRS-1 pS616 immunohistochemistry or NeuN immunofluorescence with DAPI and imaged at 100x and 200x magnification, respectively. U-Net CNNs were trained with supervision to identify DAPI boundaries for NeuN positive cells or cytoplasmic/nucleic boundaries of IRS-1 pS616 positive cells. Image analysis with trained CNNs determined cell segmentations and quantified the area, maximal diameter, and form factor (4πArea/Perimeter^2) of each cell to establish nucleic morphometric thresholds.
Results: Neuronal nuclei (n=12621; 6 normal cases) morphometrics were identified. The median area (106.4μm^2), 95th percentile diameter (19.5μm; 13.6μm mean, 2.95μm SD), and lower quartile form factor (0.81) were selected as morphometric thresholds to classify CNN-identified IRS-1 pS616 pathologies as nucleic, excluded from subsequent analysis. The density of CA1 neurons with IRS-1 pS616 cytoplasmic pathology was significantly greater in ADd than normal cases in each cohort and in the combined data set ($p<1x10^{-10}$).
Conclusions: CNNs can be used for deep-learning image analysis to identify complex cellular pathologies and to quantify tissue morphometry—which can further differentiate pathological classifications. In this study, nuclear morphometrics was used to quantify IRS-1 pS616 pathology as a biomarker of insulin resistance in the hippocampal CA1 of ADd.

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Poster

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Title: The choice-wide behavioral association study: data-driven identification of interpretable behavioral components

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Abstract: Behavior contains rich structure across many timescales, but there is a dearth of methods to identify relevant components, especially over the longer periods required for (self-)shaping, learning, and decision-making. Inspired by the goals and techniques of genome-wide association studies, we present a data-driven method--the choice-wide behavioral association study: CBAS--that systematically identifies such behavioral features. CBAS uses a powerful, resampling-based, method of multiple comparisons correction to identify sequences of actions or choices that either differ significantly between groups or significantly correlate with a covariate of interest. We apply CBAS to different tasks and species (flies, rats, and humans) and find, in all instances, that it provides interpretable information about each behavioral task. For flies, we apply CBAS to a publicly available dataset measuring left and right turns on a y-maze. CBAS identifies differences in the number of turns in a row between different outbred strains. For rats, we apply CBAS to a dataset that we collected in rats performing a series of spatial alternation contingencies. CBAS identifies a phenotype consistent with restrictive and repetitive behavior when comparing wild-type rats to rats haploinsufficient for a high confidence, large effect, ASD risk gene (*Scn2a*). For humans, we apply CBAS to a publicly available dataset of subjects performing a two-step task to measure the interplay between model-based and model-free decision making. The subjects in the dataset also completed psychiatric symptom questionnaires, and CBAS identifies sequences of choices in the task that correlate with compulsive behavior and intrusive thought severity. CBAS provides a data-driven way to extract relevant information from behavior, enabling evidence to falsify and refine hypotheses or to develop hypothesis when less is known about the behavior.

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Poster

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Title: A high-throughput pipeline for precise pupil size measurement using deep learning in mice and humans

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Abstract: DeepVision: A High-Throughput Pipeline for Precise Pupil Size Measurement Using Deep Learning in Mice and Humans
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Pupillometry is a non-invasive method to study autonomic nervous system function. By measuring changes in pupil size, this technique provides insights into the dynamic interaction between sympathetic and parasympathetic systems. Additionally, pupillometry informs about an individual's behavioral state, including their levels of arousal, emotional responses, and cognitive engagement. Despite its importance in research and clinic, standardizing pupillometry across different laboratories has been challenging, primarily due to the absence of standardized computational analysis pipelines. The development of a fast, high-precision, and minimally supervised pupil analysis pipeline would facilitate both research and clinical applications. In this study, we compared the efficiency of several open-source Deep Learning packages, including DeepLabCut, to establish an optimal pipeline. Remarkably, our pipeline achieved exceptional precision, surpassing 95%, with training on only 0.01% of the video dataset and enabled robust and rapid pupil identification across diverse experimental conditions in large rodent populations. We also tested the applicability of our analysis pipeline in human pupil recordings. Similar to rodent results, analysis of human pupil data yielded precision rates exceeding 95%, supporting the reliability and accuracy of our method for human data. Additionally, we successfully applied our methodology to analyze pupil datasets originating from neurodevelopmental and

neurodegenerative preclinical rodent models, supporting our method's versatility and applicability across varied research contexts. Lastly, by leveraging advanced high-performance computational (HPC) systems, we reduced data analysis time significantly, processing approximately 20 million mouse and human pupil images in just 10 hours. The novel deep learning-based high-throughput pupil analysis pipeline (DeepVision) offers a reproducible, fast, and high-precision method with minimal supervision, which can accelerate human and rodent pupil analysis in research and clinical settings and effectively standardize pupil analysis results across diverse laboratory settings, addressing reproducibility concerns.

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Poster

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Topic: I.07. Data Analysis and Statistics

Support: NSF Award #2341551

Title: Preserving Privacy in Sleep Data Using Generative Adversarial Neural Networks

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Abstract: Preserving Privacy in Sleep Data Using Generative Adversarial Neural NetworksAuthors Thomas Platt[1], Laci Parker[2], Dr. Mark Allison[3], Rheygan Reed[4], Dr. Felicia Jefferson[5]**Affiliation**University of Nevada, Reno, NV 89509 [1,4,5]University of Michigan, Flint, MI 48502 [2,3]**Disclosures**Thomas Platt – None. Laci Parker – None. Dr. Mark Allison – None. Rheygan Reed -None. Dr.Felicia Jefferson – None.**Abstract**Sleep disorders affect a large portion of the world's population and can lead to significant damage anddisability if left untreated. Researchers have persisted in developing artificial intelligence-drivendiagnostic equipment to combat issues of inaccessibility, required resources, and patient compliance.Reliable algorithms that are both accurate and unbiased can be created for diagnosing sleep disorders toaddress these problems. Synthetic data can be very effective, but its uses are limited to well-establishedanalysis and needs high-quality data to be accurate. Further improvements to these machine learningsystems can make diagnosis faster, cheaper, and more convenient for patients in many more fields ofmedicine. Healthcare has increased its security and privacy concerns regarding sharing crucialknowledge. Biases in Machine Learning (ML) lead to the effects of society in disparities data collection.The data collected that is conveyed to algorithmic outputs then compounds the problems of the societaloutcomes. Data privacy for ground truth is heavily regulated. Given these constraints sharing of datamay attenuate advancement in diagnosis and

treatment. This further amplified in the context ofunderserved populations. With the imbalance of data to algorithm for sleep data, the use of GenerativeAdversarial Networks (GANs) is introduced to help mitigate. In this project, we focus on rural and agingcommunities where the adaptation of AI tools for health conditions is underrepresented. Currentapproaches to GAN sleep data synthesis are mostly constrained to a particular subset of the data used indiagnosis. Our position is for synthetic data be more reflective of ground truth and to be more useful inexpanding diagnosis and treatment efforts. This work seeks to address a gap in the body of knowledgeby exploring the nontrivial aspect to generating high precision multi-dimensional datasets typical ofPSGs. We propose that GAN technology will allow us to use learning models to increase the diagnosis ofsleep disorders. This will expand the state of the practice to allow sleep clinics and laboratories to betterserve all patient populations.

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Poster

PSTR098: Human Data: MRI, Image, Video and Other Database

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Topic: I.07. Data Analysis and Statistics

Title: A cloud-based pipeline to prioritize disease predisposition genes and variants in rare disease studies using public summary counts data as control

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Abstract: Most rare disease studies only have patient samples without matched healthy control samples, making it difficult to find disease risk genes in these studies. Previously, we developed CoCoRV (consistent summary counts based rare variant burden test), which is a computational tool to help prioritize disease predisposition genes and genetic variants in rare diseases. CoCoRV implements consistent variant quality control and filtering, ethnicity-stratified rare variant association test, accurate inflation factor estimation and powerful FDR control, which minimize the chance of false positives due to batch effects between cases and controls. However, the full pipeline involves multiple steps such as variant QC, annotation, and ethnicity inference, which can be either computationally intensive or requiring large physical memory, such as preprocessing gnomAD control data. Here, we develop a cloud version of CoCoRV based on the popular workflow language ‘nextflow’ and the Docker container. Our cloud-based pipeline includes pre-processed and annotated gnomAD count data, and it is simple to run the full analyses once required inputs are specified. The Docker containerization of each step relieves the users from installing all dependencies for their specific platform. The pipeline is deployed in the cloud platform ‘Amazon AWS HealthOmics’. We plan to create other cloud-based instances in DNANexus, Illumina ICA, etc. The nextflow based pipeline is also portable, which includes

configuration for running conda environment or docker/singularity containers and can be easily downloaded and run in a local environment, e.g., a high-performance computing cluster. Previously, we applied CoCoRV to identify disease-predisposition genes in adult brain tumors and Amyotrophic Lateral Sclerosis data from CReATe cohort. We are currently analyzing more ALS data from TargetALS and AnswerALS cohorts and other in-house neurodegenerative diseases, e.g., Schizophrenia. As there have been a large amount of sequencing data in the cloud environment and it is easy to upload and share data in cloud platforms, researchers around the world can analyze their datasets using our cloud implementation to make potential discoveries on novel disease predisposition genes.

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